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Predictive Adaptive Control of Neuromuscular Relaxation

B. Andrade Costa, and J. M. Lemos

***Abstract*— This paper explores the application of a multi-step predictive adaptive controller to control the level of neuromuscular relaxation during a general anaesthesia. The problem of neuromuscular relaxation in humans is characterized by a large variability of the pharmacokinetics (PK) and pharmacodynamics (PD) among patients. Because the administrating potent drugs may cause side effects it is important to obtain the adequate level of neuromuscular blockade but avoiding the administration of drug overdoses. To tackle the problem of the variability among patients, the data obtained with the response to the first bolus can be analyzed to extract information of the patient/drug pharmacokinetics/pharmacodynamics. However this approach does not provide a complete solution for the problem, therefore an online model identification based on a nonlinear transformation is explored with the multi-step predictive adaptive controller. Computer simulations are used to evaluate the performance and the main difficulties of its applicability.**

***Index Terms*— Adaptive Control, Model Identification, Neuromuscular Relaxation.**

I. INTRODUCTION

This paper describes the work that is being developed to apply an adaptive predictive control algorithm to the neuromuscular relaxation control during general anaesthesia. The aim is to assess the potential use of the adaptive control algorithm, Musmar, and the main difficulties caused by the nonlinear pharmacokinetics/pharmadynamics.

The problem of neuromuscular relaxation in humans is characterized by a large variability of the pharmacokinetics and pharmacodynamics among patients. Due to several side-effects such as toxicity, drugs must be administrated precisely. This means that variability among patients must be considered, to avoid side-effects caused by drug overdoses or lower perfusion rates. One possible approach to solve the problem is to use adaptive control techniques that perform online identification to tune the controller.

This paper is organized as follows, section II describes the main characteristics pharmacokinetics and pharmacodynamics models. Section III briefly describes the difficulties of using the response to the first bolus to extract information to identify the pharmacokinetics and pharmacodynamics, this motivates the application of the predictive adaptive control algorithm Musmar, which is described in section IV-A. Simulation results with the Musmar control algorithm are shown in section V. Conclusions and future work are described at the end of the paper.

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II. NEUROMUSCULAR BLOCKADE MODEL

The relationship between the administration of a bolus/perfusion level ($u(t)$) and the drug concentration at site effect ($c_n(t)$) in the patients's body is described by the pharmacokinetics. Experimental data [1] [2] shows that a linear dynamic model ($c_n(s) = P(s)u(s)$) is adequate to describe the drug concentration dynamics at the effect site. The linear model with following structure is used,

$$P(s) = (\frac{a}{s+\alpha} + \frac{b}{s+\beta})\frac{\lambda}{(s+\lambda)}\frac{\mu}{(s+\mu)} \quad (1)$$

where the transfer function with parameters a, α, b, β describe the drug concentration in blood and the other parameters describe the relation between the blood drug concentration and the drug concentration at the effect site (muscle).

The relationship between the drug concentration at the effect site (muscle) and the observed muscle activity measured by an index $m_a(t)$ is described by pharmacodynamics. A nonlinear static function (Hill function) characterized by two parameters C_{50} and γ is used for this purpose

$$m_a(t) = \frac{100}{1 + (c_e(t)/C_{50})^{\gamma}} + \eta(t) \quad (2)$$

where maximum muscle activity is represented by $m_a(.) = 100$, and the absence of activity is represented by $m_a(.) = 0$. The noise presented in measurements is represented by $\eta(t)$. The parameter C_{50} represents the drug concentration level at effect site to obtain 50% of the full range of the index. The parameter γ defines the slope of the nonlinear function.

Fig.(1) shows the response of the neuromuscular relaxation models obtained with the first bolus ($500 mcg/kg$) of atracurium where the normalized concentration at the effect site $c_n(t) = c_e(t)/C_{50}$ is shown. During a general anesthesia, the anesthetist has access to the $m_a(t)$ index record and to the bolus/perfusion records, but the normalized concentration at the effect site $c_n(t)$ is not accessible. When the recover to the first bolus is detected, that is when $m_a(t)$ increases and $m_a(t) \geq> 5\%$, the anesthetist must start an continuous infusion or can inject a bolus, the aim is to control the muscle activity such that $m_a(t) \leq 10\%$.

III. USING THE RESPONSE OF THE FIRST BOLUS TO IDENTITY THE PK/PD MODEL

During a general anaesthesia, after the induction of loss of awareness and being the patient in a safe depth of anesthesia (DoA), the process to induce total muscle paralysis starts with the administration of the first bolus to obtains a fast

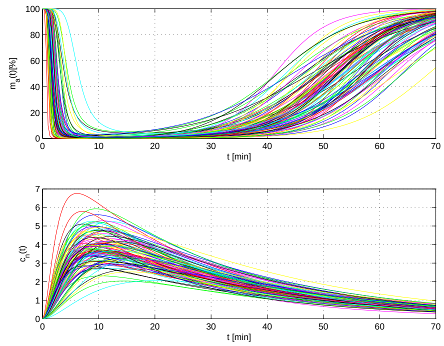

Fig. 1. Response of the neuromuscular blockade models to the first bolus (top), and the corresponding normalized concentration at the effect site ($c_n(t) = c_e(t)/C_{50}$) (bottom).

muscle relaxation for intubation. From a system perspective this corresponds to obtain the impulsive response of the pharmacokinetics model which is transformed by the nonlinear function of the pharmacodynamics. This motivates the study of the response of the first bolus to characterize the PK/PD of the patient being anaesthetized.

Experiment tests show that the pharmacokinetics of several injectable neuromuscular-blocking drugs, such as atracurium, can be approximated by a second or third linear dynamic system that has a dominant "slow" pole. The impulsive response of the PK ($h(t)$) can be written as $h(t) = e^{-at}g(t)$ for $t >= 0$, where $-a$ represents the magnitude of the slow pole, $g(t)$ represents the contribution of other fast dynamics.

In order to set up the identification procedure, the fast dynamics is approximated by a power series $g(t) = g_0(0) + g_1(0)t + g_2(0)t^2/2! + ... + g_{k-2}(0)t^{k-2}/((k-2)!) + ...$, where $g_i(0)$ represents the time derivative of order i taken at time $t = 0$. Using the fact that the drug concentration at the side effect at $t = 0$ is zero then $g_0(0) = 0$. Other additional terms of the $g(t)$ series may be zero, this depends, for example, on the relative degree of rational transfer function. As such, let the terms $g_0(0)$ up to $g_{k-2}(0)$ be zero, then the impulsive response $h(t)$ can be written as

$$h(t) = e^{-at}\frac{g_{k-1}(0)}{(k-1)!}t^{(k-1)}w(t) \qquad (3)$$

with

$$w(t) = 1 + \frac{(k-1)!}{k!}\frac{g_k(0)}{g_{k-1}(0)}t + \frac{(k-1)!}{(k+1)!}\frac{g_{k+1}(0)}{g_{k-1}(0)}t^2 + ... \qquad (4)$$

Because the impulse response is transformed by the Hill function, in particular by the γ parameter, which is assumed to be unknown, then it can be written,

$$h_u^{\gamma}(t) = e^{-\gamma at}(\frac{g_{k-1}(0)}{(k-1)!})^{\gamma}t^{\gamma(k-1)}w^{\gamma}(t)u_b^{\gamma} \qquad (5)$$

where u_b represents the dose of the first bolus. With "small" noise, the samples of $h_u^{\gamma}(t)$ can be obtained using $h_u^{\gamma}(t) = (100/m_a(t) - 1)$. Equation 5 can be transformed using the $\ln()$ function to expose the unknown parameters,

$$\ln h_u^{\gamma}(t) = f_0 + f_1 t + f_2 \ln(t) + \ln(w^{\gamma}(t)) \qquad (6)$$

TABLE I

COMPUTING γ AND g_s

$\hat{\gamma}$	θ	$h_u(t,\hat{\gamma})$
7.7	1	$(g_s\frac{\alpha\beta}{\beta-\alpha})(e^{-\alpha\times t} - e^{-\beta\times t})$
3.85	2	$(g_s\frac{\alpha\beta}{\beta-\alpha})^2u_b^1(e^{-\alpha\times t} - e^{-\beta\times t})^2$
2.56	3	$(g_s\frac{\alpha\beta}{\beta-\alpha})^3u_b^2(e^{-\alpha\times t} - e^{-\beta\times t})^3$

with $f_0 = (\frac{g_{k-1}(0)}{(k-1)!}u_b)^{\gamma})$, $f_1 = -\gamma \times a$, $f_2 = \gamma \times (k-1)$

Equation 6 shows a problem of parameter identifiability. Even in the special case of $w(t) = 1$, which corresponds to a transfer function of the type $1/(s+a)^k$ the problem of parameter identifiability is present. It is not possible to identify the four parameters, $g_{k-1}(0)$, k, a and γ from the parameters f_0, f_1, and f_2. However this can be solved in part if there is additional information from previous studies that provides information about the range and bound of γ or the relative degree. In the more general case where $w(t)$ is not equal to 1, the $\gamma ln(w(t))$ can be approximate by $a_0 t + a_1 t^2/2 + ...$ The selection of the number of terms depend on the number of data points obtained during the initial phase of the neuromuscular relaxation response and during the initial recovering phase. Therefore it is not possible to have a precise measure of the process parameters. This suggests that an adaptive control algorithm must be used to identify the local model of the operating point of interest.

However there cases with different finite PK/PD models that have the same time response and the parameters values belong to set of plausible values.

To illustrate this problem, consider the following second order PK, where $c_n(t) = c(t)/C_{50}$

$$c_n(t) = g_s\frac{\alpha\beta}{\beta-\alpha}(e^{-\alpha\times t} - e^{-\beta\times t})u_b \qquad (7)$$

and define $z(t) = c_n^{\gamma}(t)$ where γ represents the "true" parameter. Considering that $z(t)$ can be written as $z(t) = (c_n^{\hat{\gamma}}(t))^{\theta}$, with $\theta = (\gamma/\gamma_0)$. Selecting $\hat{\gamma}$ as a positive integer such that $\hat{\gamma} \times \theta$ is equal to γ, then $z(t) = (h_u(t,\hat{\gamma}) \times u_b)^{\theta}$, where $h(t,\hat{\gamma})$ represents the impulsive response of a finite dimensional linear system.

$$h_u(t,\hat{\gamma}) = (g_s\frac{\alpha\beta}{\beta-\alpha})^{\hat{\gamma}}u_b^{\hat{\gamma}-1}(e^{-\alpha\times t} - e^{-\beta\times t})^{\hat{\gamma}} \qquad (8)$$

Table (I), shows an example where $\gamma = 7.7$ and $\theta = \{1, 2, 3\}$. The time response of the PK/PD systems described in table (I) with parameters $g_s = 0.32$, $\alpha = 0.035$ and $\alpha = 0.82$ for a $500mcg/kg/min$ bolus are shown in fig.(2). For the three systems the time responses to the first bolus are equal. The time responses are different, only, after the application of a continuous infusion. This example shows that the model identification based on the time response to the first bolus does not provide adequate information to characterize the patient/drug PK/PD. The decision to select or to apply a controller must be postponed until enough information is obtain with the application of a continuous infusion.

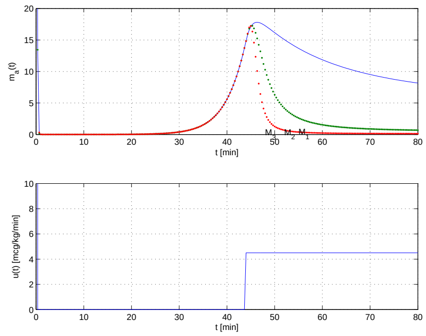

Fig. 2. Three PK/PD systems with identical time responses to the first bolus but different responses to continuous infusions. The time response M_1 is from the "true" system, $\theta = 1$.

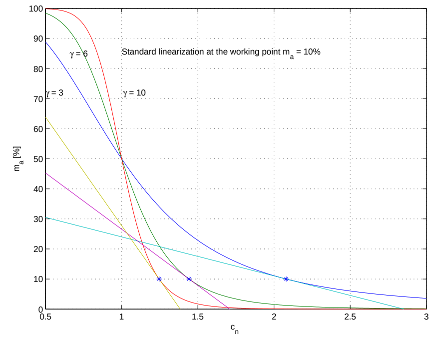

Fig. 3. Depending on the working point defined by the reference $rm_a = 10\%$ and on the value of γ, a linear approximation can be obtained. But the linear approximations are valid on a small interval $8 \le m_a \le 12$.

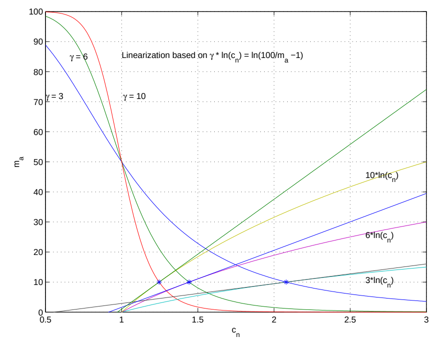

Fig. 4. By applying the transformation $ln(100/m_a - 1)$ the linear approximations at the working points are valid on a larger interval $5 \le m_a \le 20$. The linear approximations are shown for three values of γ, 3, 6 and 10. This approach can help on the design of linear controllers.

IV. NONLINEAR NEUROMUSCULAR BLOCKADE CONTROL

To overcome the difficulties presented in the previous section, the design of the controller is based on the drug prescribing information (Rules of Infusion in the Operating Room) and on the detection of certain events that must occur during the neuromuscular blockade process. A state machine [5] is used to monitor $m_a(t)$ and its time derivative during the response to the first bolus, that is, to detect the decrease (suppression) of $m_a(t)$ and its recover. The aim is to detect the time instant to apply the infusion rate to counteract the spontaneous recover such that $m_a(t)$ stays below the 20% value and to define the nominal infusion rate u_0 and to start the local controller that keeps $m_a(t)$ near the reference $rm_a(t) = 10\%$. According with [4], the drug prescribing information of the Atracurium Besylate injection, for continuous infusion in the operating room has the the following rules/guidelines:

r.1) After administration of a recommended initial bolus dose of atracurium (Besylate) injection (0.3 to 0.5 mg/kg), a diluted solution of atracurium besylate can be administratef by infusion to adults and pediatric patients aged 2 or more years for maintenance of neuromuscular block during extended surgical procedures. r.2) Infusion of atracurium should be individualized for each patient. The rate of administration should be adjusted according to the patient's response as determined by peripheral nerve stimulation. Accurate dosing is best achieved using a precision infusion device. r.3) Infusion of atracurium should be initiated only after early evidence of spontaneous recovery from the bolus dose. An initial infusion rate of 9 to 10 mcg/kg/min may be required to rapidly counteract the spontaneous recovery of neuromuscular function. Thereafter, a rate of 5 to 9 mcg/kg/min should be adequate to maintain continuous neuromuscular block in the range of 89% to 99% in most pediatric and adult patients under balanced anesthesia. Occasional patients may require infusion rates as low as 2 $mcg/kg/min$ or as high as 15 $mcg/kg/min$. r.4) Spontaneous recovery from neuromuscular block following discontinuation of atracurium infusion may be expected to proceed at a rate comparable to that following administration of a single bolus dose.

Knowing that the Hill function is the source of the nonlinear behavior of the PK/PD, a standard linearization technique can be used to design a local controller. Figure 3 shows the linearization of the Hill function around the working point $rm_a(t) = 10\%$ for three values of γ. The main problem is that the linear approximations are valid on a small interval $8 \le m_a \le 12$. To extent the interval where the linear approximations are valid, the following nonlinear transformation is used.

$$z(t) = ln(\frac{1}{(m_a(t)/100)} - 1) = ln(c_n^{\gamma}(t) = \gamma ln(c_n(t)) \qquad (9)$$

Figure 4 shows the Hill function for several γ values with the nonlinear transformation defined by eq. (9) and its linearization. With this transformation the linear approximations are valid on a larger interval, $5 \le m_a \le 20$, that covers the operational region of $m_a(t)$ for the plausible values of γ. However the steady state value z_0 corresponding to $rm_a = 10\%$ depends on the steady state infusion rate value u_0 by the nonlinear function $z_0 = \gamma ln(g_s u_0)$, where g_s represents the static gain of PK. From a practical point of view, u_0 can be selected from the drug prescribing information for example $5\, mcg/kg/min$ and if necessary it can be adjusted by the anaesthetist during the surgery. To tackle the controller design, a linearization of eq. (9) around z_0 is performed and the tracking error is defined according with $e_z(t) = z_0 - z(t)$, yielding

$$e_z(t) \approx -\sigma(c_n(t) - g_s u_0) \qquad (10)$$

with $\sigma = \frac{\gamma}{g_s u_0}$. Considering that the PK/PD is sampled using a ZoH with a sampling period T_s, a discrete-time version of

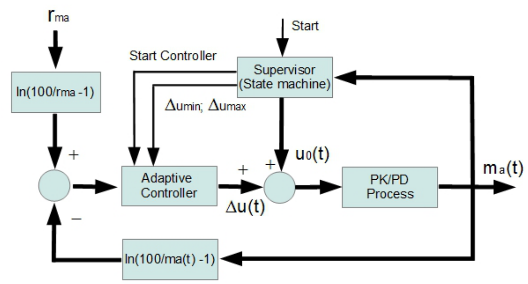

Fig. 5. Proposed structure for the nonlinear NMB adaptive controller.

the continuous-time PK can be written as

$$c_n(t+n_a)+a_{n_a-1}c_n(t+n_a-1)+...+a_0c_n(t)= \quad (11)$$
$$b_{m_b}u(t+m_b)+...+b_0u(t)$$

where $n_a > m_b \geq 0$ define the orders of the polynomials, that have coefficients $\{a_i\}$ and $\{b_j\}$. Using equations (11), (10) and the backward shift operator q^{-1} a discrete-time local linear approximation of the error dynamics of the PK/PD is obtained.

$$e_z(t)+a_{n_a-1}e_z(t-1)+...+a_0e_z(t-n_a)= \quad (12)$$
$$-\sigma[b_{m_b}(u(t+m_b-n_a)-u_0)+...+b_0(u(t-n_a)-u_0)]$$

This defines the framework to explore adaptive control, the proposed structure for the nonlinear NMB adaptive controller is presented in figure (5). Note that in order to identify the process, the parameter σ must be absorbed by coefficients b_j.

A. The adaptive predictive control algorithm

The MUSMAR algorithm [3] is an adaptive predictive control algorithm that was developed to tackle the control of linear plants with unknown time delays but with a known lower delay bound. MUSMAR was also tested in situations such as in the control of slow-time varying plants.

MUSMAR relies on the minimization of the multistep quadratic cost function:

$$J_T = E\left[\frac{1}{T}\sum_{i=0}^{T-1}(y(t+i+1)-r)^2+\rho.u^2(t+i)\mid O^t\right] \quad (13)$$

where $E[\cdot|O^t]$ denotes the mean conditioned on the $\sigma-$algebra O^t induced by the observations made up to time t, T is an integer hereafter referred as the "prediction horizon" and $\rho \geq 0$ is a penalty in the manipulated variable effort. The variables u and y denote the plant manipulated variable and output and r denotes the reference to track. For the sake of minimizing (13), the plant is described by the set of predictive models for $i = 1, ..., T$:

$$\begin{array}{c}\hat{y}(t+i\mid t)=\theta_i u(t)+\Psi_i' s(t)\\ \hat{u}(t+i-1\mid t)=\mu_{i-1}u(t)+\Phi_{i-1}' s(t)\end{array} \quad (14)$$

where $\hat{y}(t+i\mid t)$ and $\hat{u}(t+i-1\mid t)$ are predictors in least squares sense given O^t, of, respectively $y(t+i)$ and $u(t+i-1)$, and $s(t)$ is the so called pseudo-state defined by:

$$s(t)=[y(t)\ ...\ y(t-n_a+1)\ u(t-1)\ ...\ u(t-n_b)\ r(t)]' \quad (15)$$

where n_a and n_b are integers to be selected. The entries of $s(t)$ define the structure of the controller. The coefficients θ_i, μ_{i-1} and vectors Ψ_i, Φ_{i-1} in equation (14) are parameters to be online estimated from measured plant input/output data by using Recursive Least Squares (RLS) with directional forgetting factor. Minimization of (13) assuming (14) yields the control law:

$$u(t)=F's(t)+\eta(t) \quad (16)$$

with the vector of optimal gains given by:

$$F=-\frac{\sum_{i=1}^{T}\theta_i\Psi_i+\rho\sum_{i=1}^{T-1}\mu_i\Phi_i}{\sum_{i=1}^{T}\theta_i^2+\rho\left(1+\sum_{i=1}^{T-1}\mu_i^2\right)} \quad (17)$$

and $\{\eta\}$ a low power (with respect to the power of $\{e\}$) dither noise injected in order to fulfill a persistency of excitation condition.

V. Simulation Results

In order to illustrate the performance and the main problems involving the application of the adaptive controller, the PK/PD model (patient model P_{31}) with the following parameters, $a = 0.0089$, $\alpha = 0.2629$, $b = 0.0057$, $\beta = 0.0377$, $\lambda = 0.1044$, $\mu = 2.0579$, $C_{50} = 0.6315$ and $\gamma = 6.1561$, is used. This PK model is a 4th order with a near pole-zero cancelation $(p = -0.1044, z = -0.1256)$ that has a high γ value.

In order to apply the Musmar control algorithm, the following list of parameters must be selected: the sampling time $T_s = 2min$, the polynomial orders of the discrete process $na = 2$, $nb = 1$, the prediction horizon $T = 10$, the control weighting factor $\rho = 1 \times 10^{-3}$. The rationality of this choice is, Ts and T were selected such that $T_s * T$ has a value similar to the time constant of the process ($20min$) [4]. The orders $na = 2$, $nb = 1$ were selected to capture the main dynamics but also the simulate uncertainty about the process. The value of $\rho = 1 \times 10^{-3}$ was selected on trial and error approach. The nominal control value u_0 is selected according with the drug prescribing information. Hard bounds were applied on the control signal such that $u_{min} = 0$ and $u_{max} = 10[mcg/kg/min]$. Figure 6 shows the computer simulation results obtained with the Musmar control algorithm. The simulation starts with the administration of the first bolus $500mcg/kg$. After the administration of the first bolus the neuromuscular relaxation index decrease from 100%, to a value near 0.0%, and stays at a very low level until it starts recover at time $t = 37min$. During this phase it is not possible to control the neuromuscular relaxation. With the confirmation that the $m_a(t)$ is increasing and when $m_a(t) = 4\%$, an initial drug perfusion rate, $9mcg/kg/min$, is applied until $dm_a(t)/dt < 0$. At this moment that state machine

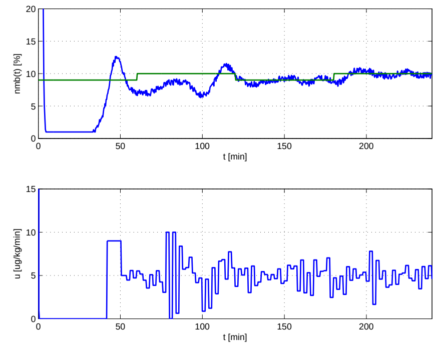

Fig. 6. Patient model P_{31}: Reference signal and response of the neuromuscular blockade (top), and the control signal (bottom).

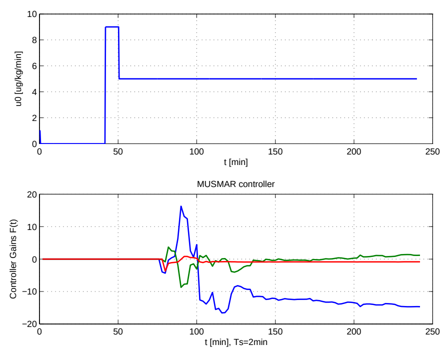

Fig. 7. Patient model P_{31}: Nominal control signal and evolution of the Musmar gains, $T_s = 2min$, $n_a = 2$, $n_b = 1$, $T = 5$.

applies the nominal control value $u_0 = 5mcg/kg/min$ and enables the adaptive controller as shown in figure (7). In this computer simulation, the Musmar controller starts without any information about the process PK/PD. It takes some time, which depends on the sampling time T_s, the orders n_a, n_b and T, to fill the internal data structures of the controller and only at $t > 120min$ it is able to track the NMB reference. The evolution of the controller gains are shown in the figure (7). Between $t = 75min$ and $t = 110min$ the controller has incorrect gains that cause a large activity on the control signal, but this activity helped on the identification of the controller gains. It is clear that one of the main problems with the use of adaptive control is the initial transient caused by the start of the controller. Figures (8) and (9) show the results of the Musmar controller applied to patient model P_{31}, but now the Musmar controller is initialized with the gains obtained from the previous simulation. The initial transient of Musmar controller is better and it is able to quickly track the NMR reference.

In practice it is not possible to use the controller gains as in the previous computer simulation, because it implies that data was obtained from the patient before it was anesthetized. What can be done is to use information from a previous patient to control the PK/PD of a new patient, and hope that the adaptive controller is able to compensate the dynamics mismatch. In order to simulate this scenario a second PK/PD model (P_{69}) [2] with the following parameters is used, $a = 0.0124$, $\alpha = 0.2999$, $b = 0.0061$, $\beta = 0.0360$, $\lambda = 0.0996$,

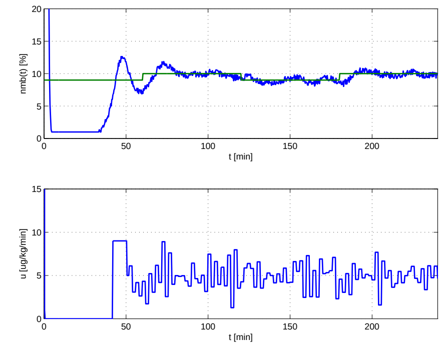

Fig. 8. Patient model P_{31}: Reference signal and response of the neuromuscular blockade (top), and the control signal (bottom).

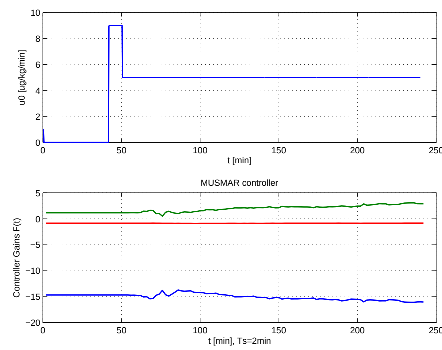

Fig. 9. Patient model P_{31}: Nominal control signal and evolution of the Musmar gains. The initial Musmar gains were obtained from the previous simulation fig.(7).

$\mu = 13.8351$, $C_{50} = 0.6163$ and $\gamma = 4.2189$. The main diference of this model to the P_{32} is that the dynamics does not has a near zero/pole cancelation and the value of the γ parameter is lower, that causes P_{69} to be slower than P_{32}. The Musmar control algorithm was applied with the same parameters values as in the P_{32}. The results are shown in fig.s (10) and (11) where the controller gains are initialized with gains obtained from first computer simulation corresponding to P_{32}. Note however that the selection of the controller parameters may led to a unstable controller, figure (12) shown the performance of Musmar measured by

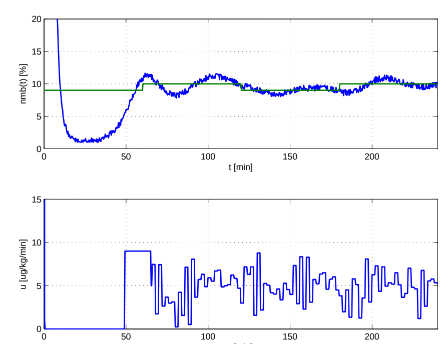

Fig. 10. Patient model P_{69}: Reference signal and response of the neuromuscular blockade (top), and the control signal (bottom). The initial Musmar gains were obtained from the previous simulation fig.(7).

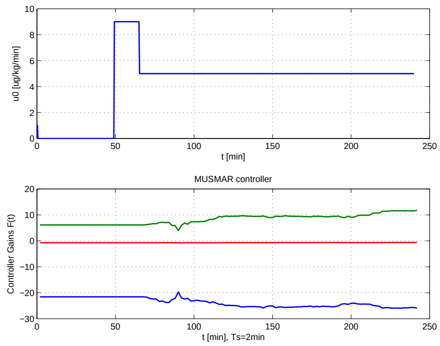

Fig. 11. Patient model P_{69}: Nominal control signal and evolution of the Musmar gains. The initial Musmar gains were obtained from the previous simulation fig.(7).

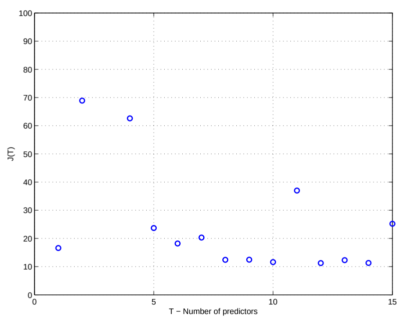

Fig. 12. Performance of Musmar measured by the cost function J_T for several T.

the cost function J_T for several values of T. Note that for $T = 3$ ($6min$), the performance is poor as shown in fig.s (13) and (14). With this configuration and probably due to the control saturation that cause problems on the parameter identification of the predictors, the controller is not able to track the reference and $m_a(t)$ has unacceptable behavior.

VI. CONCLUSIONS AND FUTURE WORK

A multi-predictive adaptive controller (Musmar) was evaluated with computer simulation in the framework of neuromuscular blockade control as an effort to automate anesthesia in general human surgery. The aim is to help on the administration of the drugs, to reduce the workload of the anaesthetist, and to cope with the large variability of pharmokinetics/pharmacodynamics that may cause inadequate administration of drugs. An analysis of the PK/PD response to the first bolus was performed to extract information that may be used on the identification of the PK/PD model. It was concluded that the PK/PD is not identifiable using the response to the first bolus.

To address the control problem a nonlinear transformation was used to obtain a linear representation around the operating zone of the NMB. This enables the application of adaptive control algorithms that were developed to control linear processes. In this work the Musmar algorithm was evaluated. The computer simulation results show that the Musmar control algorithm is able to control the neuromuscular relaxation with adequate performance. Practical rules were used to select the controller parameters, a tradeoff between the sampling time, prediction horizon and polynomial orders was used. Large initial transient with poor performance may occur if the algorithm starts without knowledge about the process. This suggests that a supervisor must be used to online assess the performance of the adaptive controller, and if the performance is not adequate, it must be able to showdown or to switch to another controller that provides an acceptable closed-loop performance.

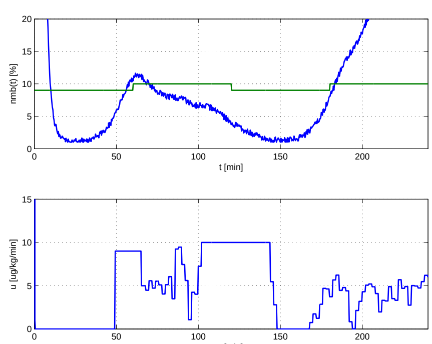

Fig. 13. Patient model P_{69}: Reference signal and response of the neuromuscular blockade (top), and the control signal (bottom). Musmar starts with null gains and $T = 3$.

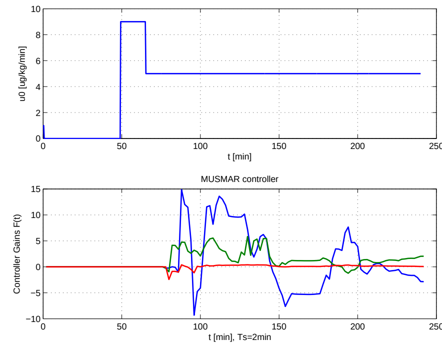

Fig. 14. Patient model P_{69}: Nominal control signal and evolution of the Musmar gains. Musmar starts with null gains and $T = 3$.

REFERENCES

[1] T. Mendonça, P. Lago *PID control strategies for the automation control of neuromuscular blockade*, Control Engineering Pratice, Vol. 6, pp. 1225-1231, 1998

[2] H. Alonso, J.M. Lemos, T. Mendonça *A Target Control Infusion method for neuromuscular blockade based hybrid parameter estimation*, 30th Annual International IEEE EMBS Conference Proceedings, August 20-24, pp. 707-1231, 2008

[3] E. Mosca, G. Zappa, J.M. Lemos (1989). "Robustness of multipredictor adaptive regulators: MUSMAR", *Automatica*, N.25, pp.521-529.

[4] Drugs.com (2012). "Atracurium Besylate Injection ", *http://www.drugs.com/*

[5] Bertinho A. Costa, João M. Lemos (2012). *Neuromuscular blockade control based on self-oscillating adaptive systems*, Submitted to 10th Portuguese Conference on Automatic Control CONTROLO12, Funchal, Madeira Island, July 16th to 18th, 2012.