A compartmental model-based control strategy for NeuroMuscular Blockade level. ⋆

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Abstract: This paper presents a compartmental model-based control strategy to drive the NeuroMuscular Blockade level of patients undergoing general anesthesia to a predefined target. For that purpose, a compartmental realization of a minimally parameterized nonlinear Wiener model was derived and used on an adapted version of the standard compartmental control law for linear systems. The identification of the model parameters was recursively performed by one Extended Kalman Filter during the initial bolus induction period and stopped afterwards. To overcome the fact that this identification is stopped during the closed-loop control period, uncertainties in the parameters are assumed to be present and included in the control law. Information taken from the identification of real collected cases was used to tune the parameter uncertainties. The feasibility of the whole strategy was evaluated in a bank of simulated models, giving rise to good reference tracking results even in the presence of noise.

Keywords: Automatic control systems, Positive feedback, Compartmental Systems, Anesthesia.

1. INTRODUCTION

Compartmental models are a type of mathematical models that have been widely used in biomedicine. A dynamical system is a positive system composed by a finite number of interconnected homogeneous subsystems that may be modeled as compartments that exchange positive quantities of material among themselves 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. The automatic control of the amount of material being transfered/stored in the compartments is becoming more and more common in biomedical fields such as in pharmacology. In what concerns the administration of drugs in anesthesia, these control strategies are of paramount importance since then enable a controlled administration of drugs adapted to the clinical needs in terms of storage/use of the drug in the human body.

One example of this is the automatic control of the NeuroMuscular Blockade (NMB) level, that is usually monitored during general anesthesia. This signal quantifies the level of muscle paralysis in patients as result of the administration of muscle relaxants. The NMB level is usually modeled by PharmacoKinetic/PharmacoDynamic (PK/PD) models where the PK model describes the relationship between the administered drug dose and the resulting blood concentration, while the PD model relates this blood concentration with the measured effect (e.g. the NMB level in the case of muscle relaxant administration).

This paper presents a control strategy for the NMB level using a positive control law for a new minimally parameterized compartmental model describing the effect of the muscle relaxant *atracurium* in the NMB level, Silva et al. (2011). The positive control law for feedback stabilization of compartmental systems of Bastin and Provost (2002) is used. The proposed control strategy is developed and it is also applied for cases where uncertainties in the model parameters are present, as in Sousa et al. (2007).

The novelty of this work is the use of the minimally parameterized model proposed in Silva et al. (2011) in the

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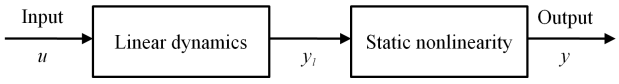

Fig. 1. Block diagram of the NMB nonlinear SISO Wiener model. The input u is the *atracurium* dose and the output y is the measured NBM level. The signal y_l between the linear block and the static nonlinearity is not available for direct measurement.

framework of compartmental systems. A compartmental realization of the referred model was derived in order to fulfill the requisites in Bastin and Provost (2002).

The contents of the paper are as follows: section 2 presents the novel compartmental control strategy, describing the minimally parameterized model for the NMB level, the positive control law and the identification strategy that is used. In Section 3 the conditions for testing the proposed strategy in simulation are described while in section 4 the results of those tests are shown. Section 5 draws the conclusions.

2. CONTROL STRATEGY FOR THE NMB LEVEL

This section presents a positive control law for the NMB level that uses a compartmental description of the system. The minimally parameterized model used in this paper is first introduced, being followed by the description of the identification algorithm used for the identification of the model parameters. Later in the section the positive control law is derived.

2.1 Minimally parameterized NMB model

The model that is used to derive the proposed control strategy was introduced in Silva et al. (2011) and describes the effect of the non-depolarizing muscle relaxant *atracurium* in the NMB level. It is a parsimonious SISO Wiener model, Söderström and Stoica (1989), with only two patient-dependent parameters: one in the linear dynamics and one in the static nonlinearity of the Wiener structure (Fig. 1).

The linear dynamics is a third-order model with unit static gain that may be represented in frequency domain as in Silva et al. (2011):

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

where $Y_l(s)$ is the Laplace transform of the continuous-time output $y_l(t)$ of the model linear dynamic part; $U(s)$ is the Laplace transform of the input signal $u(t)$ (*atracurium* infusion rate).

For the purpose of developing a control law for the Wiener system in Fig. 1 a compartmental state-space realization of (1) is used.

A state-space model

$$\begin{aligned} \dot{x}(t) &= A\,x(t) + B\,u(t)\,, \\ y_l(t) &= C\,x(t) \end{aligned} \qquad (2)$$

is said to be compartmental if the components of B and C are nonnegative and the matrix A is a compartmental matrix, *i.e.*, if A satisfies the following conditions, Godfrey (1983):

- A is a matrix with nonnegative off-diagonal entries, *i.e.*, A is a *Metzler* matrix:
$$a_{ij} \geq 0, \qquad \forall\, i,j \text{ and } i \neq j$$
- A is a matrix with nonpositive diagonal entries:
$$a_{ii} \leq 0, \qquad \forall\, i$$
- A is diagonally dominant:
$$|a_{ii}| \geq \textstyle\sum_{j\neq i} a_{ji}, \qquad \forall\, i$$

More concretely the following realization will be used,

$$\begin{aligned} \dot{x}(t) &= A(\alpha)\,x(t) + B(\alpha)\,u(t)\,, \\ y_l(t) &= C\,x(t) \end{aligned} \qquad (3)$$

$$A(\alpha) = \begin{bmatrix} -\,k_3\,\alpha & 0 & 0 \\ k_2\,\alpha & -\,k_2\,\alpha & 0 \\ 0 & k_1\,\alpha & -k_1\,\alpha \end{bmatrix}, \quad B(\alpha) = \begin{bmatrix} k_3\,\alpha \\ 0 \\ 0 \end{bmatrix}, \qquad (4)$$

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

In (4) k_1, k_2 and k_3 are constants fixed in $1, 4$ and 10, respectively, according to Silva et al. (2011) and α is a positive patient-dependent parameter. The choice of this particular type of realization is motivated by the existence of suitable compartmental control law.

It is then trivial to see that, with the considered values for k_1, k_2 and k_3, the matrix $A(\alpha)$ verifies the previous properties and the components of vectors $B(\alpha)$ and C are nonnegative. Hence, the realization in (3), (4) is indeed compartmental and the control law proposed in Bastin and Provost (2002) to compartmental systems may be applied.

The static nonlinearity of the Wiener model is given by the Hill equation, Weatherley et al. (1983):

$$y(t) = \frac{100\, C_{50}^{\gamma}}{C_{50}^{\gamma} + y_l^{\gamma}(t)}\,, \qquad (5)$$

where C_{50} and γ are also patient-dependent parameters and $y_l(t)$ is the output of the linear block, given by (3). Following the work in Silva et al. (2011) C_{50} is fixed, being γ the only patient-dependent parameter in the static nonlinearity (5).

2.2 Compartmental control law

The compartmental law used for the control of the NMB level was proposed by Bastin and Provost (2002) and stands as follows:

$$\begin{aligned} u(t) &= max(0, \tilde{u}(t)) \\ \tilde{u}(t) &= -\left([1 \quad 1 \quad 1]\, B(\alpha)\right)^{-1} \times \\ &\quad \times \left([1 \quad 1 \quad 1]\ A(\alpha)\,x + \lambda(M(x) - M^*)\right), \end{aligned} \qquad (6)$$

where λ is a design parameter. For the sake of simplicity the state-space vactor $x(t)$ is denoted by x. This control law ensures the convergence of the total mass $M(x) = \sum_{i=1}^{3} x_i$ of the system to a given set point M^*. In order

words the state trajectories $x = [x_1 \quad x_2 \quad x_3]^T$ are driven to the set

$$\Omega_{M^*} = \{x \in \Re^3_+ : M(x) = \sum_{i=1}^{3} x_i = M^*\}, \tag{7}$$

known as an *iso-mass* set.

Substituting $A(\alpha)$ and $B(\alpha)$ from (4) in (6), the positive compartmental control law proposed in this paper becomes:

$$\begin{aligned} u(t) &= max(0, \tilde{u}(t)) \\ \tilde{u}(t) &= \frac{1}{k_3}\left((k_3 - k_2)x_1 + (k_2 - k_1)x_2 + k_1 x_3\right) \\ &\quad - \frac{\lambda}{k_3\,\alpha}(M(x) - M^*). \end{aligned} \tag{8}$$

Note that, when $M(x) = M^*$, the state-space form (3) can be written as

$$\dot{x}(t) = \tilde{A}(\alpha)\, x(t), \tag{9}$$

$$y_l(t) = C\, x(t) \tag{10}$$

where $\tilde{A}(\alpha) = A(\alpha) + \frac{B(\alpha)}{[1 \quad 1 \quad 1]B(\alpha)}[1 \quad 1 \quad 1]\, A(\alpha)$.

Let

$$x^e = [x_1^e \quad x_2^e \quad x_3^e]^T, \tag{11}$$

be an equilibrium point of (9). It follows from the equilibrium condition $\tilde{A}(\alpha)x^e = 0$, that x^e is given by

$$x^e = [x_3^e \quad x_3^e \quad x_3^e]^T,$$

and therefore by (7)

$$M^* = \sum_{i=1}^{3} x_i^e = 3x_3^e. \tag{12}$$

It is possible to show that similarly to what happens in Magalhães et al. (2005), the control law (7) not only drives the state trajectories to the *iso-mass* Ω_{M^*} but also forces them to converge to the equilibrium point

$$x^e = [M^*/3 \quad M^*/3 \quad M^*/3]^T. \tag{13}$$

Since the clinical set point for the control is the NMB level and (5) is a static nonlinear function, the equilibrium point y_l^e for the linear system can be calculated inverting the Hill equation:

$$y_l^e = \left(\frac{100}{y^{ref}} - 1\right)^{1/\gamma} C_{50}. \tag{14}$$

From (10), $y_l(t) = x_3(t)$ and in equilibrium, $y_l^e = x_3^e$. Therefore in order to drive the system to the NMB set point y^{ref} it is enough to force a linear part into the iso-mass Ω_{M^*} with $M^* = 3y_l^e$.

2.3 Parameter identification

The identification of the model parameters α and γ is here recursively performed by the Extended Kalman Filter (EKF), Söderström (2002). For that, the model in (3) is discretized using the zero-order hold method, Åström and Wittenmark (1984), and the EKF is developed according to Silva et al. (2011). To enable the estimation of the model parameters with the EKF, a coupled identification model is defined, merging the sampled model and a random walk model for the parameter estimates, Söderström and Stoica (1989).

According to Bastin and Provost (2002), the compartmental control law (8) is applicable to models with fixed parameters. However, the derived EKF structure provides online estimates of the model parameters. A strategy was hence developed to use fixed parameters in the compartmental control law (8) but not using a nominal model to simulate the patient. The main idea is to run the EKF for the identification of the model parameters until a certain time t^* and to fix the parameters α and γ in the last obtained estimate for each parameter: $\alpha(t^*)$ and $\gamma(t^*)$, respectively. The point t^* where the identification of the parameters is stopped is given by the OLARD (OnLine tuned Algorithm for Recovery Detection), Silva et al. (2009), which detects the point for the beginning of the patient recovery after the initial *atracurium bolus*. In the clinicians' point of view, t^* is a good indicator of the recovery time for each patient and should be used to indicate the beginning of further drug dose administration e.g. by one automatic controller.

3. SIMULATION

In order to access the performance of the proposed compartmental control strategy a bank $\mathcal{R}$ of sixty models $R_i = (\alpha_i, \gamma_i)$, $\{i = 1, ..., 60\}$ was used. These models result from the identification of sixty real cases collected in the surgery room with the offline algorithm described in Silva (2011).

As mentioned before, the values of the states x_i in (3) must be known to be used in the compartmental control law (8). In the clinical practice only the output is accesible from the patient and not the states for the model parameters. In order to overcome this an identification strategy (EKF) is developed to R_i (considered as the real patient). The parameters α and γ of the model are hence identified online until t^*. During the control time window a simulated patient using these estimates runs in parallel with the real one to provide the value of the states x_i.

Since $y^{ref} = 10\%$ due to the clinical needs, M^* in (8) becomes,

$$M^* = 3x_3^e = 3y_l^e = 3 \times 9^{\frac{1}{\gamma}} C_{50}. \tag{15}$$

The compartmental control strategy presented in this paper is schematically represented in Fig. 2 and can be summarized in the following steps:

Step 1 $t = 0$: A model R_i from the database $\mathcal{R}$ is chosen to simulate the real patient dynamics. A typical *bolus* of $500\mu g/kg$ is given to the patient (u_δ in Fig. 2).

Step 2 $0 < t < t^*$: The EKF algorithm (block A in Fig. 2) identifies the parameters $\alpha(t)$ and $\gamma(t)$.

Step 3 $t \geq t^*$: The time instant t^* is detected by the OLARD (block not shown in Fig. 2). The patient is simulated using (3), (4) and (5) with $\alpha = \alpha(t^*)$ and

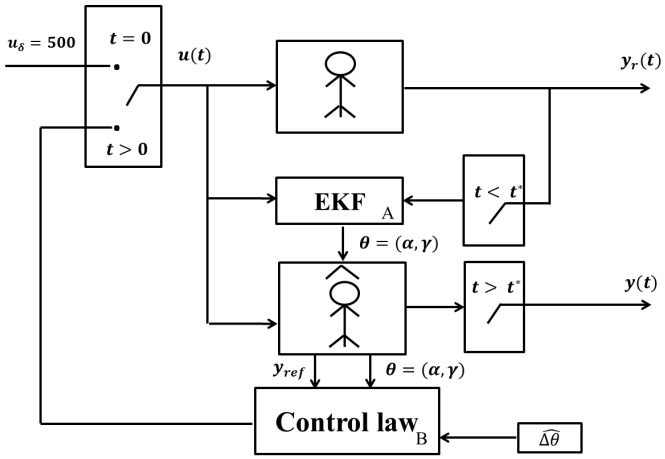

Fig. 2. Block diagram of the control system composed by the real patient, the patient model, the identification block (EKF) and feedback controller.

$\gamma = \gamma(t^*)$. The control law defined by (8) is applied both to the real and the simulated patient with $\alpha = \alpha(t^*)$ and $\gamma = \gamma(t^*)$.

Since the parameters identification is stopped in t^*, it is natural assume that the parameters α and γ may be affected by uncertainties in $t > t^*$. A control law that takes into account this fact is then obtained.

Estimates for the uncertainties $\hat{\Delta\alpha}$ and $\hat{\Delta\gamma}$ present in the parameters α and γ were then obtained. The EKF was applied to each real case of the previously collected database Silva (2011) and the online estimates of α and γ were obtained. The OLARD was used to detect the recovery time for each real case ('•' in Fig. 3).

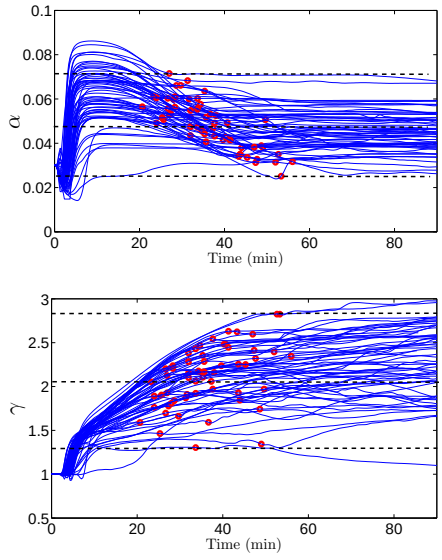

Fig. 3. The estimates of parameters α and γ updated by the EKF algorithm for the sixty cases in the real database. The dashed lines represent the minimum, mean and maximum values in t^* for the parameters estimates.

For each parameter and each patient i a coefficient of variation c_v was calculated as follows:

$$c_v^i = \frac{sd^i}{m^i} \quad \{i = 1, ..., 60\} \tag{16}$$

where sd^i is the standard deviation of the estimated parameter between the time t^* and the time corresponding to the end of the drug infusion and m^i is the parameter mean in the same interval. Afterwards, the uncertainties $\hat{\Delta\alpha}$ and $\hat{\Delta\gamma}$ to be added to $\alpha(t^*)$ and $\gamma(t^*)$ were obtained equal to value of the $c_v^i \{i = 1, ..., 60\}$ for α and γ, respectively.

4. RESULTS

With the purpose of testing the global approach comprising the dedicated identification and control algorithms, simulation studies have been carried out using the model bank $\mathcal{R}$. After the typical *bolus* administration the NMB level decreases very quickly and full paralysis is induced in a few minutes (clinical requirement). In all figures in this section the star in the xx-axis indicates the estimated beginning of recovery according to the OLARD specifications. This time instant t^* is used as the decision flag to enable the start of the *atracurium* continuous infusion. The control purpose is to stabilize the system mass on the value M^* (corresponding to a 10% level of NMB) using the control law (8).

Case number 31 in $\mathcal{R}$, $R_{31} = (0.032, 2.057)$, was used to exemplify the performance of the compartmental control strategy described in the previous section.

In order to highlight the algorithm performance the behavior of the simulated patient output ($y(t)$ in Fig. 2 is ploted in Fig. 4, 5. This exemplifies the case were no uncertainties in the model parameters exist.

In Fig. 4 the simulated patient has $\alpha = \alpha(t^*) = 0.037$ and $\gamma = \gamma(t^*) = 1.699$ in (3), (4) and (5). Here, the control objective is to stabilize the system mass on the value $M^* = 36.29\,\mu g/kg$. In Fig. 5, $\alpha = \alpha(t^*) = 0.028$ and $\gamma = \gamma(t^*) = 1.269$ and $M^* = 55.62\,\mu g/kg$. In both cases the design parameter λ was set to 0.2.

The simulation results in Fig. 5 were performed in the presence of noise taken from a typical NMB real record (chosen from the database of real cases previously collected in the surgery room). The filter algorithm in Mendonça et al. (2004) was applied to the real signal and the obtained residuals were used as the noise vector to be added to the output signal in simulation. The simulations present a good performance of the controller and the small differences observed when comparing the two situations (with and without noise in Fig. 4 and Fig. 5, respectively) are related with the different value of t^* identified by the OLARD algorithm.

In Fig. 6 different values for the design parameter λ are considered in order to illustrate the sensitivity behavior of the control law. As it is clear in Fig. 6, as higher λ as rapid is the converge of the mass of the system $M(x)$ to M^*, as expected.

The following simulations aim to evaluate the control algorithm performance in the presence of parameter uncertainties. Fig. 7 shows the results of a simulation scenario where $\hat{\Delta\alpha} \neq 0$ and $\hat{\Delta\gamma} = 0$. In Fig. 8 $\hat{\Delta\alpha}$ and $\hat{\Delta\gamma}$ are equal

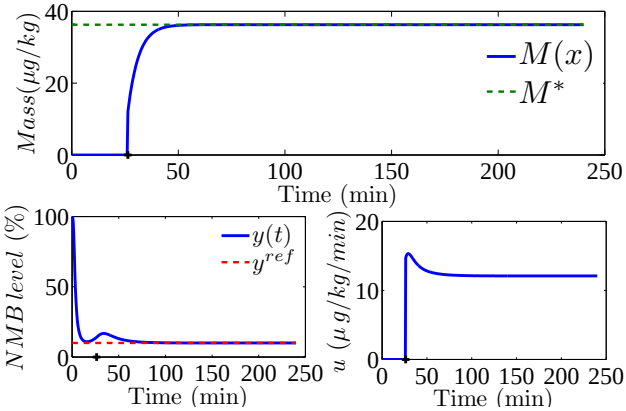

Fig. 4. Simulations for the NMB level control with $\lambda = 0.2$, $M^* = 36.29\mu g/kg$, $\alpha = 0.037$, $\gamma = 1.669$, $\hat{\Delta\alpha} = 0$ and $\hat{\Delta\gamma} = 0$. Upper plot: system mass (solid line) and the desired mass (dashed line). Simulated patient controlled NMB level (left bottom plot) using the control signal represented in the right bottom plot. The star in the xx-axis represents $t^* = 26.3\,min$ detected by the OLARD.

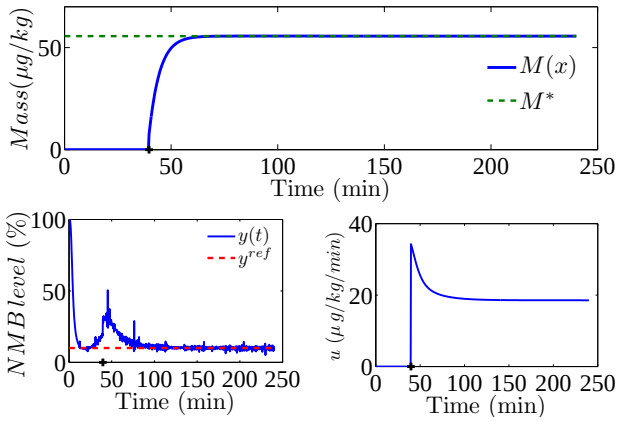

Fig. 5. Simulations for the NMB level control with noise $\lambda = 0.2$, $M^* = 55.62\mu g/kg$, $\alpha = 0.028$, $\gamma = 1.260$, $\hat{\Delta\alpha} = 0$ and $\hat{\Delta\gamma} = 0$. Upper plot: system mass (solid line) and the desired mass (dashed line). Simulated patient controlled NMB level (left bottom plot) using the control signal represented in the right bottom plot. The star in the xx-axis represents $t^* = 25.3\,min$ detected by the OLARD.

to 0.0143 and 0.3425, respectively. These values were given by the mean value of the coefficient of variation as referred in section 3. Note that in both situations the system mass converges to a fixed value M^*, as expected.

Fig. 7, 8 aim to represent the responses that may be obtained in the clinical environment, when the control action is actually given to the real patient. Two NMB level responses are hence plotted: $y(t)$ (as referred in Fig. 2) that was obtained when the control was applied to the simulated model and $y_r(t)$ that results from applying the control strategy to the real patient model.

In both figures, the system mass $M(x)$ stabilizes in M^*, which indicates that the control law is functioning properly

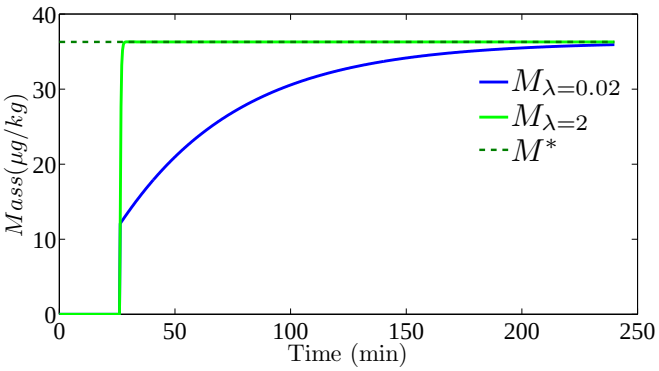

Fig. 6. Simulations for the NMB control considering $\hat{\Delta\alpha} = 0$, $\hat{\Delta\gamma} = 0$ and different values for λ. (a) $\lambda = 0.02$. (b) $\lambda = 2$.

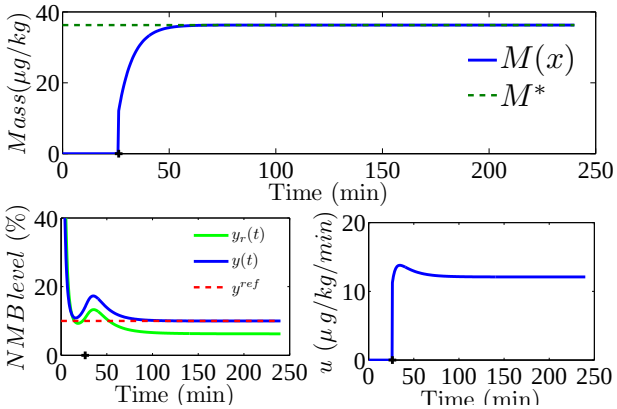

Fig. 7. System mass with $\lambda = 0.2$, $M^* = 36.29\,\mu g/kg$, $\hat{\Delta\alpha} = 0.0143$ and $\hat{\Delta\gamma} = 0$.

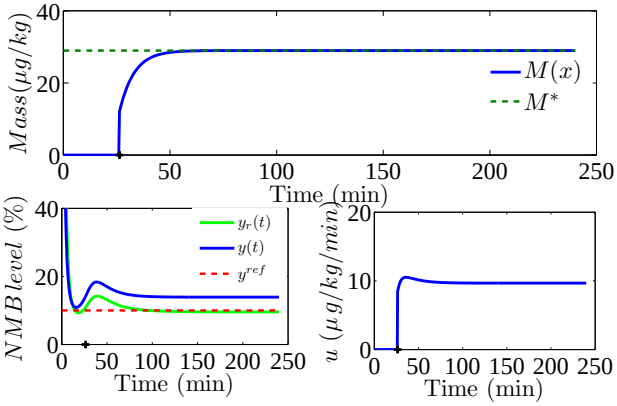

Fig. 8. System mass with $\lambda = 0.2$, $M^* = 29\,\mu g/kg$, $\hat{\Delta\alpha} = 0.0143$ and $\hat{\Delta\gamma} = 0.3425$. Notice that, the M^* is smaller than M^* in Fig. 7, so in this case the NMB is above by 10%.

for the simulated model. However, due to the presence of uncertainties in the model parameters, specially in γ, the NMB level from the patient model stabilizes in 6% in Fig. 7. From the clinical point of view, this value is completely satisfactory. In Fig. 8 uncertainties in γ were considered and hence the real patient response $y_r(t)$ stabilizes in 10%.

As a final test, instead of using a patient from the simulated database $\mathcal{R}$, one of the real records ($y_r(t)$ and $u_r(t)$) in the previouly collected database was used for the identification step (step 2 in section 3). In Fig. 9 the real patient output $y_r(t)$ and the NMB signal controller by the proposed compartmental control strategy ($y(t)$ in Fig. 9) are plotted. For this case, the obtained parameter estimates were $\alpha(t^*) = 0.0603$ and $\gamma(t^*) = 2.2035$. As it is clear in the upper plot of Fig. 9, the controlled signal $y(t)$ has the same behavior as the real one $y_r(t)$. Moreover, the infusion rate $u(t)$ calculated by the controller ($9.8\mu g/kg/min$) is similar to the average rate of the drug that was administered to the real patient $u_r(t)$ ($9.9\mu g/kg/min$).

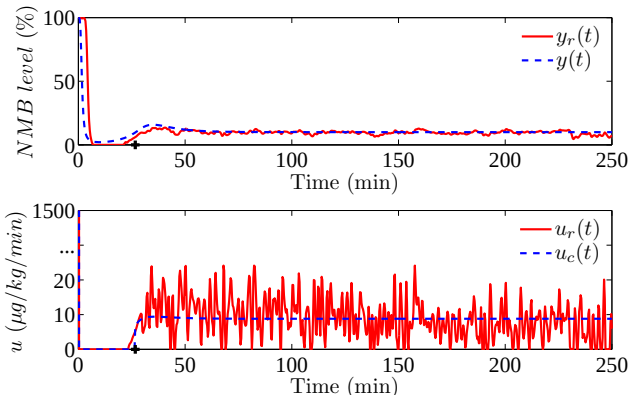

Fig. 9. Performance of the controller for NMB level: Upper plot: comparison between the real NMB level (solid line) and the controller NMB level (dashed line). Bottom plot: comparison between the real drug administration (solid line) and the drug administration given by (8).

5. CONCLUSION

A control law strategy of mass conservation applied to the NeuroMuscular Blockade (NMB) case study is derived in this paper. This particular application enables a quite accurate evaluation of any automatic control delivery system since the sensor used to quantify the NMB level is widely accepted in clinical environment. A minimally parameterized SISO nonlinear Wiener model for the NMB level is considered and a compartmental realization of the referred model was derived. The developed scheme comprises individual identification of the two model parameters performed by one EKF coupled to a total mass control scheme for compartmental systems. Parameters uncertainties are assumed to be present in the model and are hence included in the control law. These uncertainties were calculated using information taken from the identification of previously collected real cases. The results are convincing and encourages the implementation of this control strategy in a real platform for control of the NMB level. For this, a more detailed analysis of the performance of the proposed controller for compartmental systems in the presence of uncertainties is needed.

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