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# Automatic control of the NMB level in general anaesthesia with a switching total system mass control strategy

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**Abstract** This paper presents a model based switching control strategy to drive the neuromuscular blockade (NMB) level of patients undergoing general anaesthesia to a predefined reference. A single-input single-output Wiener system with only two parameters is used to model the effect of two different muscle relaxants, *atracurium* and *rocuronium*, and a switching controller is designed based on a bank of total system mass control laws. Each of such laws is tuned for an individual model from a bank chosen to represent the behavior of the whole population. The control law to be applied at each instant corresponds to the model whose NMB response is closer to the patient's response. Moreover a scheme to improve the reference tracking quality based on the analysis of the patient's response, as well as, a comparison between the switching strategy and the *Extended Kalman Filter (EKF)* technique are presented. The results are illustrated by means of several simulations, where switching shows to provide good results, both in theory and in practice, with a desirable

reference tracking. The reference tracking improvement technique is able to produce a better reference tracking. Also, this technique showed a better performance than the (EKF). Based on these results, the switching control strategy with a bank of total system mass control laws proved to be robust enough to be used as an automatic control system for the NMB level.

**Keywords** Automatic delivery system · Switching control · Positive control system · Minimally parameterized parsimonious models

## 1 Introduction

Anesthesia can be defined as a drug-induced reversible state where three variables must be controlled: hypnosis, analgesia, and areflexia. Areflexia is defined as the lack of movement. It is induced and maintained by the administration of muscle relaxants, such *atracurium* and *rocuronium*, whose goal is to achieve an appropriate level of paralysis during surgical procedures. The neuromuscular blockade (NMB) can be clinically measured by electrical stimulation of the adductor pollicis muscle in the patient's hand where the NMB level corresponds to the first single response calibrated by a reference twitch.

The NMB level can be modeled by pharmacokinetics/pharmacodynamics (PK/ PD) models that relate in a first step the administered drug dose with the drug concentration in the relevant part of the patient's body, known as the effect compartment, and then relate, in a second step, the effect concentration with the actual drug effect (here, the NMB level).

Compartmental systems are widely used to model the PK/PD of intravenously administered drugs [4]. A

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compartmental system is a system that has a finite number of homogeneous, well-mixed subsystems, called compartments that exchange material among them and with the environment. These interchanges are described by laws that take into account the transfer of material, accumulation and elimination in each compartment and to the environment.

When compared with manual drug administration, automatic control strategies may carry considerable advantages like avoiding under or overdosing. In order to implement automatic control, reliable models are needed for the patients. This implies setting up a suitable class of models as well as automatic strategies able to identify the patient model taking into account the inter- and intra-individual variability. The switching control strategy proposed in this paper is precisely a contribution in this direction, as it allows to on-line tune the controller based on the choice of a suitable model for the patient within a given model bank. Since the patient model may change along the procedure, besides taking into account inter-individual variability, this allows to overcome the variation of the patient characteristics during the surgery (intra-individual variability). The novelty of the present switching strategy consists in the type of patient models and control laws upon which it is based.

More concretely, this paper presents a control strategy for the NMB level using a total system mass control law for a new minimally parameterized parsimonious (MPP) compartmental model [8] describing the effect of the muscle relaxant *rocuronium* in the NMB level [8]. The total system mass control law for feedback stabilization of compartmental systems of [3] is used and a switching control strategy is applied in order to perform the parameter identification needed to obtain the control input. A scheme to improve the reference tracking quality based on the analysis of the patient's steady-state response is presented. Also, a comparison between the technique here presented with the *EKF* technique is shown.

The contents of the paper are as follows: Sect. 2 presents the model for neuromuscular blockade control, describing the MPP Wiener model for the NMB level and the total system mass control law used to drive the NMB level to the desired reference. In Sect. 3 the switching control strategy used to define the control law is described together with the scheme to improve the reference tracking, while in Sect. 4 the simulation results of the implementation of such control strategy are presented. In Sect. 5 a comparison between the switching strategy and the *EKF* technique is performed. In Sect. 6 the practical results of the implementation of such control strategy are presented. Finally, in Sect. 7 the conclusions are drawn.

## 2 A model for neuromuscular blockade control

### 2.1 Minimally parameterized parsimonious NMB model

In this paper we consider the model proposed in [8] for the effect of a muscle relaxant in the neuromuscular blockade level. This is a Wiener model whose linear part relates the administered drug dose,  $u(t)$ , to the drug effect concentration,  $C_e(t)$ , and is given by a transfer function of the form:

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

where  $k_1, k_2, k_3$  are fixed, and  $\alpha$  is a patient dependent parameter. According to [8], where a brute force search on the real database was performed, the values of  $k_1, k_2, k_3$  are fixed to 1, 4, 10, respectively.

The nonlinear part of the model relates the drug effect concentration,  $C_e(t)$ , to the produced neuromuscular blockade,  $r(t)$ , and is given by the Hill equation [10]:

$$r(t) = \frac{100 C_{50}^\gamma}{C_{50}^\gamma + C_e(t)^\gamma}, \tag{2}$$

where  $\gamma$  is a patient dependent parameter. Moreover  $C_{50}$  does not represent as usual the concentration at half of the maximal drug-related effect, but is rather a modified value that incorporates the gain of the linear part. This parameter is taken to be fixed and equal to 3.24 for *atracurium* and 1 for *rocuronium*. Here  $r(t)$  varies in a scale from 0 to 100 % where 0 corresponds to full paralysis and 100 to full muscular activity.

Note that although the linear part of this model can be realized through a compartmental state-space model, its parameters do not have a physical meaning, for an explanation in full detail we refer to [8]

In order to apply the proposed control strategy the transfer function  $h(s)$  is realized by means of a 3-compartmental state-space model of the form:

$$\begin{cases} \dot{x}(t) = A(\alpha)x(t) + B(\alpha)u(t) \\ C_e(t) = Cx(t). \end{cases} \tag{3}$$

where  $A(\alpha) = \alpha A, B(\alpha) = \alpha B$ , with

$$A = \begin{bmatrix} -k_3 & 0 & 0 \\ k_2 & -k_2 & 0 \\ 0 & k_1 & -k_1 \end{bmatrix}, \quad B = \begin{bmatrix} k_3 \\ 0 \\ 0 \end{bmatrix} \quad e$$

$$C = [1 \quad 0 \quad 0].$$

### 2.2 Total system mass control law

It has been shown in [1] that the following positive control law proposed in [3] for total mass control:

$$\begin{cases} u(t) = \max(0, \tilde{u}(t)) \\ \tilde{u}(t) = \left(\sum_{i=1}^3 b_i(\alpha)\right)^{-1} ([111]A(\alpha)x(t) + \lambda(M(x) - M^*)), \end{cases} \quad (4)$$

where  $-1 < \lambda < 1$  is an arbitrary convergence parameter. This control action  $u(t)$  not only leads the total system mass  $M(x(t)) = \sum_{i=1}^3 x_i(t)$  (in compartmental systems, the sum of the state components usually corresponds to the total substance mass present in the system) to a reference value  $M^*$ , but also leads the effect concentration,  $C_e(t)$ , to the reference value  $C_e^* = M^*/3$  [1]. This can be used to control the NMB level in the following way. Given a desired reference value  $r^*$  for the  $r(t)$  (measured signal for the NMB level), compute the corresponding reference level for the effect concentration  $C_e^*$  by inverting the Hill equation, i.e.

$$C_e^* = \left(\frac{100}{r^*} - 1\right)^{1/\gamma} \times C_{50}, \quad (5)$$

and set  $M^* = 3C_e^*$  in the control law (4). This guarantees that the NMB follows the desired reference level,  $r^*$ .

Note however that this control strategy strongly rests on knowledge of the patient dependent parameter  $\gamma$ , which is unknown in practical cases. In order to overcome this situation, a switching control strategy is introduced in the next section.

### 3 Switching control strategy

#### 3.1 Switching control

It is shown in [6] that a switching controller is robust enough even in the presence of noise and artifacts in order

to solve a reference tracking problem, this also applies in the particular case of the NMB level studied in this paper. In order to take into account parameter variability, the following model based switching control strategy is adopted. A bank  $\mathcal{P} = \{\mathcal{P}_1, \dots, \mathcal{P}_N\}$  of representative Wiener models is considered, together with a bank of corresponding controllers  $\mathcal{K} = \{\mathcal{K}_1, \dots, \mathcal{K}_N\}$  each of them tuned according to what has been explained in the previous section. More concretely if  $\mathcal{P}_i = \mathcal{P}(\alpha_i, \gamma_i)$  then  $\mathcal{K}_i$  produces the control law:

$$u_i(t) = \max(0, \tilde{u}_i(t)),$$

with

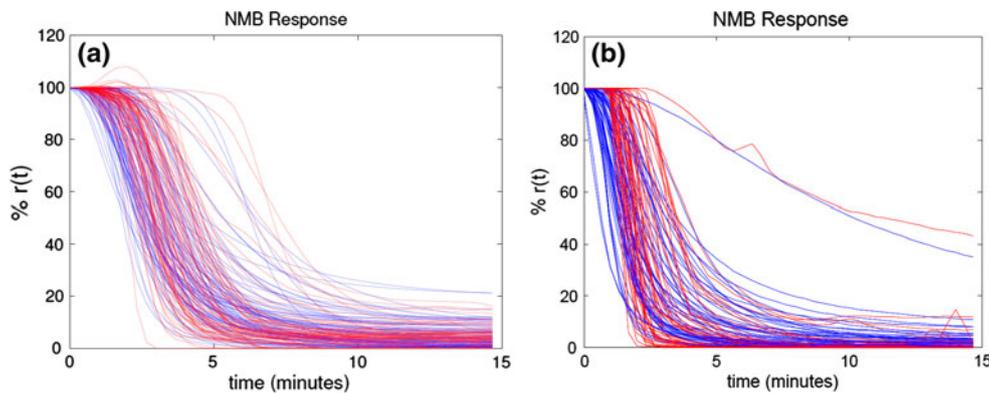
$$\begin{aligned} \tilde{u}_i(t) = & \frac{1}{k_3} [(k_3 - k_2)x_1 + (k_2 - k_1)x_2 + k_1x_3] \\ & - \frac{\lambda}{k_3\alpha_i} (M(t) - M_i^*). \end{aligned} \quad (6)$$

For the action of *atracurium* the bank  $\mathcal{P}$  was built taking into account real data acquired during surgeries. Based on that data the joint distribution for the parameters  $(\alpha, \gamma)$  is considered as follows [7]:

$$(\ln(\alpha), \ln(\gamma)) \sim BN(\mu, \Sigma), \quad (7)$$

where  $\mu = \begin{bmatrix} -3.2870 \\ 0.9812 \end{bmatrix}$  is the mean vector,  $\Sigma = \begin{bmatrix} 0.0250 & -0.0179 \\ -0.0179 & 0.1196 \end{bmatrix}$  is the covariance matrix and  $BN$  is the bivariate normal distribution. The standard bank of representative Wiener models was generated from this distribution as can be seen in Fig. 1, the responses of the models in the bank replicate quite satisfactorily the patient responses during surgery.

A similar study of the action of *rocuronium* is still being performed, and at this point only a set of real data acquired



**Fig. 1 a** Red: real NMB responses acquired during surgery performed with *atracurium*; these responses may be corrupt by measurement noise and sensor faults. Blue: NMB responses of the *atracurium* models from the bank  $\mathcal{P}$ . In both NMB responses an initial bolus of  $500 \mu \text{g/kg}$  was administered. **b** Red: real NMB responses

acquired during surgery performed with *rocuronium*; these responses may be corrupt by measurement noise and sensor faults. Blue: NMB responses of the *rocuronium* models from the bank  $\mathcal{P}$ . The doses applied to the real cases were applied to the respective models of the bank

during 50 surgeries is available. For each of these real cases, the parameters  $\alpha$  and  $\gamma$  were identified with the *Prediction Error Method*, and the corresponding models were taken as the standard bank of models to perform switching control.

The switching controller computes at each instant the “nearest model” to the patient and applies the corresponding control input to the patient. Proximity is here measured by the cumulative quadratic error between the patient response and the responses of each of the models in the bank (see Fig. 2).

### 3.2 Reference tracking improvement

Since the parameters  $(\alpha, \gamma)$  as well as the real value for  $M^*$  for the real patient are unknown it is expected to have a reference steady state tracking error. In order to overcome this drawback a scheme to improve the tracking quality is here proposed. This strategy relying on the NMB response at steady state performs the on-line tuning of the patient parameter  $\gamma$ .

For this purpose the input applied to the patient must be at steady state,  $u_{SS}$ , and the corresponding steady state NMB level response,  $r_{SS}$ , is supposed to be reached. At this stage the following equation described in [2] and suitably adapted to this model structure is applied for obtaining the correct value,  $\gamma^*$ , of  $\gamma$ :

$$\gamma^* = \frac{\ln\left(\frac{100}{r_{SS}} - 1\right)}{\ln\left(\frac{u_{SS}}{C_{50}}\right)}. \tag{8}$$

It turns out that a correct identification of this parameter will lead to the improvement of the control law, since the value of  $M^* = 3C_e^*$  only depends on the parameter  $\gamma$  (5). After this step the parameter  $\gamma$  is fixed as  $\gamma^*$  and each control law  $\tilde{u}_i$  is adapted as:

$$u(t) = \max(0, \tilde{u}(t))$$

$$\tilde{u}_i(t) = \frac{1}{k_3} [(k_3 - k_2)x_1 + (k_2 - k_1)x_2 + k_1x_3] - \frac{\lambda}{k_3\alpha_i} (M(t) - M^*). \tag{9}$$

Moreover the choice of the control law to be applied at each instant is now made based on the cumulative quadratic error between the  $C_e$  response of the patient and the response  $C_e^i$  of the  $i$ -th model in the bank ( $i = 1, \dots, N$ ). This cumulative error is obtained since the instant where the control of the patient NMB level starts using (11).

## 4 Simulation results

In order to assess the performance of the proposed switching control strategy a bank of one hundred nonlinear dynamic models for *atracurium* and a bank of fifty nonlinear dynamic models for *rocuronium* were used to describe a wide range of patient dynamics. According to the muscle relaxant used in the sequel the bank  $\mathcal{P}$  will consist of the models of the action of the corresponding drug.

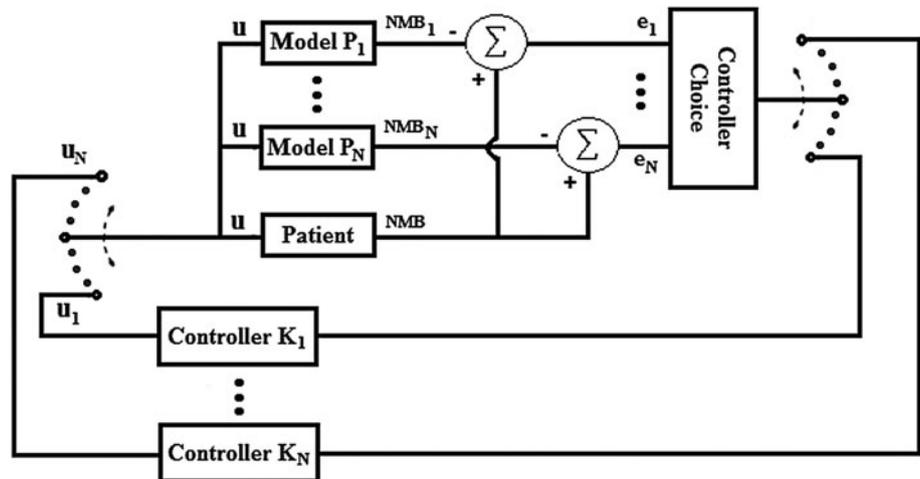
In each simulation, a model assumed to describe the patient is taken out from the model bank and the corresponding controller is also removed from the controller bank. The control law applied at each time instant is the one produced by the controller corresponding to the model with the most similar response to the patient response.

This can be summarized in the following steps:

**Preparation:** A model  $\mathcal{P}_j$  from the bank  $\mathcal{P}$  is chosen as describing the real patient dynamics.

**Step 1**  $t = 0$ : A standard bolus of  $500 \mu g/kg$  for *atracurium* or  $600 \mu g/kg$  for *rocuronium* is given to the patient.

**Fig. 2** Switching control strategy



**Step 2**  $0 < t < t^*$  (before recovery from the initial bolus): The input remains zero.

**Step 3**  $t = t^*$  (the time instant  $t^*$  is detected automatically by the on-line tuned algorithm for recovery detection (OLARD) introduced in [9] and corresponds to the recovery from the initial bolus): A random controller from bank  $\mathcal{K}$  is chosen in order to start the control of the NMB response of the patient.

**Step 4**  $t \geq t^*$ : A controller  $\mathcal{K}_i$  is chosen at each time instant based on the minimization of the cumulative error between the patient response and the responses of each of the models in the bank  $\mathcal{P} \setminus \{\mathcal{P}_j\}$ .

**Step 5** (if applied): Corresponds to the reference tracking improvement where  $\gamma$  is fixed as  $\gamma^*$  given by (6), and the selection of the controller  $\mathcal{K}_i$  is then based on the minimization of the cumulative error between the  $C_e$  response of the patient and the  $C_e$  responses of each of the models in the bank  $\mathcal{P} \setminus \{\mathcal{P}_j\}$  in order to obtain  $\alpha_i$  for the control law (9).

The corresponding simulations are described in Figs. 3, 4, 5, 6, 7 and 8. Figures 3, 4 and 5 represent the simulations for *atracurium* where Fig. 3 refers to a good case of switching control, and Figs. 4 and 5 represent a poor case of switching control without and with reference tracking improvement, respectively. The other three figures (Figs. 6,7,8) describe the switching control strategy applied to the case of *rocuronium*, where Fig. 6 concerns a good case of switching control and the last two Figs. 7 and 8, refer to a poor case of switching control without and with reference tracking improvement, respectively.

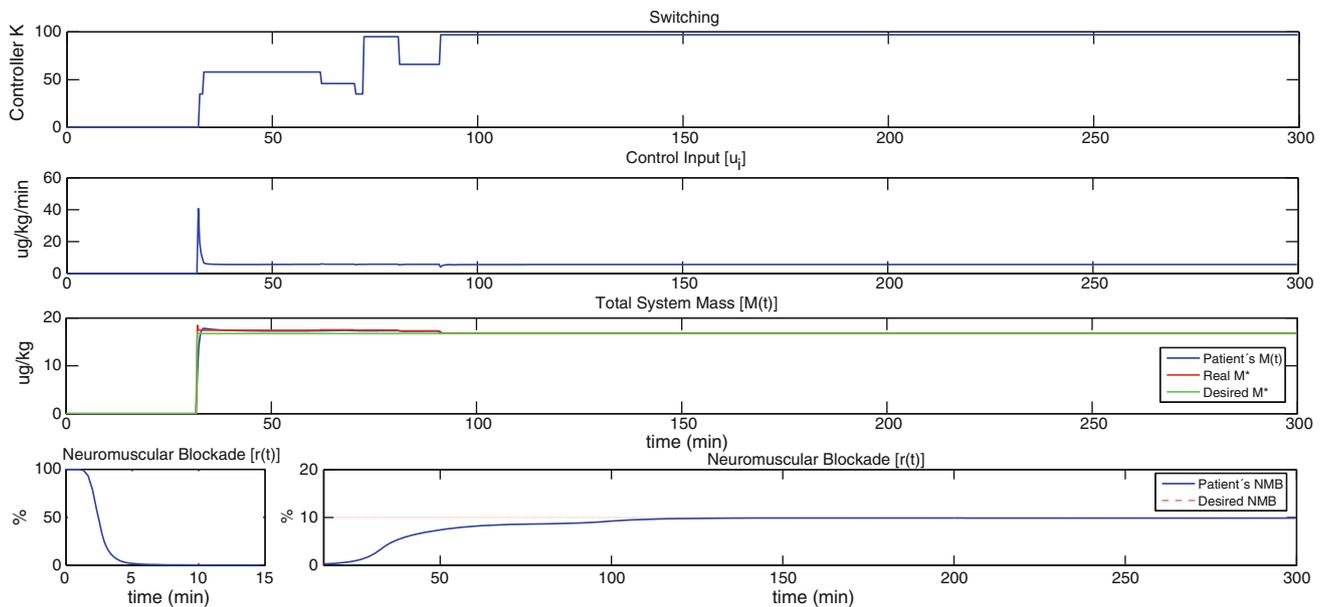
In each of the figures, the upper subplot displays the indices  $i$  of the controllers  $\mathcal{K}_i$  chosen during the control procedure. The subplot below refers to the control input,  $u_i$  [ $\mu$  g/kg/min] which remains zero until the recovery from the initial bolus occurs. The third subplot corresponds to the total system mass for the patient under consideration,  $M(t)$  [ $\mu$ g/kg], (blue line) and to the evolution of the values of  $M^*$  during control (red line), as well as the real value of  $M$  necessary to drive the patient's NMB level to the desired reference of 10 % (green line). Finally the lower subplots show the patient's NMB (blue line) and the NMB control target (red line), 10 % (*ref*), where the left subplot represents the NMB response to the initial bolus, and the right subplot shows the patient NMB response during the recovery to the initial bolus and the control. All variables are functions of time, expressed in minutes.

Figure 3 shows a case where the switching control strategy has a good performance. The last active controller is the one corresponding to model 97, and the total system mass tends to  $M_{97}^*$ , which corresponds to a steady state value for the patient's NMB level with an absolute error of 0.14 with respect to the desired reference value of 10 %.

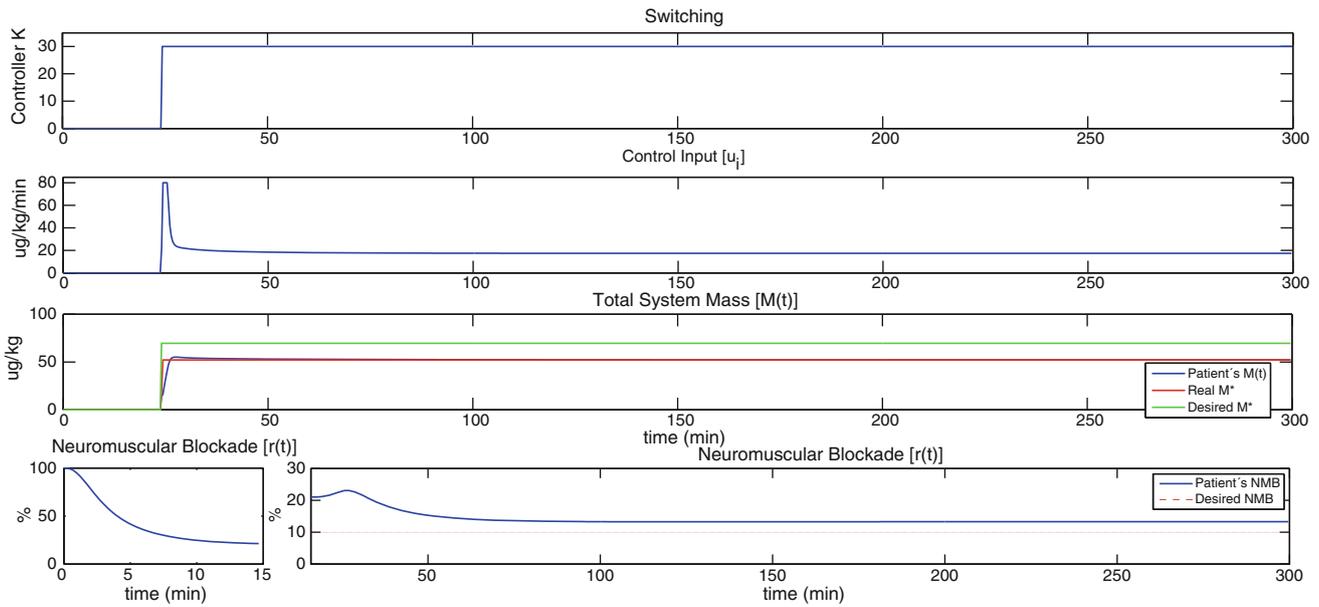
Figure 4 illustrates a case with relatively poor performance, where the last active controller is the one corresponding to model 30 with an absolute steady state error of 3.30.

Figure 5 shows the result of the application of the reference tracking improvement technique to this case. The calibration was performed at minute 74, and the absolute steady state error was reduced to only 1.02.

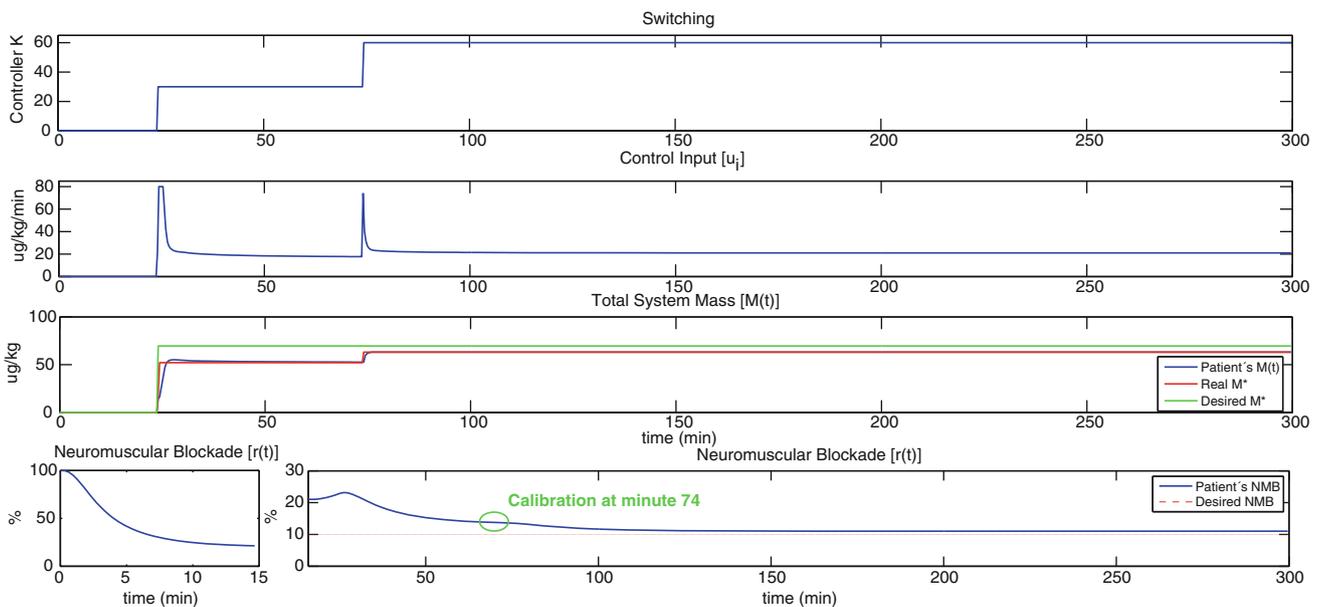
As for *rocuronium*, Fig. 6 exhibits a case where the performance of the switching control strategy is good. The



**Fig. 3** Results obtained for *atracurium*  $\mathcal{P} = M_{59}$  with  $\alpha = 0.0474$  and  $\gamma = 4.0478$  presenting a good reference tracking



**Fig. 4** Results obtained for *atracurium*  $\mathcal{P} = M_{38}$  with  $\alpha = 0.0345$  and  $\gamma = 1.1170$  presenting a poor reference tracking

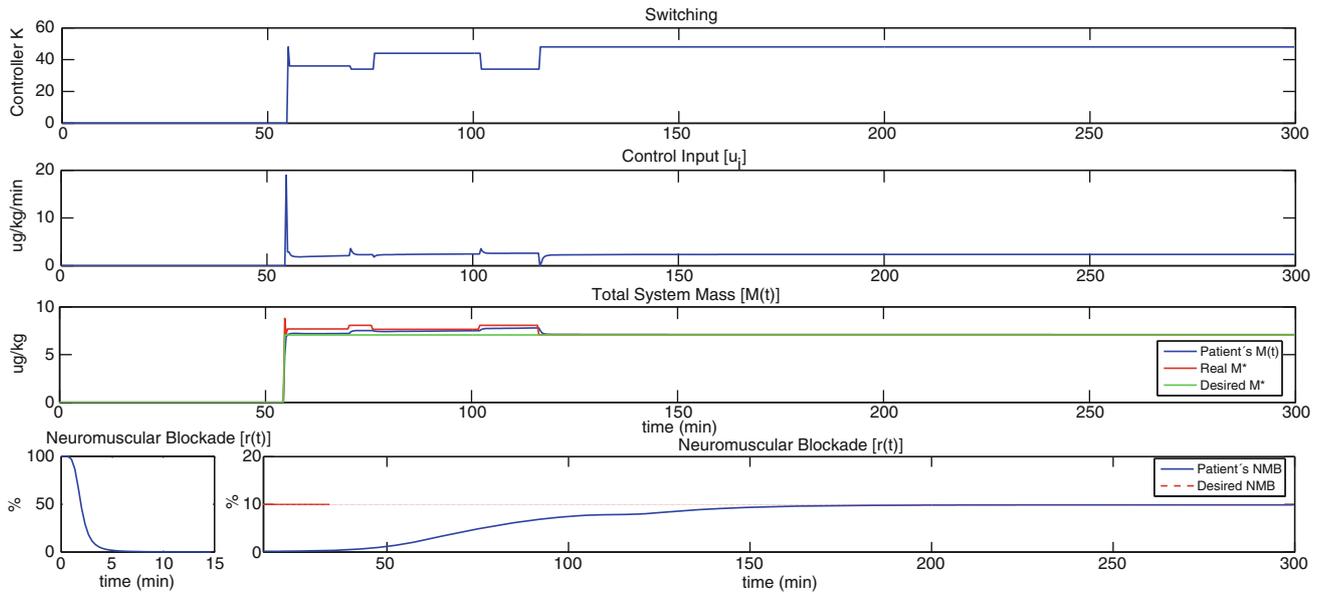


**Fig. 5** Results obtained for *atracurium*  $\mathcal{P} = M_{38}$  with  $\alpha = 0.0345$  and  $\gamma = 1.1170$  with reference tracking improvement performed at minute 74

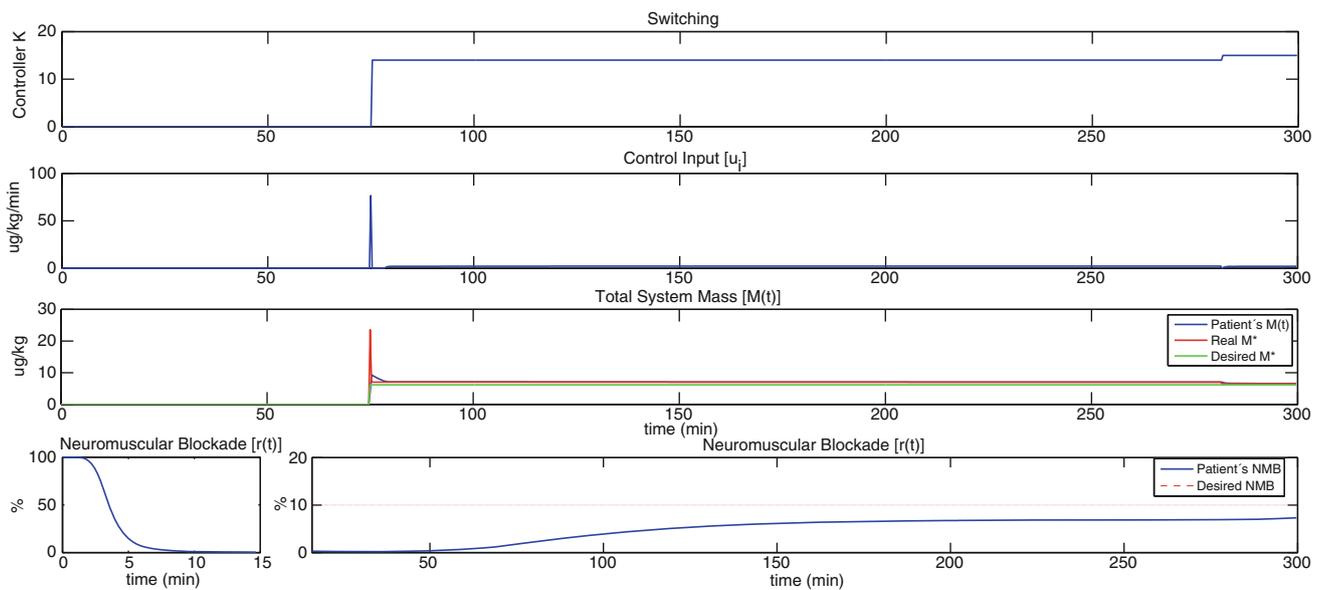
last active controller is the one corresponding to model 48, and the total system mass tends to  $M_{48}^*$ , which corresponds to a steady state value for the patient's NMB level with an absolute error of 0.10 with respect to the desired reference value of 10 %.

The case illustrated in Fig. 7 has a worse performance, with a 2.69 absolute steady state error. Again, the application of the reference tracking improvement, here applied at minute 200, reduces that error, now to a value of only 0.59, as can be seen in Fig. 8.

Finally it is important to highlight that in the most part of the cases the control signal presents always several switching situations between controllers of the associated bank, mainly during transient period. Moreover, it may be observed that in most cases the effect (NMB) approaches the desired reference profile (*ref*), despite the occurrence of a difference between both signals, in some cases. This latter situation may occur whenever there are not enough models in the bank that are sufficiently close to the model of the real patient. The scheme proposed in order to



**Fig. 6** Results obtained for rocuronium  $\mathcal{P} = M_6$  with  $\alpha = 0.0329$  and  $\gamma = 2.5669$  presenting a good reference tracking



**Fig. 7** Results obtained for rocuronium  $\mathcal{P} = M_{24}$  with  $\alpha = 0.0219$  and  $\gamma=3.0520$  presenting a poor reference tracking

improve the reference tracking quality proved to deliver very good results.

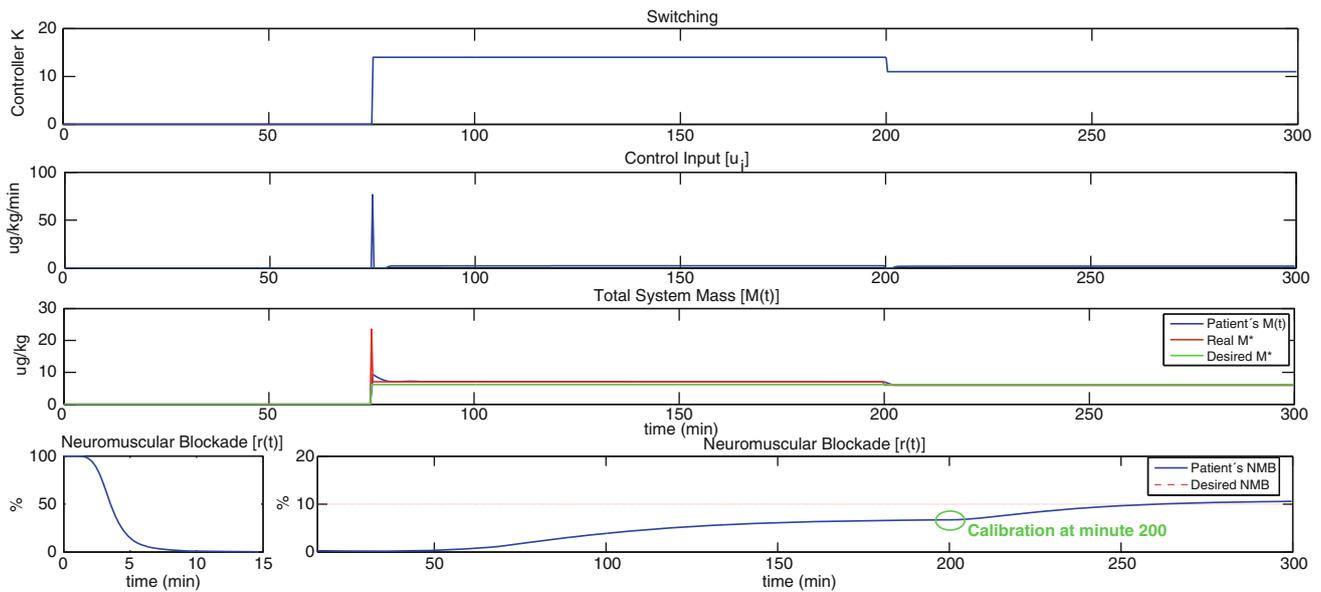
### 5 Analyzing the switching strategy

In order to analyze the switching strategy a comparison was made with the *Extended Kalman Filter (EKF)* [5]. The *EKF* performs the identification of the model parameters used in the total system mass control law (4) in order to control the NMB level.

For the purpose of obtaining data the bank  $\mathcal{P}$  with 100 models for *atracurium* and the bank  $\mathcal{P}$  with 50 models for *rocuronium* were used and a simulation of 300 minutes was performed for each model, according to what was explained in Sect. 4. Thereafter the two strategies were analyzed using the following as comparison features:

- The *normalized drug amount*, given by:

$$\sum_{k=t^*}^{t_{end}} u(k), \quad (10)$$



**Fig. 8** Results obtained for rocuronium  $\mathcal{P} = M_{24}$  with  $\alpha = 0.0219$  and  $\gamma = 3.0520$  with reference tracking improvement performed at minute 200

where  $u(k)$  ( $\mu\text{g}/\text{kg}/\text{min}$ ) is the dose of administered drug at step  $k$ , and  $t^*$  is the recovery time, detected by the OLARD algorithm [9].

- The *set-point*, which corresponds to the value (in %) where NMB level stabilizes;
- The *settling time*, which is the time that patient's NMB level takes to reach the *set-point* value, with an error not greater than 2 %;
- The *tracking quality*, measured by:

$$\frac{1}{n} \sum_{k=\text{settling time}}^{t_{\text{end}}} \sqrt{(r(k) - r_{\text{ref}})^2}, \quad (11)$$

where  $n = t_{\text{end}} - \text{settling time}$ ,  $r(k)$  is the NMB level at step  $k$  and  $r_{\text{ref}}$  is the desired reference value of 10 %.

The results can be visualized in Tables 1 (for atracurium), and 2 (for rocuronium).

In Tables 1 and 2 it can be seen that in average, the total mass control with switching spends less dose than the total mass control with *EKF* (*EKF+TMC*). Also the input values in the switching are much closer among themselves than the *EKF+TMC* input values. This can be seen by the smaller value of the standard deviation, and of the range.

As for the set-point reached with these two techniques, switching presents a better mean NMB value for a desired target of 10 %. Moreover the switching has set-point values closer to the average than the *EKF+TMC*, as can be seen by the smaller value of the corresponding standard deviation.

The settling times are higher with the switching than with the *EKF+TMC*. These results can be explained due to the nature of the *EKF+TMC* strategy, which identifies the parameters to be used in the control law when the recovery to the initial bolus is detected; in opposition, as the name suggests, the switching strategy causes changes between

**Table 1** Comparison between total mass control with *Switching* and with *Extended Kalman Filter (EKF)* (*atracurium*)

|                | Total input ( $\mu\text{g}/\text{kg}$ ) |       | Set-point (%) |       | Settling time (min) |     | Ref track error (%) |       |       |
|----------------|---|-------|---------------|-------|---------------------|-----|---------------------|-------|-------|
|                | Switching                               | EKF   | Switching     | EKF   | Switching           | EKF | Switching           | EKF   |       |
| Mean           | 2,800                                   | 2,999 | 9.96          | 8.87  | 167                 | 116 | 0.493               | 1.009 |       |
| Median         | 2,504                                   | 2,667 | 9.85          | 9.10  | 155                 | 123 | 0.277               | 0.756 |       |
| Std. Deviation | 999                                     | 1,074 | 0.86          | 0.88  | 64                  | 29  | 0.633               | 0.838 |       |
| Range          | 3,261                                   | 4,823 | 5.55          | 4.10  | 226                 | 115 | 3.240               | 3.720 |       |
| Minimum        | 1,596                                   | 1,662 | 6.95          | 6.05  | 69                  | 51  | 0.070               | 0.050 |       |
| Maximum        | 4,857                                   | 6,485 | 12.50         | 10.15 | 296                 | 166 | 3.310               | 3.770 |       |
| Percentiles    | 25                                      | 1,955 | 2,229         | 9.60  | 8.30                | 113 | 100                 | 0.162 | 0.355 |
|                | 75                                      | 3,470 | 3,668         | 10.43 | 9.53                | 218 | 135                 | 0.507 | 1.492 |

**Table 2** Comparison between total mass control with *Switching* and with *Extended Kalman Filter (EKF) (rocuronium)*

|                | Total Input ( $\mu$ g/kg) |        | Set-point (%) |       | Settling time (min) |     | Ref track error (%) |      |      |
|----------------|---------------------------|--------|---------------|-------|---------------------|-----|---------------------|------|------|
|                | Switching                 | EKF    | Switching     | EKF   | Switching           | EKF | Switching           | EKF  |      |
| Mean           | 6,847                     | 8,293  | 9.90          | 6.33  | 290                 | 168 | 0.27                | 3.90 |      |
| Median         | 6,118                     | 7,629  | 9.90          | 6.38  | 244                 | 173 | 0.14                | 3.68 |      |
| Std. Deviation | 2,584                     | 2,872  | 0.62          | 1.64  | 155                 | 64  | 0.48                | 1.70 |      |
| Range          | 11,315                    | 16,342 | 7.30          | 8.25  | 658                 | 257 | 3.30                | 8.26 |      |
| Minimum        | 3,750                     | 4,725  | 6.10          | 1.40  | 86                  | 68  | 0.01                | 0.49 |      |
| Maximum        | 15,065                    | 21,067 | 13.40         | 9.65  | 744                 | 325 | 3.31                | 8.75 |      |
| Percentiles    | 25                        | 5,014  | 6,177         | 9.80  | 5.08                | 193 | 111                 | 0.06 | 2.66 |
|                | 75                        | 8,101  | 9,758         | 10.05 | 7.59                | 340 | 219                 | 0.24 | 5.12 |

controllers over time, and only when the last controller is selected the final set-point is achieved and the settling time is measured.

Finally, analyzing the tracking error (*Ref Track Error* column) the mean value for switching is much lower than the one verified for the *EKF+TMC*. The same happens to all the other variables except the minimum values with the *atracurium* models, showing that the switching is better than the *EKF+TMC*. So it can be concluded that the switching strategy has a better reference tracking quality than the *EKF+TMC* strategy.

In summary, the switching strategy has better results than the *EKF+TMC* strategy with respect to the total dose used during NMB control, follows better the NMB target with a better reference tracking quality. As for the settling time, the *EKF+TMC* obtained better results due to the nature of the switching strategy.

## 6 Practical results

The NMB control strategy presented in this work based on a switching total system mass control law was implemented at the *Unidade Local de Saúde de Matosinhos - Hospital Pedro Hispano (ULSM-HPH)* with the supervision of an anesthesiologist.

The NMB control system applied at the ULSM-HPH consists of:

- A Datex-Ohmeda device (a modular monitoring family with a full line-up of monitors and accessories, a complex solution for anesthesia patient monitoring during surgeries), along with a NMT (neuromuscular transmission) module in order to obtain the NMB level of the patient during surgery;
- A drug delivery system: an Alaris GH syringe pump was used in order to administer the muscle relaxant to the patient;

- A computer: a portable computer with two USB serial ports for connecting the Datex-Ohmeda device and the infusion pump, in order to run the NMB control software.
- Galeno software: a program design to collect all the information produced by the Datex-Ohmeda device, to run the switching control strategy, and to inflict the control input produced by the switching control strategy to the Alaris GH pump infusion.

The protocol used during the surgeries was designed by the anesthesiologist in accordance with the ethical standards practiced by the *ULSM-HPH* and the characteristics of the patient:

- a. For the hypnotic induction a *bolus* of *propofol* was used in order to achieve a quick induction. After this induction the maintenance was made with *sevoflurane*, a volatile drug.
- b. For analgesia a single *bolus* of *fentanyl* was used at the beginning.
- c. Finally, for the areflexia, the drug rocuronium was used. This drug is nowadays the most widely used due to its special properties, such as: it allows a quick induction of the patient's muscle paralysis and is not affected by renal failure. At the end of the surgery the NMB was reversed either with *neostigmine* with *atropine* or with *sugammadex*, as considered appropriate.

The process of general anesthesia with NMB control during surgeries can be summarized as follows:

- **Step 1** Administration of a *fentanyl bolus*.
- **Step 2** Administration of a *propofol bolus* for induction, followed by *sevoflurane* administration for maintenance.
- **Step 3** Calibration of the NMB Sensor.
- **Step 4**  $t = 0$ : Administration of an initial *bolus* of *rocuronium* to the patient (Automatic administration

performed by the *Monitoring and Control in Anesthesia software*).

- **Step 5**  $0 < t < t^*$  (before recovery from the initial bolus of rocuronium): The control input remains zero.
- **Step 6**  $t = t^*$  ( $t^*$  computed by the OLARD algorithm introduced in [9]): A random controller from bank  $\mathcal{K}$  is chosen in order to start the control of the NMB response of the patient.
- **Step 7**  $t \geq t^*$ : A controller  $\mathcal{K}_i$  is chosen at each time instant based on the minimization of the cumulative error between the patient response and the responses of each of the models in the bank  $\mathcal{P}$ .
- **Step 8** At the end of the surgery: Administration of NMB reversal drugs, *neostigmine* with *atropine* or *sugammadex*, according to the patient characteristics and his/her NMB level at this stage.

The upper plots of Figs. 9 and 10 contain all the information about the drugs administered to the patient that have effect on the NMB level. The lower plots contain the

NMB level of the patient (blue line) and the desired NMB target (red line).

For the real cases collected at ULSM-HPH (Figs. 9, 10), the anesthesiologist considered that the controller performance was satisfactory since the NMB level was kept within a very reasonable interval, and never reached any abnormal values. The controller did not give an overall excessive dose of *rocuronium* to the patient, and no complains were registered either from surgeons or from the anesthesiologist. Therefore one can conclude that, although for practical cases the reference tracking performance was not as high as for simulated cases, the obtained results were still very satisfactory. The application of the reference tracking improvement technique to these cases was not possible once it is very difficult to achieve a steady state input dose with the equivalent steady state response created by such dose. As a final note, the changes that occurred in the *rocuronium* infusion rate during the control are the sign that switching among the controllers in the bank occurred.

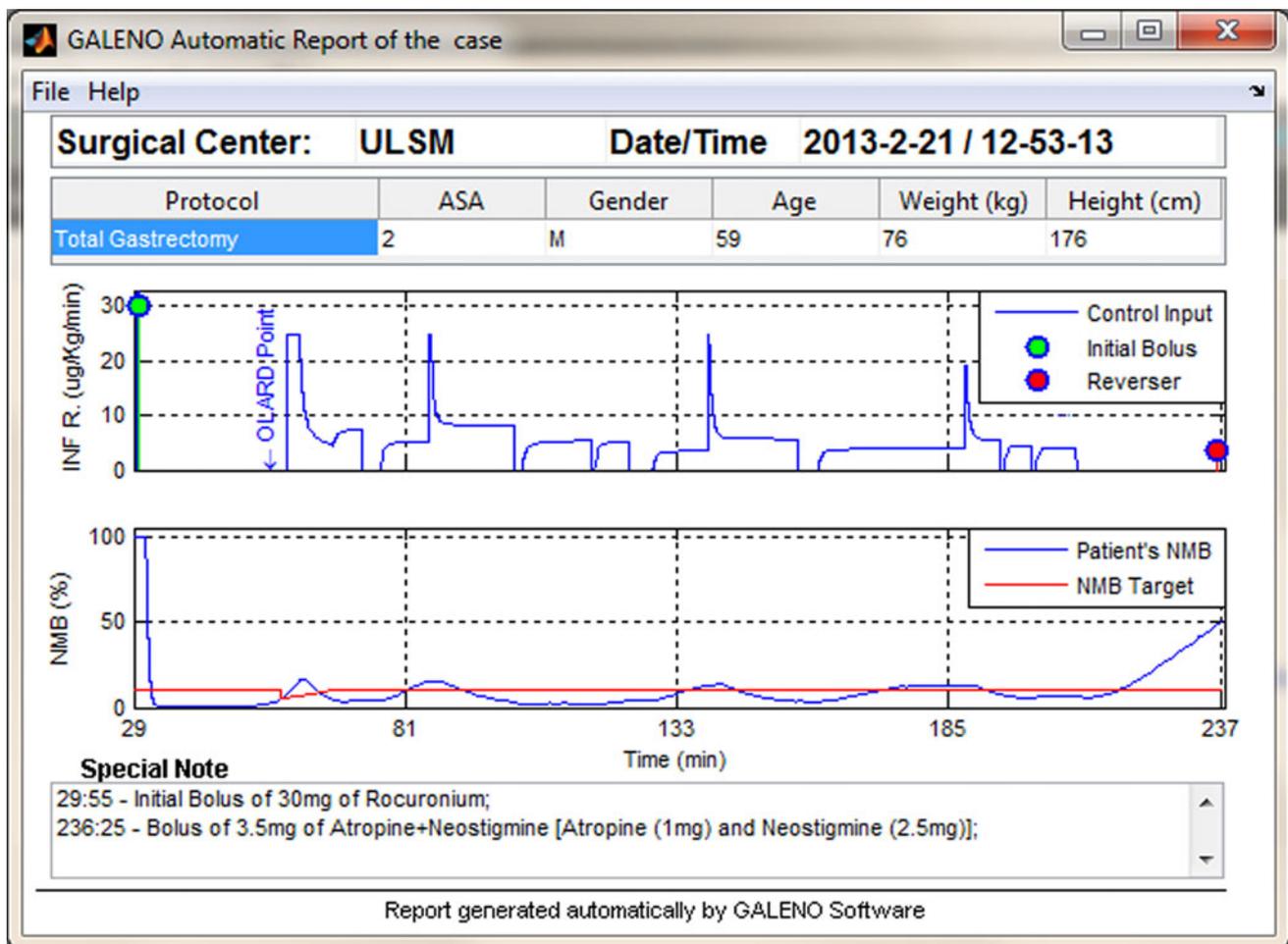
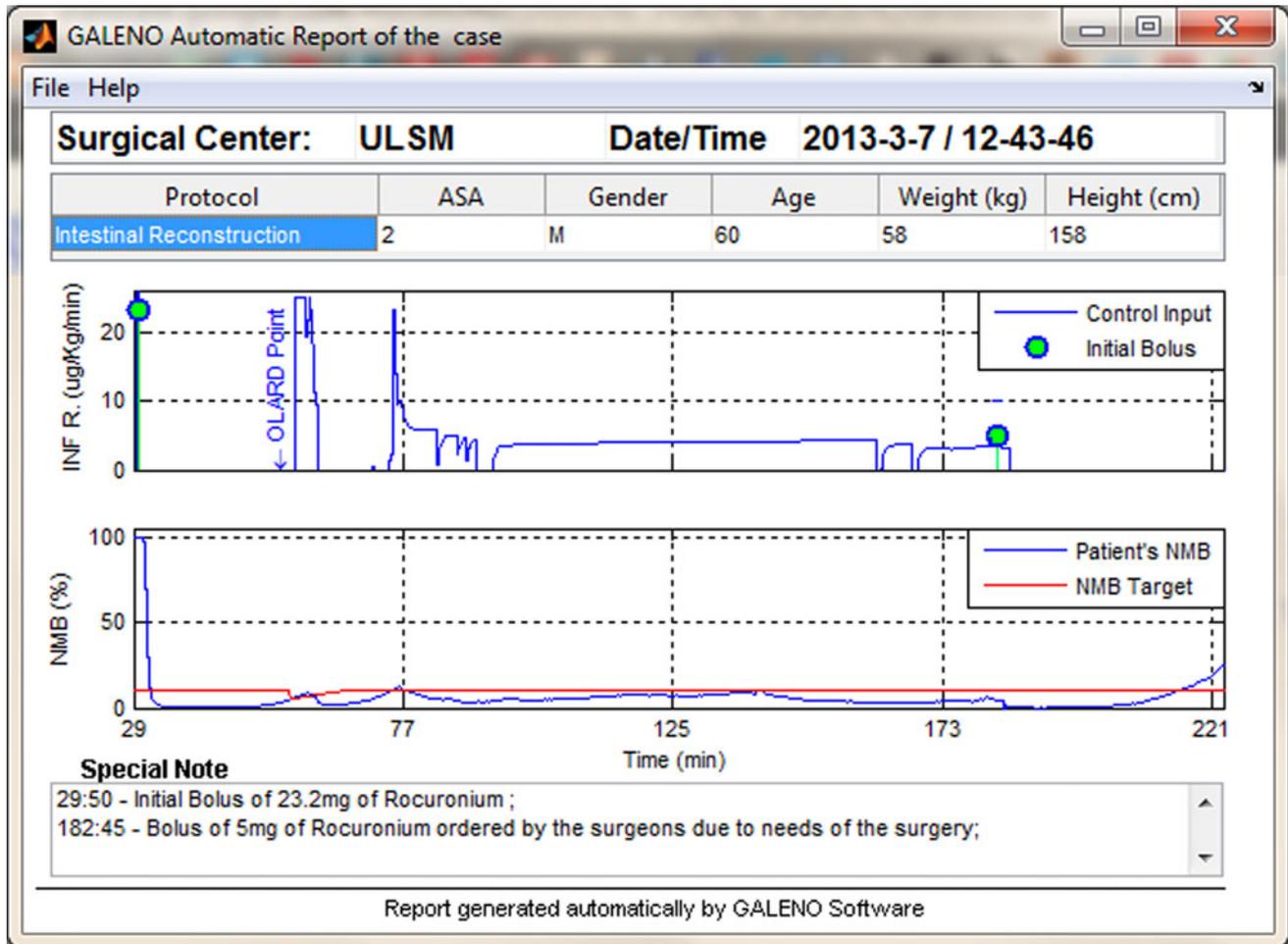


Fig. 9 Real case acquired at ULSM-HPH (2013/02/21 - Case 1)



**Fig. 10** Real case acquired at ULSM-HPH (2013/03/07 - Case 1)

As a conclusion it can be said that the switching strategy shows to provide good results for the NMB level control during general anesthesia. The NMB level was kept between good minimum and maximum values, the patient muscle stiffness was never a point of discussion for the surgeons, and the anesthesiologist never had to perform any manual control on the patient muscle relaxation. Another aspect of this control strategy is its ability to adapt to the intra-variability of a patient dynamics in the course of time.

## 7 Conclusion

This paper presented a new strategy for the control of the NMB level of patients undergoing general anesthesia in the presence of patient-parameter variability. This consists in using a MPP model previously presented in the literature, which has a compartmental structure. This special structure

enables the design of a controller based on the total system mass in order to track a desired NMB level with a switching strategy. In the cases where the reference tracking is not achieved, an improvement of the convergence is performed based on the obtained steady state response of the patient. The presented control strategy shows to provide good theoretical results for both *atracurium* and *rocuronium*. Also, it is shown that the switching control strategy presents better results than the *EKF* technique. Finally, this strategy shows to provide good results when applied in real surgeries.

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