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An improved strategy for NeuroMuscular Blockade control with parameter uncertainty

J. Almeida, T. Mendonça and P. Rocha

Abstract— **This paper presents a control strategy for exact reference tracking in the presence of parameter uncertainty for the NeuroMuscular Blockade (NMB) level of patients undergoing general anesthesia. For this control application, a compartmental realization of a minimally parameterized Wiener model was used in [1] in which the parameters were estimated from a bank of collected real data using the Extended Kalman Filter (EKF). Due to the parameter uncertainty this procedure did not achieve the desired tracking goal. Here a modified control strategy is presented to overcome this drawback.**

I. INTRODUCTION

Control and modeling of dynamical systems is an important step in applied mathematics, in particular, when applying mathematical methods to address biomedical problems. Among the commonly used models are the nonnegative compartmental models. These models are characterized by conservation laws and composed by a finite number of interconnected homogeneous, well-mixed subsystems called compartments. The exchange of nonnegative quantities of material among the compartments of the system and with the environment is described by laws that take into account the conservation, dissipation and transfer of material (mass) among the compartments and to the environment.

Compartmental models are widely used in pharmacology and in particular in the control of drug dosing in general anesthesia. One example of this application is the automatic control of the NeuroMuscular Blockade (NMB) level, that is usually monitored during general anesthesia. This condition is obtained by the administration of a muscle relaxant to provide adequate surgical conditions. Mathematically, the NMB level is modeled by PharmacoKinetic/PharmacoDynamic (PK/PD) models that relate the administration drug dose with the NMB measure.

In this context, system identification is an important component in controller design since it is used to get adequate models for the conception of a prediction algorithm or simulation, see *e.g.* [9]. In this paper a control strategy for the NMB level of patients undergoing general anesthesia is developed based on a new minimally parameterized model. This control strategy consists of a positive control law for feedback stabilization of compartmental systems proposed by [3]. The Extended Kalman Filter (EKF), see *e.g.* [9], is used to estimate the individual patient parameters to be used in that control law. As expected, due to the parameter uncertainty, this procedure does not yield the desired tracking goal. However, the analysis of the system response allows to take advantage of the model structure and estimate the steady-state parameter error. In a second stage, this knowledge is used to correct the original control law and achieve the desired control objective.

J. Almeida and T. Mendonça are from Departamento de Matemática, Faculdade de Ciências da Universidade do Porto, Rua do Campo Alegre, 4169-007 Porto (jualmeida@fc.up.pt and tmendo@fc.up.pt)

P. Rocha is form Faculdade de Engenharia da Universidade do Porto, Rua Dr. Roberto Frias, 4200-465 Porto (mprocha@fe.up.pt)

T. Mendonça and P. Rocha are also from Center for Research and Development in Mathematics and Applications, Departamento de Matemática, Campus Universitário de Santiago, 3810-193 Aveiro, Portugal

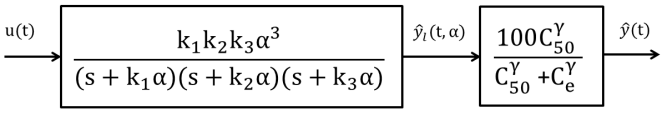

Fig. 1. Block diagram that relates the *atracurium* dose, $u(t)$, with the NMB response, $y(t)$. The signal $y_l(t,\alpha)$ corresponds to the effect concentration

II. CONTROL LAW FOR NMB DRUG

In this section a relationship between the drug dose of *atracurium* and its measured effect (NMB) is described using a minimally parameterized model. Furthermore, a positive control law for feedback stabilization of compartmental systems, [3], is used and its accommodation to the specific dynamical system structure under study is analyzed.

A. NeuroMuscular Blockade minimally model

This section describes a model for the relationship between the administrated drug dose of the muscle relaxant *atracurium* and the measured effect, which in this case is the NMB level. This relationship can be modeled by a SISO Wiener model, as illustrated in Figure 1.The new minimally parameterized model for NMB level used in this paper was proposed by [4] and results from an approximation of the PharmacoKinetic/PharmacoDynamic (PK/PD) model presented in the literature, [7].This PK/PD model involves a total of eight parameters and the poor excitation of the input and output signals is not enough to enable the identification of a such a high number of parameters. In order to overcome this difficulty, [4] proposed this new model with only two patient-dependent parameters to be identified: one in the linear dynamics (parameter α in first block in Figure 1) and the other in the static nonlinearity of the Wiener structure (parameter γ in second block in Figure 1). Contrary to what happens with the PK/PD model, this new minimally parameterized model does not have a direct physiological meaning,

but, as shall be seen in the sequel, produces good results when used for control purposes. The relationship between the drug dose administration and the drug concentration in the effect compartment can be described by the following third-order linear dynamic model,

$$Y_l(s) = \frac{k_1 k_2 k_3 \alpha^3}{(s+k_1\alpha)(s+k_2\alpha)(s+k_3\alpha)} U(s), \qquad (1)$$

where $Y_l(s)$ is the Laplace transform of the output of the linear of dynamic model $y_l(t)$ that corresponds to the effect concentration, and the $U(s)$ is the Laplace transform of the input signal, *i.e.*, the *atracurium* dose. The values of $k_1 < k_2 < k_3$ are positive constants and fixed according to [4]. Furthermore, note that the linear part is stable if $\alpha > 0$.

The model (1) can be written through the following state-space model,

$$\left\{ \begin{array}{rcl} \dot{x}(t) & = & A(\alpha)x(t) + B(\alpha)u(t) \\ y_l(t) & = & Cx(t) \end{array} \right. \qquad (2)$$

with,

$$A(\alpha) = \begin{pmatrix} -k_3\alpha & 0 & 0 \\ k_2\alpha & -k_2\alpha & 0 \\ 0 & k_1\alpha & -k_1\alpha \end{pmatrix}, \quad B(\alpha) = \begin{pmatrix} k_3\alpha \\ 0 \\ 0 \end{pmatrix},$$

$$C = \begin{pmatrix} 0 & 0 & 1 \end{pmatrix}.$$

where $x(t)$ is the state vector. The state x_3 corresponds to the effect concentration, $y_l(t)$, and the states x_1 and x_2 are auxiliary variables.

The second block in Figure 1 represents the static non-linearity of the Wiener structure given by the Hill equation, [11]:

$$y(t) = \frac{100 C_{50}^{\gamma}}{C_{50}^{\gamma} + y_l^{\gamma}(t)}, \qquad (3)$$

where C_{50}, *i.e.* the effect concentration at half of the maximal effect, and γ are patient-dependent parameters. The output of the model $y(t)$ corresponds to the NMB level and varies between 100% (for normal muscular activity) and 0% (for totally paralysis).

B. Mass control

For the purpose of applying a positive control law for feedback stabilization of compartmental systems proposed in [3] it is necessary to check that the state-space model (2) has a compartmental structure. For this sake the components of the vectors $B(\alpha)$ and C must be nonnegative and $A(\alpha)$ must satisfy the following conditions, [5].

- $A(\alpha)$ is a *Metzler* matrix, *i.e.*, it has nonnegative off-diagonal entries,
$$a_{ij}(\alpha) \geq 0, \quad \forall i,j \quad and \quad i \neq j$$
- $A(\alpha)$ has negative diagonal entries,
$$a_{ii}(\alpha) \leq 0 \quad \forall i$$
- $A(\alpha)$ is diagonally dominant,
$$|a_{ii}(\alpha)| \geq \sum_{j \neq j} a_{ji}(\alpha) \quad \forall i$$

If the matrix $A(\alpha)$ satisfies these conditions it is called as a compartmental matrix. Since, the values for $k_1 < k_2 < k_3$ and α are positive, it is easily seen that the matrix $A(\alpha)$ in (2) is indeed compartmental and that the components of the vectors $B(\alpha)$ and C are nonnegative.

The control law proposed by [3] is shown to stabilize the total mass $M(x(t))$ of a compartmental system at a given positive set point M^*. For the sake of simplicity $M(x(t))$ is here after denoted by $M(x)$.

This control law is obtained from the following equation,

$$u(t) = -\left(\sum_{i=1}^{3} b_i(\alpha)\right)^{-1} \left[(1\ 1\ 1)\, A(\alpha)x(t) + \lambda\,(M(x) - M^*)\right],$$

where $\sum_{i=1}^{3} b_i(\alpha)$ is equal to $(1\ 1\ 1)B(\alpha)$, by imposing a positivity constraint, which yields:

$$u(t) = max(0, \tilde{u}(t)) \qquad (4)$$

$$\tilde{u}(t) = -\left(\sum_{i=1}^{3} b_i(\alpha)\right)^{-1} \left[(1\ 1\ 1)A(\alpha)x(t) + \lambda\,(M(x) - M^*)\right]$$

where λ is a positive design parameter, $x(t)$ is the state vector and the total mass of the system is given by the amount of mass in each compartment, $x_i(t)$,

$$M(x) = \sum_{i=1}^{3} x_i(t). \qquad (5)$$

The following theorem guarantees the convergence of the state trajectories of the closed-loop system to the set $\Omega_{M^*} = \left\{x \in \Re^3 : M(x) = M^*\right\}$, known as the *iso-mass* corresponding to the value M^*.

Theorem 2.1: For the closed-loop system (2)-(4) with the arbitrary initial conditions $x(0) \geq 0$

- the *iso-mass* Ω_{M^*} is forward invariant;
- the state vector $x(t)$ is bounded for all $t > 0$ and converges to the *iso-mass* Ω_{M^*}.

The proof of this theorem is given in [3].

The idea now is to use the mass control in order to achieve the control of the NMB level. More concretely, it turns out that the control law (4) not only drives the system mass to the value M^*, but it also drives the system to a steady-state in the iso-mass Ω_{M^*}, and consequently to a certain value of the effect concentration. Therefore, by suitably choosing the value of M^*, one can obtain the desired steady-state value for the effect concentration y_l^{ref}, and consequently drive the NMB response to a desired reference value. Here this reference value is taken to be 10%, as usually required by clinical practice.

Note that, when $M(x) = M^*$, the closed-loop system (2)-(4) can be written as

$$\left\{ \begin{array}{rcl} \dot{x}(t) & = & \tilde{A}(\alpha)x(t) \\ y_l(t) & = & Cx(t) \end{array} \right. \qquad (6)$$

where $\tilde{A}(\alpha) = A(\alpha) + \frac{B(\alpha)}{\sum_{i=1}^{3} b_i(\alpha)} (1\ 1\ 1)\, A(\alpha)$.

This system has an equilibrium point x^e which is the solution of the equation $\tilde{A}(\alpha)x^e = 0$ that satisfies $M(x^e) = M^*$, which is given by

$$x^e = (M^*/3 \quad M^*/3 \quad M^*/3)^T. \tag{7}$$

Moreover, it can be shown that this equilibrium point is asymptotically stable. Therefore, setting as desired system mass

$$M^* = 3x^e = 3y_l^{ref}(\gamma), \tag{8}$$

where $y_l^{ref}(\gamma)$ can be calculated by the inversion of the Hill equation

$$y_l^{ref}(\gamma) = \left(\frac{100}{y^{ref}} - 1\right)^{1/\gamma} C_{50}, \tag{9}$$

and y^{ref} corresponds to the NMB response reference of 10%, forces the system to follow this desired reference.

C. Identification of system parameters

The identification of the dynamic system by the Extended Kalman Filter (EKF) is described in this section. Similarly to what happens in [4] the unknown parameters are identified using the EKF by a coupled identification model. In order to implement the proposed model structure in the identification algorithm, the system is discretized using the zero-order hold method [2], considering the time sampling frequency h=1/3 imposed by the sampling in the surgery room.

The control law previously described is applicable to models with fixed parameters [3], which does not agree with the identification procedure given by the EKF algorithm. Therefore and meeting the clinical procedures, the idea is to give the patients an initial bolus, run the EKF until a certain time t^*, and simulate the system (2) using the last obtained estimate for each parameter, $\alpha(t^*)$ and $\gamma(t^*)$, respectively. The time t^* is given by the OLARD (OnLine tuned Algorithm for Recovery Detection) algorithm [10], that produces an estimate for the beginning of the patients recovery after the initial *atracurium bolus* administration, according to the clinicians' point of view.

D. Parameter uncertainties

The identified parameters, α and γ may be affected by uncertainties and the main goal of this paper is to analyze and derive a control law for reference tracking of the NMB level which is not sensitive to these uncertainties. The performance of this new approach is also illustrated by simulation studies.

Note that the value of the desired mass M^* given by (8), to be used in the control law, is independent of the parameter α, so the identification of this parameter does not affect the reference value of the effect concentration y_l^{ref}, given by $y_l^{ref} = Cx^e$. Nevertheless, this parameter influences how quick is the converge of the mass of the system, $M(x)$, to M^*. Thus, the only parameter that affects the convergence of the system mass is the parameter γ present in nonlinear static equation. It is assumed that

$$\gamma = \gamma^* + \Delta\gamma$$

where $\gamma^* = \gamma(t^*)$ is considered as the nominal value of the parameter γ, and $\Delta\gamma$ is the parameter uncertainty.

In order to obtain realistic values for simulations, the uncertainties $\Delta\alpha$ and $\Delta\gamma$ present in parameters α and γ, respectively, are obtained by analyzing the set of parameter estimates obtained in previously collected real data $\mathscr{R}$. This database presents 60 real patients submitted to general anesthesia for abdominal surgeries where the closed-loop control software *Hipocrates*, [8], was applied.

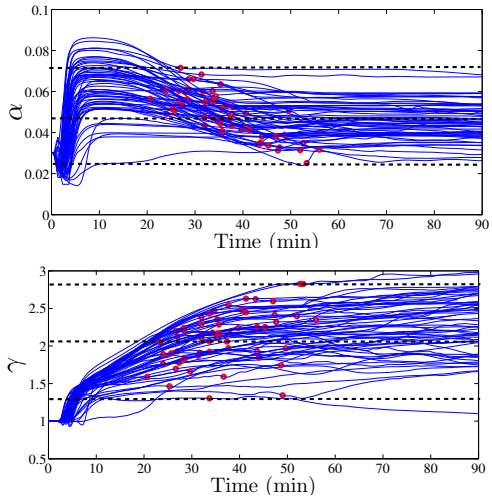

Fig. 2. The estimates of parameters given by EKF algorithm in real database $\mathscr{R}$. The dashed lines represent the minimum, mean and maximum values for the nominal value of the parameters α and γ at recovery time t^*.

Figure 2 illustrates the variation of the parameters α and γ identification given by the EKF. The EKF was applied to each real case and the online estimates of α and γ were obtained. The OLARD was also applied to detect the recovery time for each real case ('•' in Figure 2) in order to evaluate γ^*, nominal value for the parameter γ. Hence, for each patient i in this database and for each parameter a coefficient of variation c_v^i, was calculated, given by

$$c_v^i = \frac{sd^i}{\bar{x}^i} \quad \{i = 1, ..., 60\} \tag{10}$$

where sd^i is the standard deviation of the estimated parameter calculated between the time t^* and the end of the surgery, and $\bar{x}^i$ is the corresponding mean value for each parameter and each patient. Thus, an adequate choice for the parameter uncertainties is given by the mean value of c_v^i, {i=1,...,60}.

III. APPLICATION TO THE NMB CASE STUDY

In this section simulated cases of the application of the NMB compartmental control law are presented, based on a bank $\mathscr{P}$ of hundred nonlinear dynamic models P_j $\{j = 1, ..., 100\}$ used [6] .

As mentioned before, the nominal values of the parameters $\alpha(t^*)$ and $\gamma(t^*)$ given by the EKF algorithm at time instant t^* were used for the application of the compartmental control law.

Moreover, desired NMB level is taken to be 10%, as also mentioned before.

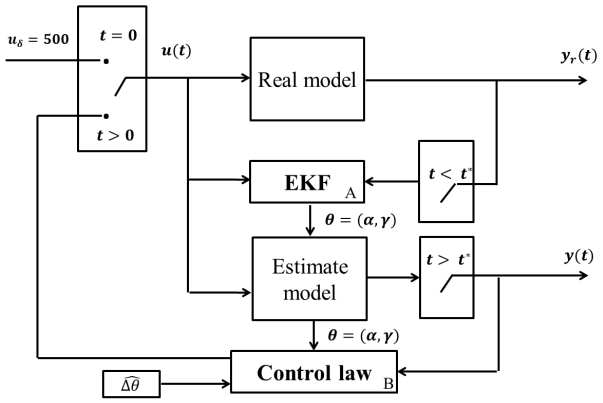

Fig. 3. Feedback control system block diagram composed by the real patient, the patient model, the identification and the controller blocks.

The strategy for the NMB control with parameter uncertainties used here is schematically represented in Figure 3 and can be summarized in the following steps:

1º The real patient dynamics is simulated from the models of the database $\mathscr{P}$, after the administration of an initial *bolus* of muscle relaxant of $500\mu g/kg$;

2º Until time t^*, the model parameters α and γ and the state vector are identified by the EKF algorithm;

3º The OLARD algorithm determines the time instant t^* and from this instant on the control law (tuned for the nominal parameter values α^* and γ^*) is applied to the simulated patient model with $\alpha = \alpha(t^*) + \Delta\alpha$ and $\gamma = \gamma(t^*) + \Delta\gamma$ considering two distinct simulation scenarios. In a first stage it is considered that $\Delta\alpha = \Delta\gamma = 0$ and in a second stage it is considered that $\Delta\alpha \neq 0$ and $\Delta\gamma \neq 0$.

With the purpose of testing the global approach comprising the dedicated identification and control algorithms previously described, simulation studies have been carried out using the bank model $\mathscr{P}$. The behavior of the system mass $M(x)$, the desired system mass M^*, the drug dose profile $u(t)$ obtained by the compartmental control law and the NMB response $y(t)$ controlled by this dose profile are plotted in order to illustrate the performance of the control strategy. From a previous study [1], it turns out that an adequate choice of the design parameter λ is 0.2.

Figure 4 shows the control algorithm performance when the exact parametrization of the simulated patient is given by (2) and (3) and the $\Delta\alpha = \Delta\gamma = 0$. In particular for patient P_{60} the parameters are $\alpha = 0.068$ and $\gamma = 2.682$ and the control objective of achieving a NMB level of 10% amounts to stabilize the system mass on the value $M^* = 22.08\mu g/kg$. As shown in Figure 4, the NMB level was driven to the target value (10%) and the system mass $M(x)$ converges to the desired mass M^*. Figure 5 illustrates a simulation for patient model P_{60} assuming non zero values for the uncertainties $\Delta\alpha$ and $\Delta\gamma$, 0.0134 and 0.3425, respectively, obtained using, for each parameter, the mean value of the coefficient of variation $c_v^i \quad \{i = 1, \ldots, 60\}$ (10).

As shown in Figure 5, the system mass $M(x)$ converges to the desired $M^* = 22.08\mu g/kg$ and the NMB level converges to a value which is different from the desired target.

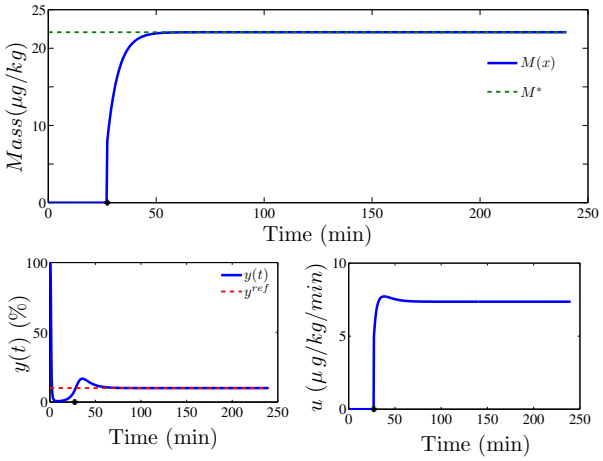

Fig. 4. Simulation for the NMB control level of the patient P_{60} with $\Delta\alpha = \Delta\gamma = 0$, $M^* = 22.08\mu g/kg$, $\alpha = 0.068$ and $\gamma = 2.682$. Upper plot: system mass (solid line) and the desired mass (dashed line). Controller NMB level (left bottom plot) using the control signal represented in the right bottom plot. The star in *xx*-axis represents $t^* = 27.33\,min$ detected by the OLARD.

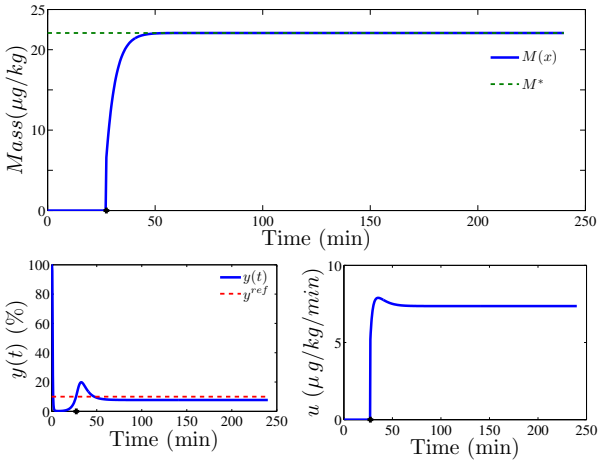

Fig. 5. Simulation for the NMB control level of the patient P_{60} with $\Delta\alpha \neq 0$ and $\Delta\gamma \neq 0$, $M^* = 22.08\mu g/kg$, $\alpha = 0.068 + \Delta\alpha$ and $\gamma = 2.682 + \Delta\gamma$. Upper plot: system mass (solid line) and the desired mass (dashed line). Controller NMB level (left bottom plot) using the control signal represented in the right bottom plot. The star in *xx*-axis represents $t^* = 27.33\,min$ detected by the OLARD.

This is due to the fact that M^* depends on γ and is hence affected by the uncertainty in this parameter. More concretely, the value of M^* is obtained from (8) with $\gamma = \gamma^*$, *i.e.*:

$$M^* = 3\,y_l^{ref}(\gamma^*), \tag{11}$$

whereas the correct value for the desired mass should be

$$\bar{M}^* = 3\,y_l^{ref}(\gamma^* + \Delta\gamma). \tag{12}$$

In particular, the term $y_l^{ref}(\gamma^* + \hat{\Delta}\gamma)$ in the last equation can be written as

$$y_l^{ref}(\gamma^* + \Delta\gamma) = y_l^{ref}(\gamma^*) + \Delta y_l \tag{13}$$

where the value of Δy can be approximated as follows,

$$\Delta y_l = \left(y_l^{ref}\right)'\Big|_{\gamma=\gamma^*} \Delta\gamma \tag{14}$$

where $\left(y_l^{ref}\right)'\Big|_{\gamma=\gamma^*} = \frac{dy_l^{ref}}{d\gamma}(\gamma^*)$.

So, substituting Δy_l given by the equation (14) in equation (13), the value of the reference for the output of the linear part is given by

$$y_l^{ref}(\gamma^*+\Delta\gamma) \approx y_l^{ref}(\gamma^*) + \left(y_l^{ref}\right)'\Big|_{\gamma=\gamma^*} \Delta\gamma \tag{15}$$

Therefore, the value for the system desired mass, $\bar{M}^*$ is obtained by equation (12) as:

$$\bar{M}^* \approx 3\times y_l^{ref}(\gamma^*) + 3\times \left(y_l^{ref}\right)'\Big|_{\gamma=\gamma^*} \Delta\gamma, \tag{16}$$

So, it is possible to see that the difference obtained in the NMB level in the last simulation case is due to the uncertainty in the desired mass that corresponds to the second term in the right-hand of equation (16).

Note that, for real patients, the uncertainty $\Delta\gamma$ is unknow. However, from (14) it is possible to approximately determine this value as

$$\Delta\gamma = \frac{\Delta y_l}{\left(y_l^{ref}\right)'\Big|_{\gamma=\gamma^*}}, \tag{17}$$

once Δy_l is known. The value of Δy_l is obtained by making the difference between the desired effect concentration and the observed effect concentration when the system begins to stabilize, *i.e.* after a certain time t_{ss}.

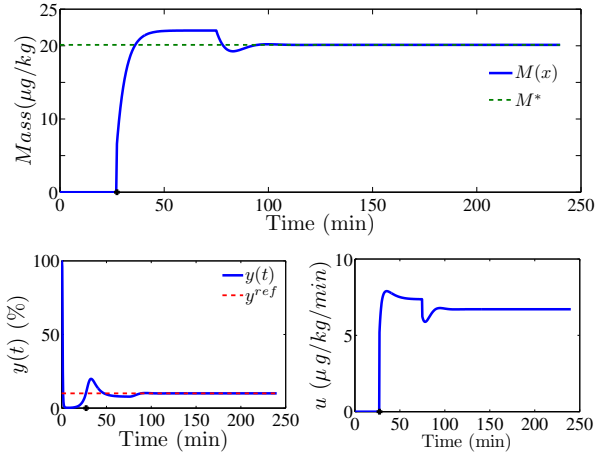

Fig. 6. Simulation for the NMB control level of the patient P_{60} with $\Delta\alpha = 0.0134$ and rectification of M^*, assuming $\alpha = 0.068$ and $\gamma = 2.682$. Upper plot: system mass (solid line) and the desired mass (dashed line). Controller NMB level (left bottom plot) using the control signal represented in the right bottom plot. The star in *xx*-axis represents $t^* = 27.33\,min$ detected by the OLARD.

Figure 6 shows what happens when the initial guess for the M^* is rectified and replaced in the control law by the value $\bar{M}^*$ obtained from (16) with $\Delta\gamma$ given by (17), which happens after minute 75. This correction is an *online* adaptive process that changes the desired mass for the system and consequently changes the drug administration profile and the NMB level. The simulation results in Figure 7 were performed in the presence of noise taken from a typical NMB case from real database $\mathscr{R}$. The filter algorithm presented in [8] was applied to the real signal and the obtained residuals were used as the noise vector to be added to the output signal in the simulation. In this case the parameters are $\alpha = 0.063$, $\gamma = 2.455$, the desired mass $M^* = 23.81\mu g/kg$ and the $t^* = 25.33\,min$. As it is possible to see this simulation presents a good results for the controller even in the presence of noise.

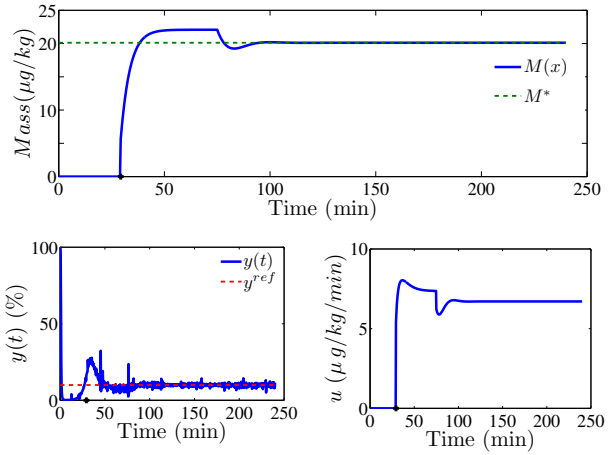

Fig. 7. Noisy simulation for the NMB control level of the patient P_{60} with $\Delta\alpha = 0.0134$ and rectification of M^*, assuming $\alpha = 0.063$ and $\gamma = 2.455$. Upper plot: system mass (solid line) and the desired mass (dashed line). Controller NMB level (left bottom plot) using the control signal represented in the right bottom plot. The star in *xx*-axis represents $t^* = 25.33 min$ detected by the OLARD.

IV. CONCLUSIONS

This paper presents a new strategy for the control of the NeuroMuscular Blockade (NMB) of patients undergoing general anesthesia in the presence of parameter uncertainties. This consists in using a minimally parametrized model previously presented in the literature, which is here shown to have a compartmental structure. This special structure enables the design of a controller for tracking a desired NMB level, by driving the system to an adequate total mass. The presence of uncertainties in the model parameters does not affect the mass control algorithm, but affects the computation of the adequate set-point for the total mass that corresponds to the desired NMB level. However an analysis of the system response allows to estimate the uncertainties in the parameters and rectify the control law in order to obtain the desired NMB level set-point.

V. ACKNOWLEDGMENTS

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