Tracking the NMB level via a switching system mass control strategy

M. Teixeira∗ T. Mendonça∗∗ P. Rocha∗∗∗

∗ Faculdade de Engenharia da Universidade do Porto, Rua Dr. Roberto Frias, 4200-465 Porto, Portugal. (e-mail: meb09018@fe.up.pt)
∗∗ Dep. Matemática, Fac. Ciências da Universidade do Porto and Center for Research and Development in Mathematics and Applications. (email: tmendo@fc.up.pt)
∗∗∗ Faculdade de Engenharia da Universidade do Porto, Rua Dr. Roberto Frias, 4200-465 Porto, Portugal and Center for Research and Development in Mathematics and Applications. (e-mail: mprocha@fe.up.pt)

Abstract: This paper presents a model based switching control strategy to drive the neuromuscular blockade (NMB) level of patients undergoing general anesthesia 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 is presented. The results are illustrated by means of several simulations.

Keywords: Automatic Delivery System, Switching Control, Positive Control System, Minimally Parameterized 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 as 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 [Godfrey (1983)]. A 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 parameterized models as well as automatic parameterized identification strategies based on those models able to identify the patient parameters taking into account the inter- and intraindividual variability. If such controls could be successfully achieved, the drawback of using standardized procedures in drug administration based on population studies can be overcome.

This paper presents a control strategy for the NMB level using a total system mass control law for a new minimally parameterized compartmental model [Silva and Mendonça (2012)] describing the effect of the muscle relaxant atracurium and rocuronium in the NMB level [Silva and Mendonça (2012)]. The total system mass control law for feedback stabilization of compartmental systems of Bastin and Provost (2002) 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 response is also presented.
The contents of the paper are as follows: Section 2 presents the model for neuromuscular blockade control, describing the minimally parameterized Wiener model for the NMB level and the total system mass control law used to drive the NMB level to the desired reference. In Section 3 the switching control strategy used to define the control law is described as well as the scheme to improve the reference tracking, while in Section 4 the simulation results of the implementation of such control strategy are presented. In Section 5 the conclusions are drawn.

2. A MODEL FOR NEUROMUSCULAR BLOCKADE CONTROL

2.1 Minimally parameterized NMB model

In this paper we consider the model proposed in Silva and Mendonça (2012) 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:

\[
h(s) = \frac{(k_2 k_3 \alpha)^3}{(s + k_1 \alpha)(s + k_2 \alpha)(s + k_3 \alpha)},
\]

where \( k_1, k_2, k_3 \) are fixed, and \( \alpha \) is a patient dependent parameter. According to Silva and Mendonça (2012), 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 [Weatherley and Neill (1983)]:

\[
r(t) = \frac{100 C_50^{\gamma} C_e(t)^\gamma}{C_50 + C_e(t)^\gamma},
\]

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.

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:

\[
\begin{cases}
\dot{x}(t) = A(\alpha)x(t) + B(\alpha)u(t) \\
C_e(t) = Cx(t)
\end{cases}
\]

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

\[
A = \begin{bmatrix}
-k_3 & 0 & 0 \\
0 & -k_2 & 0 \\
0 & k_1 & -k_3
\end{bmatrix}, \quad B = \begin{bmatrix}
k_3 \\
0 \\
0
\end{bmatrix} \quad C = \begin{bmatrix} 1 & 0 & 0 \end{bmatrix}.
\]

2.2 Total system mass control law

It has been shown in Almeida et al. (2011) that the following positive control law proposed in Bastin and Provost (2002) for total mass control:

\[
\begin{cases}
u(t) = \max(0, \tilde{u}(t)) \\
\tilde{u}(t) = \frac{\lambda}{3} \sum_{i=1}^{3} x_i(t) - \lambda \beta(3M(t) - M^*)
\end{cases}
\]

not only leads the total system mass \( M(t) = \sum_{i=1}^{3} x_i(t) \) to a reference value \( M^* \), but also leads the effect concentration, \( C_e(t) \), to the reference value \( C_e^\star = M^*/3 \). This can be used to control the NMB level in the following way. Given a desired reference value \( r^\star \) for the NMB, compute the corresponding reference level for the effect concentration \( C_e^\star \) by inverting the Hill equation, i.e.

\[
C_e^\star = \frac{100}{r^\star - 1} \times C_{50},
\]

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

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

In order to take into account parameter variability, the following model based switching control strategy is adopted. A bank \( \mathcal{P} = \{P_1, \ldots, P_N\} \) of representative Wiener models is considered, together with a bank of corresponding controllers \( \mathcal{K} = \{K_1, \ldots, K_N\} \) each of them tuned according to what has been explained in the previous section. More concretely if \( P_i = P(\alpha_i, \gamma_i) \) then \( K_i \) produces the control law:

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

with

\[
\tilde{u}_i(t) = \frac{k_3}{k_3 - k_2} x_1 + \frac{k_2 - k_1}{k_3} x_2 + \frac{k_1}{k_3} x_3 - \frac{\lambda}{k_3 \alpha_i} (M(t) - M^*).
\]

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 (Rocha et al. (2011)):

\[
(\ln(\alpha), \ln(\gamma)) \sim BN(\mu, \Sigma),
\]

where \( \mu = \begin{bmatrix} -3.2870 \\ 0.9812 \end{bmatrix} \) is the mean vector and \( \Sigma = \begin{bmatrix} 0.0250 & -0.0179 \\ -0.0179 & 0.1196 \end{bmatrix} \) is the covariance matrix. The standard bank of representative Wiener models was generated from this distribution (See Fig. 1) 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 during 41 surgeries is available. For each of these
Fig. 1. Red: real NMB responses acquired during surgery performed with atracurium; these responses may be corrupted by measurement noise and sensor faults. Blue: NMB responses of the atracurium models from the bank $P$. In both NMB responses an initial bolus of 500µg/kg was administered.

Fig. 2. Switching Control Strategy

real cases, the parameters $\alpha$ and $\gamma$ were identified, 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 of the patient and the corresponding steady state $C_r$ of the $i$-th model in the bank ($i = 1, \ldots, N$). This cumulative error is obtained since the instant where the control of the patient NMB level starts using (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 $C_r$ response of the patient and the $r_i$ response of the $i$-th model in the bank.

4. SIMULATIONS 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 forty one 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 $P$ 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 $P_i$ from the bank $P$ is chosen as describing the real patient dynamics.

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

**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 OLARD algorithm introduced in [Silva and Esteves (2009)] and corresponds to the recovery from the initial bolus): A random controller from bank $K$ is chosen in order to start the control of the NMB response of the patient.

**Step 4** $t \geq t^*$: A controller $K_i$ 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 $P \setminus \{P_i\}$.

**Step 5** (if applied): Corresponds to the reference tracking improvement where $\gamma$ is fixed as $\gamma^*$ given by (8), and the selection of the controller $K_i$ is then based on the

\[
\gamma^* = \frac{\ln \left( \frac{100}{r_{SS}} - 1 \right)}{\ln \left( \frac{\mu_g}{C_{r,\gamma}} \right)}.
\]  

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

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

\[
\tilde{u}_i(t) = \frac{1}{k_3} [(k_3 - k_2)x_1 + (k_2 - k_1)x_2 + k_1x_3] - \frac{\lambda}{k_3 \alpha_3} (M(t) - M^*).
\]  

Moreover the choice of the control law to be applied at each instant is now made based on the cumulative quadratic error between the $C_r$ response of the patient and the $r_i$ response of the $i$-th model in the bank ($i = 1, \ldots, N$). This cumulative error is obtained since the instant where the control of the patient NMB level starts using (9).
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 to 8. Figs. 3 to 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 to 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 figures, 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 refers to the control input, $u_i\ [\mu g/kg.min]$ which remains zero until the recovery from the initial bolus. The subplot below corresponds to the total system mass of the patient, $M(t)\ [\mu g/kg]$, (blue line) and to the evolution of the values of $M^*$ during control (red line). The third subplot displays the indices $i$ of the controllers $\mathcal{K}_i$ chosen during the control

**Fig. 3.** Results obtained for atracurium $\mathcal{P}=M_{39}$ with $\alpha=0.0474$ and $\gamma=4.0478$ presenting a good reference tracking.

**Fig. 4.** Results obtained for atracurium $\mathcal{P}=M_{34}$ with $\alpha=0.0258$ and $\gamma=6.7175$ presenting a poor reference tracking.

**Fig. 5.** Results obtained for atracurium $\mathcal{P}=M_{34}$ with $\alpha=0.0258$ and $\gamma=6.7175$ with reference tracking improvement performed at minute 90.

**Fig. 6.** Results obtained for rocuronium $\mathcal{P}=M_{33}$ with $\alpha=0.0682$ and $\gamma=1.4824$ presenting a good reference tracking.

**Fig. 7.** Results obtained for rocuronium $\mathcal{P}=M_{26}$ with $\alpha=0.0317$ and $\gamma=6.324$ presenting a poor reference tracking.
procedure. 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.

Fig. 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 $M^*_0$, 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%.

Fig. 4 illustrates a case with relatively poor performance, with an absolute steady state error of 2.64.

Fig. 5 shows the result of the application of the reference tracking improvement technique to this case, which reduces the absolute steady state error to only 0.04.

As for rocuronium, Fig. 6 exhibits a case where the performance of the switching control strategy is good, with an absolute steady state error of less than 0.01.

The case illustrated in Fig. 7 has a worse performance, with a 1.80 absolute steady state error. Again, the application of the reference tracking improvement reduces that error, now to a value of only 0.17, as can be seen in Fig. 8.

Finally it is important to highlight that 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 improve the reference tracking quality proved to deliver very good results.

5. CONCLUSION

This paper presents 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 minimally parametrized 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 of the patient 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 results for both atracurium and rocuronium.

ACKNOWLEDGEMENTS

This work was supported by FEDER founds through COMPETE-Operational Programme Factors of Competitiveness (“Programa Operacional Factores de Competitividad”) and by Portuguese founds through the Center for Research and Development in Mathematics and Applications (University of Aveiro), the Portuguese Foundation for Science and Technology (FCT–Fundação para a Ciência e a Tecnologia”), within project PEst-C/MAT/UI4106/2011 with COMPETE number FCOMP-OP/COMPETE/022690 and the Project GALENO-Modeling and Control for personalized drug administration, FCT PTDC/SAU-BEB/103667/2008.

REFERENCES