Preprints of the 3rd IFAC Conference on Advances in Proportional-Integral-Derivative Control, Ghent, Belgium, May 9-11, 2018

WeAT2.2

Optimized PID tuning for the automatic control of neuromuscular blockade

Luca Merigo [*] **Fabrizio Padula** [**] **Nicola Latronico** [***]
Teresa Mendonça [****] **Massimiliano Paltenghi** [†] **Paula Rocha** [‡]
Antonio Visioli [§]

[*] *Dipartimento di Ingegneria dell'Informazione, University of Brescia, Brescia, Italy, (e-mail: l.merigo001@unibs.it)*
[**] *School of Electrical Engineering, Computing, and Mathematical Sciences, Curtin University, Perth, Australia, (e-mail: fabrizio.padula@curtin.edu.au)*
[***] *Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy, (e-mail: nicola.latronico@unibs.it)*
[****] *Faculdade de Ciências, Universidade do Porto Research Center for Systems and Technologies (SYSTEC), Porto, Portugal (e-mail: tmendo@fc.up.pt)*
[†] *Department of Anesthesiology, Critical Care and Emergency, Spedali Civili University Hospital, Brescia, Italy, (e-mail: maxpaltenghi@gmail.com)*
[‡] *Departamento de Matemtica, Universidade do Porto, Research Center for Systems and Technologies (SYSTEC), Porto, Portugal, (e-mail: mprocha@fe.up.pt)*
[§] *Dipartimento di Ingegneria Meccanica e Industriale, University of Brescia, Brescia, Italy (e-mail: antonio.visioli@unibs.it)*

Abstract: In this paper we propose a PID-based control scheme for the automatic regulation of the neuromuscular blockade level during surgery. In particular, we introduce an optimized tuning of the PID controller parameters based on a standard set of patient models presented in literature. The tuning procedure is based on the solution of a min-max multiobjective optimization problem that takes into account the control performance, the control effort and the robustness. A genetic algorithm is used to solve the optimization problem and to find the optimal tuning. Then, in order to evaluate the control systems robustness, the optimal PID controller is tested in simulation on a database of patient models estimated from real data. The obtained results demonstrate that the performance achieved by considering an optimized PID tuning satisfies the clinical specifications and is robust to the inter-patient variability.

Keywords: General anesthesia, neuromuscular blockade, PID controller, optimized tuning, robustness, genetic algorithms.

1. INTRODUCTION

Feedback control in drugs dosing in clinical pharmacology has received in the last decade an increasing attention. In general, the automatic controller exploits measurements of different vital signals of the patient to determine drugs infusion profiles that satisfy clinical specification. One of the most interesting application of this kind of systems is the automatic administration of anesthetics in total intravenous anesthesia (TIVA). General anesthesia provides the consciousness suppression (hypnosis), the pain inhibition (analgesia), and the muscle contraction inhibition (or relaxation) by means of specific drugs. Examples of automatic control systems for the regulation of hypnosis and analgesia have been proposed in (Struys et al., 2001; Dumont et al., 2009; Soltesz et al., 2013; Nascu et al., 2015; Liu et al., 2012; Merigo et al., 2017;

Padula et al., 2017, 2016). The obtained results show that a more stable depth of hypnosis can be achieved with less drug administration, which is advantageous both for the patient and for the anesthesiologist, whose workload is reduced. These advantages are further improved by implementing a feedback control system also for the third pillar of general anesthesia: muscle relaxation. In fact, the use of non-depolarizing types of muscle relaxants allows the blocking of the neuromuscular transmission so that intubation and surgical procedures are facilitated. The neuromuscular blockade (NMB) level is measured by using a supra-maximal train-of-four (TOF) stimulation of the ulnar nerve (McGranth and Hunter, 2006). The procedure consists of an evoked electromyography at the hand by electrical stimulation of the adductor policies muscle. The level varies between 100%, which corresponds to a full muscle activity, and 0%, that is the full paralysis of

the patient. Clinical practice usually consists of a first induction phase with a standard bolus calibrated on the patient weight (for atracurium muscle relaxant it is 500 $[\mu g/kg]$) followed by a maintenance phase where a constant NMB level of 10% is typically required. A Wiener model is usually employed to mathematically describe the pharmacokinetic/pharmacodynamic (PK/PD) human body response to muscle relaxants. In particular, the PK part consists of a mammillary compartmental model that describes the drug distribution in the human body by linear dynamics equations (Ward et al., 1983). The output of the PK model is the blood concentration of the drug, which is also the input of the PD model, that describes the clinical effect of the drug. In particular, the blood concentration is related with the effect-site concentration through a linear transfer function, and to the clinical effect by a nonlinear static function, referred to as Hill function (Weatherley et al., 1983). In this model there are eight parameters that depend on the patient. A set of twelve individual PK models and the average values of the PD parameters are reported in (Ward et al., 1983; Weatherley et al., 1983) for the atracurium muscle relaxant.

An alternative model called parsimoniously parameterized model (PP) for the NMB response has been presented in (Silva et al., 2012). Even though the PP is not a physiological model, it maintains a Wiener structure, but it requires a reduced number of patient-dependent parameters. The accuracy of the PP model has been proven in (Silva et al., 2013), and in (Rocha et al., 2013) the estimation of the PP model parameters based on clinical data has been provided and a dataset of sixty patients models is reported.

Several approaches for the NMB control problem have been proposed in the literature, and different solutions have been considered to address the robustness issue (Mendonça and Lago, 1998; Lago et al., 1998; Zhusubaliyev et al., 2015; Kansanaho and Olkkola, 1996; Teixeira et al., 2014; Silva et al., 2015; Lourenço et al., 2013; Simanski et al., 2009; Almeida et al., 2017; Mason et al., 1999; Lemos et al., 2005). Despite of the high number of different approaches proposed, as mentioned in (Mendonça and Lago, 1998), it is unlikely for a given method to be globally better than all the other methods because of the process dynamic uncertainties. Further, a rigorous approach for the tuning of PID controllers for the NMB level regulation is still lacking. In this paper we propose a PID control scheme for the regulation of the NMB level after the standard bolus of the induction phase by considering the atracurium infusion as control variable. We exploit genetic algorithms in order to find the optimal PID parameters tuning that minimizes the worst-case fitness function over a population of 12 PK/PD models of patients (Ward et al., 1983; Weatherley et al., 1983). In this way, we explicitly consider the inter-patient variability in the tuning procedure. The considered objective functional comprises two competing objectives: the integrated absolute error (IAE) and the total variation (TV) of the control action. As such, a Pareto front determines the set of all the optimally tuned controllers from which we select the controller that allows the best trade-off between the control performance and the control effort. The obtained PID control is then applied to the dataset of PP models presented in (Rocha et al., 2013) in order to further verify the robustness against the patient variability.
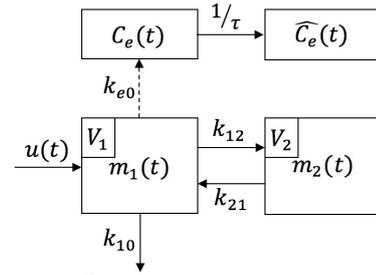

Fig. 1. Mammillary two-compartmental model for atracurium.

2. MODELS DESCRIPTION

2.1 Full PK/PD model

The neuro-muscular level achieved by the administration of atracurium is modeled by means of a Wiener PK/PD model, which is composed by a linear part in series with a static nonlinear function. The linear part of the model proposed in (Ward et al., 1983; Weatherley et al., 1983) comprises a mammillary two-compartmental model, which is used to describe the distribution and elimination of the drug, i.e., the pharmacokinetic and a pharmacodynamic fictitious effect-site compartment, that represents the lag between the plasma concentration and the drug effect. Finally, a static nonlinear function referred to as the Hill function correlates the effect-site drug concentration $C_e(t)$ and clinical effect $r(t)$. As analyzed in (Lago et al., 1998), however, the standard PK/PD model for NMB does not fit the real clinical data considering the atracurium administration. An empirical modification of the presented PK/PD model has been proposed in (Lago et al., 1998), and validated and effectively applied in (Mendonça et al., 2004). This solution consists in an augmented PD model obtained by introducing an additional effect site compartment whose concentration, $\hat{C}_e$, becomes the input for the Hill function. The overall PK/PD model is represented in Figure 1, where $u(t)$ $[\mu g\, kg^{-1} min^{-1}]$ is the atracurium infusion rate, i.e., the control variable, $m_1(t)$ and $m_2(t)$ $[\mu g/kg]$ are the drug masses in the central and peripheral compartments, V_1 and V_2 $[ml/kg]$ are the volumes of distribution, k_{12} and k_{21} $[min^{-1}]$ are the rate constants governing the transfer of the drug between the compartments, k_{10} $[min^{-1}]$ is the rate constant governing the elimination of the drug, $C_e(t)$ $[\mu g/ml^{-1}]$ and $\hat{C}_e(t)$ are $[\mu g/ml^{-1}]$ are the effect-site compartment and the augmented effect-site compartment concentrations, respectively, and k_{e0} $[min^{-1}]$ and τ $[min^{-1}]$ are the corresponding equilibration rate and time constants. The state equations for the two-compartment PK model are

$$\frac{dm_1(t)}{dt} = -(k_{10} + k_{12})m_1(t) + k_{21}m_2(t) + u(t)$$
$$\frac{dm_2(t)}{dt} = k_{12}m_1(t) + k_{21}m_2(t). \tag{1}$$

The transfer and elimination rate constants k_{ij} for $i \neq j$ are patient dependents. They are derived from the values of the volume of distribution of the central compartment V_1 $[ml/kg]$, from the clearance C_l $[ml/min/kg)]$ normalized with respect to the patient weight, and from the half lives times $t_{1/2}^\alpha$ $[min]$ and $t_{1/2}^\beta$ $[min]$:

Id	Weight [kg]	$V_1[ml/kg]$	$C_l[ml/min/kg]$	$t_{1/2}^{\alpha}[min]$	$t_{1/2}^{\beta}[min]$
1	65	46	5.0	2.8	21.7
2	66	42	4.9	1.6	23.1
3	58	47	6.0	1.7	16.9
4	89	34	5.7	1.3	21.7
5	80	25	4.8	1.4	20.4
6	63	69	6.5	2.3	19.8
7	80	78	6.2	2.2	19.8
8	97	43	4.4	2.0	19.0
9	91	28	5.5	1.0	17.8
10	79	51	5.5	2.7	22.4
11	69	53	4.9	2.4	16.1
12	66	76	6.4	3.3	20.6

Table 1. PK parameters of the considered patients models (Ward et al., 1983).

$$k_{10} = \frac{C_l}{V_1} \quad k_{21} = \frac{\alpha\beta}{k_{10}} \quad k_{12} = \alpha + \beta - k_{10} - k_{21}, \quad (2)$$

where

$$\alpha = \frac{log(2)}{t_{1/2}^{\alpha}} \qquad \beta = \frac{log(2)}{t_{1/2}^{\beta}}. \quad (3)$$

The output of the PK model is atracurium concentration in blood plasma given by

$$C_p(t) = \frac{m_1(t)}{V_1}. \quad (4)$$

In (Ward et al., 1983), the values of the parameters of the PK model for atracurium for twelve nominal patients representative of a wide range of population are reported. The parameters values are shown in Table 1. The relationship between the plasma concentration and the effect-sites concentrations $C_e(t)$ and $\hat{C}_e(t)$ are:

$$\frac{dC_e(t)}{dt} = k_{e0}(C_p(t) - C_e(t))$$
$$\frac{d\hat{C}_e(t)}{dt} = \frac{1}{\tau}(C_e(t) - \hat{C}_e(t)), \quad (5)$$

where k_{e0} $[min^{-1}]$ and τ $[min]$ are also patient-dependent. However, in this paper we consider k_{e0} fixed at 0.1 $[min^{-1}]$, which is regarded as a suitable average value to represent the patient PD (Weatherley et al., 1983). According to the assumption of average PD model parameters, also the time constant τ is fixed. A suitable value of τ is determined by calculating the difference between the average settling time $\bar{T}_{10_{std}}$ to reach a NMB level of 10% for the standard 12 patients in Table 1 and the one, denoted as $\bar{T}_{10_{real}}$, obtained in the real cases studied in (Rocha et al., 2013):

$$\tau = |\bar{T}_{10_{std}} - \bar{T}_{10_{real}}| = 6.2670 \ [min]. \quad (6)$$

The Hill function that correlates the additional effect-site drug concentration $\hat{C}_e(t)$ and clinical effect $r(t)$ is

$$r(t) = \frac{100 \cdot C_{50}^{\gamma}}{C_{50}^{\gamma} + \hat{C}_e^{\gamma}(t)}, \quad (7)$$

where the C_{50} $[\mu g/ml^{-1}]$ and γ (dimensionless) are also patient-dependent and represent, respectively, the necessary concentration of the drug to reach the half maximal effect and the steepness of the curve, i.e, the receptiveness of the patient to the drug. The clinical effect $r(t)$ [%] corresponds to the percentage of NMB level detected by the TOF sensor. In this paper, according to (Weatherley et al., 1983), we consider the average values of C_{50} and γ, which are 0.625 and 4.25 respectively.
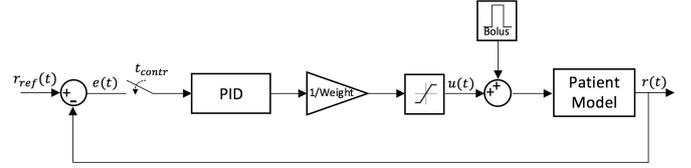

Fig. 2. Proposed PID control structure for the administration of *atracurium*

2.2 PP reduced model

Mainly due to the high number of parameters of the standard PK/PD model, a new minimally parametrized parsimonious model has been presented in (Silva et al., 2012) for NMB level description. It maintains a Wiener model structure, composed by a linear part in series with a nonlinear Hill function, but it has a reduced number of patient-dependent parameters. In (Silva et al., 2013), a comparison with the full PK/PD model has been performed and the accuracy of the PP model has been proven. The linear part of the PP model is a third-order system that relates the drug infusion $u(t)$ $[\mu g \, kg^{-1} min^{-1}]$ to the state variable $x_3(t)$ $[\mu g \, ml^{-1}]$, according to the following equations

$$\frac{dx_1(t)}{dt} = -k_3\alpha x_1(t) + k_3\alpha u(t)$$
$$\frac{dx_2(t)}{dt} = k_2\alpha x_1(t) - k_2\alpha x_2(t) \quad (8)$$
$$\frac{dx_3(t)}{dt} = k_1\alpha x_2(t) - k_1\alpha x_3(t),$$

where $x_1(t)$, $x_2(t)$, $x_3(t)$ are the state variables, $k_1 = 1$, $k_2 = 4$, $k_3 = 10$ are fixed parameters (Silva et al., 2012) and α is the only patient-dependent parameter. Finally, the state variable $x_3(t)$ is related to the output of the model, which is the NMB level $r(t)$, through the Hill equation

$$r(t) = \frac{100 \cdot \bar{C}_{50}^{\gamma}}{\bar{C}_{50}^{\gamma} + x_3^{\gamma}(t)}. \quad (9)$$

According to (Alonso et al., 2008),the parameter $\bar{C}_{50}$ in the PP model can be fixed to the value 3.2425 $[\mu g \, ml^{-1}]$ so that α and γ become the only free parameters, reducing the number of patient-dependent parameters form 8 to 2. In (Rocha et al., 2013) the estimation of the PP model parameters based on clinical data has been performed and the dataset of 60 patients models therein developed is considered for the purpose of this paper.

3. PID CONTROL ARCHITECTURE

The proposed PID control structure is shown in Figure 2, where $r_{ref}(t)$ is the set-point signal, that is, the desired NMB level $r(t)$ of the patient. The reference level is usually fixed to 10%, according to the clinical practice. The signal $e(t)$ is the error variable and, as aforementioned, $u(t)$ is the atracurium infusion rate. A standard drug bolus of 500 $[\mu g/kg]$ provides the initial induction phase. The transition between the induction phase and the maintenance phase is handled by the switch on $e(t)$ that, after a predefined time t_{contr} of 20 $[min]$ from the initial bolus, enables the PID controller. The value of t_{contr}, that is, duration of the induction phase, has been decided based on the average clinical effect-time of the atracurium bolus. After t_{contr}, the PID algorithm computes the control action in order

to achieve and maintain the set-point value. The PID controller is expressed in ideal form:

$$C(s) = K_p \left(1 + \frac{1}{T_i s} + \frac{T_d s}{1 + \frac{T_d}{N} s} \right), \qquad (10)$$

where K_p is the proportional gain, T_i is the integral time constant, T_d is the derivative time constant and T_d/N, with $N = 10$, is the filter time constant that renders the controller proper. Actually, the PID controller is implemented in discrete form by considering a sampling period of 1/3 [min]. The choice of the sampling period is related to the minimum time interval allowed by the TOF but it is in any case acceptable by considering the time constants of system. An anti-windup method has also been implemented by using a conditional integration technique (Visioli, 2006). Further, the derivative action has been applied only to the feedback signal to avoid the derivative kick phenomenon. The output of the PID controller is normalized with respect to the patient weight and bounded by a saturation block, which represents the infusion rate bounds of a standard pump (Graseby 3400, Smiths Medical, London, UK). The lower saturation corresponds to the zero infusion while the maximum rate is 200 [mg/min] for atracurium 10 [mg/ml].

4. TUNING OF THE CONTROLLER PARAMETERS

The proposed control architecture requires the tuning of the PID controller parameters K_p, T_i and T_d. The procedure should consider the control specifications defined by the clinical practice. After the induction phase, handled by the standard atracurium bolus, the set-point NMB level of 10% has to be achieved as fast as possible without excessive overshoots or undershoots. During the maintenance phase, $r(t)$ has to be maintained as stable as possible, avoiding oscillations on the process output. The variations of the control action have to be minimized to obtain a stable drug infusions, that allows the clinical practice of atracurium administration to be mimicked and reduces the stress of the actuator. The typical tuning rules used for PID controller tuning, however, are not suitable for the NMB control problem because of the process complexity. To overcome this limitation, the parameters K_p, T_i and T_d have been tuned by numerically solving an optimization problem via genetic algorithms (Mitchell (1998)), which are capable to determine the global optimum of an optimization problem in a stochastic sense. In particular, an optimization function composed by two terms has been selected to comply with the required trade-off between control performance and control effort. The chosen indexes are the integrated absolute error (IAE) and the total variation of the control action (TV):

$$IAE = \int_0^\infty |r_{ref}(t) - r(t)| dt$$
$$TV = \sum_{k=0}^\infty |u_k - u_{k-1}|, \qquad (11)$$

where u_k is the current control action value and u_{k-1} is the previous one. The optimization function is defined as

$$J(\lambda) = IAE + \lambda TV, \qquad (12)$$

where λ obviously weights the contribution of the TV on the performance. The optimal tuning of the controller is
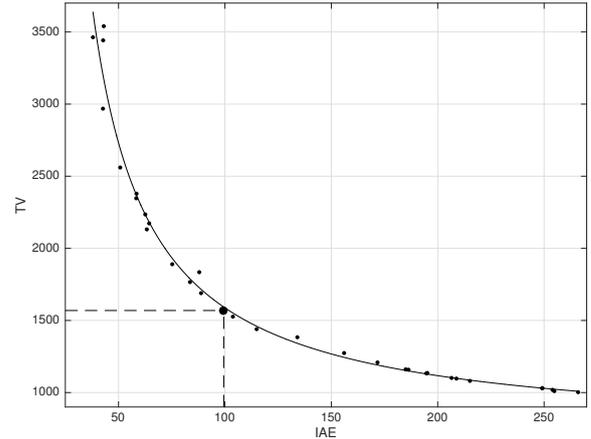

Fig. 3. Pareto curve for optimized tuning with different λ values

finally obtained by solving the following min-max optimization problem

$$\min_{k_p, T_i, T_d} \max_{k \in \{1,...,12\}} J_k(K_p, T_i, T_d; \lambda) \qquad (13)$$

where $J_k(K_p, T_i, T_d; \lambda)$ denotes the performance index obtained for the k-th patient in Table 1. In other words, the genetic algorithm fitness function, which is calculated from the t_{contr} time instant on, considers the worst-case of the 12 patient models at each iteration of the algorithm in order to explicitly take into account the robustness porblem in the tuning process. As such, the entire set of PK patients parameters shown in Table 1 and the average parameters of the augmented PD empirical model have been considered for the tuning. Several optimizations have been performed with different values of λ in the range $[0.01, 0.5]$, obtaining the Pareto curve represented in Figure 3, where each dot represents the optimal tuning for a specific λ. The influence of λ on the control is clearly observable in Figure 4, where simulations on patient 1 are shown. In general, with small values of λ, the IAE index has the major contribution in the fitness function and overshoots and settling times of the process output are minimized by increasing the aggressiveness of the controller, which results in an higher control effort. On the contrary, high values of λ increase the contribution of TV in the fitness function delivering a smoother control action, payed by a decrement of the tracking performance. Finally, to select the controller that provides the best trade-off between the control performance and the control effort the maximum curvature point of the Pareto curve (marked with the biggest dot in Figure 3) is chosen. It represents the optimization performed with λ=0.3, and the corresponding optimal PID parameters are shown in Table 2.

Parameter	Value
K_p	64.9721 $[\mu g/min]$
T_i	17.5456 $[min]$
T_d	6.3897 $[min]$

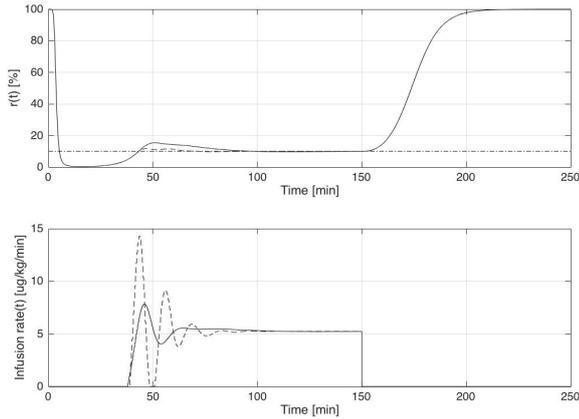Table 2. Optimal PID parameters tuning obtained with λ=0.3.

Fig. 4. Simulations on patient 1 with λ=0.01 (dashed line)
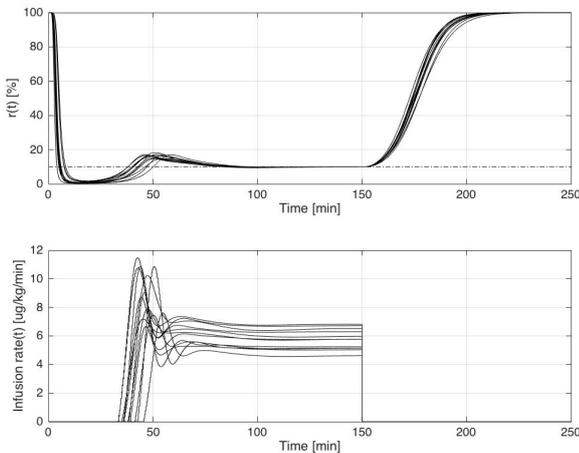and with λ=0.5 (solid line)

Fig. 5. Simulated responses of the 12 empirical models

5. SIMULATION RESULTS AND DISCUSSION

In this section the simulation results of the proposed
PID tuning are shown. A first test has been performed
on the empirical models of the 12 patients. This test is
necessary to evaluate the controller performance with the
proposed tuning procedure and consists of an induction
phase followed by a maintenance phase of 150 [min]. Then,
the controller is switched off and the NMB level naturally
increases (without using antagonist drugs). The results are
shown in Figure 5. The NMB is induced with the initial
standard bolus, as mentioned in Section 3. As it possible
to see in the top plot, the NMB levels of all patients
exhibits an undershoot. The controller initiate to regulate
the drug infusion from t_{contr}, when $r(t)$ is still below the
set-point. Therefore the atracurium infusions, shown in the
bottom plot, start increasing after t_{contr}, when the NMB
levels of the patients, naturally increasing, crosses the set-
point value. The performance is satisfactory for the clinical
practice: the NMB levels attain the set-point reference and
exhibit limited overshoots and acceptable settling times.
The control actions have smooth trends with bounded
oscillations that satisfy the technical specification on the
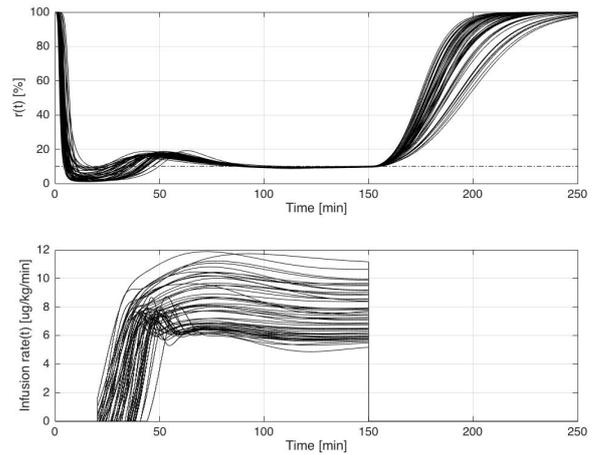control effort. The proposed control structure has been

Fig. 6. Simulated responses of the database of PP models

also tested on the PP models database reported in (Rocha
et al., 2013), to verify the inter-patient robustness, which
is an essential characteristic for the control of NMB. The
results are shown in Figure 6. The control system is robust
with respect to the inter-patient variability as all the
clinical specifications are always fulfilled. Overshoots, set-
tling times and control variables are also comparable with
those obtained with the 12 nominal patients. This result
validates the tuning procedure of the proposed control
structure that guarantees a satisfactory performance also
with models that are estimated from real clinical data.

6. CONCLUSIONS

In this paper we have presented a PID control algorithm
for the NMB level automatic regulation. The tuning of the
controller is obtained by solving a min-max optimization
based on a two-term multi-objective optimization func-
tion that considers the clinical specifications. A genetic
algorithm has been successfully employed to solve the
optimization problem, providing a suitable tuning of the
PID parameters. Simulation results have shown that the
methodology guarantees a satisfactory performance and
provides the required inter-patient robustness in spite of
the simplicity of the control architecture.

ACKNOWLEDGEMENTS

REFERENCES

Almeida, J., Mendonça, T., Rocha, P., and Rodriguesc, L.
(2017). Controller design for neuromuscular blockade
level tracking based on optimal control. *Control Engi-
neering Practice*, 59:151–158.
Alonso, H., Mendonça, T., and Rocha, P. (2008). A hybrid
method for parameter estimation and its application to
biomedical systems. *Computer Methods and Programs
in Biomedicine*, 89:112–122.

Dumont, G.A., Martinez, A., and Ansermino, J.M. (2009). Robust control of depth of anesthesia. *International Journal of Adaptive Control and Signal Processing*, 23, 435–454.

Jaklitsch, R. and Westenskov, D. (1987). A model based self adjusting two-phase controller for vecuronium-induced muscle relaxion during anesthesia. *IEEE Transactions on Biomedical Engineering*, 34:583–594.

Kansanaho, M. and Olkkola, K. (1996). Performance assessment of an adaptive model-based feedback controller: comparison between atracurium, mivacurium, rocuronium and vecuronium. *Journal of Clinical Monitoring and Computing*, 13(4): 217–224.

Lago, P., Mendonça, T., and Gonçalves, L. (1998). On-line autocalibration of a PID controller of neuromuscular blockade. In *Proceedings IEEE International Conference on Control Applications*, 363–367.

Lemos, J.M., Magalhães, H., Mendonça, T., and Dionísio, R. (2005). Control of neuromuscular blockade in the presence of sensor faults. *IEEE Transactions on Biomedical Engineering*, 52(11):1902–1911.

Liu, N., Le Guen, M., Benabbes-Lambert, F., Chazot, T., Trillat, B., Sessler, D.I., and Fischler, M. (2012). Feasibility of closed-loop titration of propofol and remifentanil guided by the spectral m-entropy monitor. *Anesthesiology*, 116, 286–295.

Lourenço, J.M., Lemos, J.M., and Marques, J.S. (2013). Control of neuromuscular blockade with Gaussian process models. *Biomedical Signal Processing and Control*, 8(3):244–254.

Mason, D., Ross, J., Edwards, N., Linkens, D., and Reilly, C. (1999). Self-learning fuzzy control with temporal knowledge for atracurium-induced neuromuscular block during surgery. *Computers and Biomedical Research*, 32(3):187–197.

McGranth, C. and Hunter, J. (2006). Monitoring of neuromuscular block. *Continuing Education in Anaesthesia Critical Care and Pain*, 6(1):7–12.

Mendonça, T. and Lago, P. (1998). PID control strategies for the automatic control of neuromuscular blockade. *Control Engineering Practice*, 6(10):1225–1231.

Mendonça, T., Lemos, J.M., Magalhães, H., Rocha, P., and Esteves., S. (2009). Drug delivery for neuromuscular blockade with supervised multimodel adaptive control. *IEEE Transactions on Control Systems Technology*, 17(6):1237–1244.

Mendonça, T., Magalhães, H., Lago, P., and Esteves, S. (2004). Hipocrates: a robust system for the control of neuromuscular blockade. *Journal of Clinical Monitoring and Computing*, 18:265–273.

Merigo, L., Beschi, M., Padula, F., Latronico, N., Paltenghi, M., and Visioli, A. (2017). Event-based control of depth of hypnosis in anesthesia. *Computer Methods and Programs in Biomedicine*, 147, 63–83.

Mitchell, M. (1998). *An Introduction to genetic algorithms*. MIT press, Cambridge, USA.

Nascu, I., Krieger, A., Ionescu, C., and Pistikopoulos, E. (2015). Advanced model-based control studies for the induction and maintenance of intravenous anesthesia. *IEEE Transactions on Biomedical Engineering*, 62, 832–841.

Padula, F., Ionescu, C., Latronico, N., Paltenghi, M., Visioli, A., and Vivacqua, G. (2016). Inversion-based propofol dosing for intravenous induction of hypnosis. *Communications in Nonlinear Science and Numerical Simulation*, 39, 481–494.

Padula, F., Ionescu, C., Latronico, N., Paltenghi, M., Visioli, A., and Vivacqua, G. (2017). Optimized PID control of depth of hypnosis in anesthesia. *Computer Methods and Programs in Biomedicine*, 144, 21–35.

Rocha, C., Mendonça, T., and Silva, M.M. (2013). Modelling neuromuscular blockade: a stochastic approach based on clinical data. *Mathemaical and Computer Modelling of Dynamical Systems*, 19:540–556.

Silva, M.M., Lemos, J.M., Coito, A., Costa, B.A., Wigren, T., and Mendonça, T. (2013). Local identifiability and sensitivity analysis of neuromuscular blockade and depth of hypnosis models. *Computer Methods Programs in Biomedicine*, 113(1):23–36.

Silva, M.M., Paz, L., Wigren, T., and Mendonça, T. (2015). Performance of an adaptive controller for the neuromuscular blockade based on inversion of a Wiener model. *Asian Journal of Control*, 17(4):1136–1147.

Silva, M.M., Wigren, T., and Mendonça, T. (2012). Nonlinear identification of a minimal neuromuscular blockade model in anaesthesia. *IEEE Transactions on Control Systems Technology*, 20(1):181–188.

Simanski, O., Janda, M., Schubert, A., Bajorat, J., Hofmockel, R., and Lampe., B. (2009). Progress of automatic drug delivery in anaesthesia: the rostock assistant system for anaesthesia control RAN. *International Journal of Adaptive Control and Signal Processing*, 23(5):504–521.

Soltesz, K., Hahna, J.O., Hagglund, T., Dumont, G.A., and Ansermino, J.M. (2013). Individualized closed-loop control of propofol anesthesia: a preliminary study. *Biomedical Signal Processing and Control*, 8, 500–508.

Struys, M.M., Smet, T.D., Versichelen, L.F., Velde, S.V.D., den Broecke, R.V., and Mortier, E.P. (2001). Comparison of closed-loop controlled administration of propofol using bispectral index as the controlled variable versus standard practice controlled administration. *Anesthesiology*, 95, 6–17.

Teixeira, M., Mendonça, T., Rocha, P., and Rabio, R. (2014). Automatic control of the NMB level in general anaesthesia with a switching total system mass control strategy. *Journal of Clinical Monitoring and Computing*, 28(6):501–512.

Visioli, A. (2006). *Practical PID Control*. Springer, London (UK).

Ward, S., Neil, S., Weatherley, B., and Corall, M. (1983). Pharmacokinetics of atracurium besylate in healthy patients (after a single i.v. bolus dose). *British Journal of Anaesthesia*, 55:113–116.

Weatherley, B., Williams, S., and Neill, E. (1983). Pharmacokinetics, pharmacodynamics and dose-response relationships of atracurium administered i.v. *British Journal of Anaesthesia*, 55:39s–45s.

Zhusubaliyev, Z.T., Medvedev, A., and Silva, M.M. (2015). Bifurcation analysis of PID-controlled neuromuscular blockade in closed-loop anesthesia. *Journal of Process Control*, 25:152–163.