Hipocrates: a robust system for the control of neuromuscular blockade

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Abstract.

Objective: Development of an automatic system (software package *Hipocrates*) for the control of neuromuscular blockade by continuous infusion of the non-depolarising types of muscle relaxant drugs presently used in anaesthesia, namely *atracurium, cisatracurium, vecuronium* and *rocuronium*. **Methods:** *Hipocrates* incorporates control strategies based upon classical, adaptive and robust control, as well as a wide range of noise reduction techniques and on-line adaptation to patient-specific characteristics. Therefore, the system provides strong robustness to inter- and intra-individual variability of the patients responses or unexpected circumstances and adaptation to the individual requirements. **Results:** The control system is easy to set up and to use in a clinical environment. It consists of a portable PC computer, a Datex AS/3 NMT sensor and a B|Braun compact perfusion pump. In the simulation mode the software package incorporates sophisticated generation of pharmacokinetic/pharmacodynamic models driven by simulated drug administration regimes (*bolus*, continuous infusion and a combination of both). **Conclusions:** *Hipocrates* is an advanced stand-alone application for the control of neuromuscular blockade with a friendly graphic interface. It has been extensively validated and it can be used on patients undergoing surgery as well as for simulation studies. Therefore *Hipocrates* also provides an excellent environment for education and training purposes.

Keywords: Computer system, biomedical simulation, MATLAB tool, neuromuscular blockade control

1. Introduction

Muscle relaxant drugs are frequently given during surgical operations. The non-depolarising types of drugs act by blocking the neuromuscular transmission, therefore producing muscle paralysis. The neuromuscular blockade level is measured from an evoked EMG obtained at the hand

by electrical stimulation. The control of the neuromuscular blockade by the continuous infusion of a muscle relaxant provides a good illustration of the main features and inherent constraints associated with the control of physiological variables for optimal therapy. The situation is characterized by a large uncertainty of the dynamic behaviour of the system under control and the need for a very high degree of reliability and robustness. Hence, the control system must present a reliable adaptation to the individual characteristics and requirements of a patient.

Figure 1 represents a standard block diagram for the automatic control of neuromuscular blockade by continuous infusion. The theoretical advances in the tuning of controllers characterized by the presence of non-linearities and large uncertainty have led to the development, over the past 15 years, of quite different control schemes [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22]. These range from simple on-off type controllers [1] to intelligent control schemes based on a variety of methods, namely adaptive, model-based, fuzzy and robust. Many authors emphasize the benefits of model-based closed-loop systems for the control of neuromuscular blockade, since the published pharmacokinetic/pharmacodynamic model was assumed to accurately reflect the actual behaviour of the system. Therefore, using the published drug model, a variety of advanced feedback control designs to derive candidate controllers has been proposed [2, 3, 4, 5, 6, 7]. However, only a few systems have proved to work satisfactory under clinical situations, since in operating theater the patient's response has high nonlinearity and individual patient dose requirements may present a high variability (e.g. with atracurium it may vary fivefold [8]). In order to overcome some of these drawbacks, several authors decided to explore fuzzy logic based methods [8, 9, 10, 11]. Fuzzy logic control is represented, from a structural point of view, by a set of rules built via guidelines normally provided by an experienced operator well aware of the process under study. Consequently, the controller looks at the process as a black box and does not need an accurate model description. A clinical evaluation of a fuzzy-logic controller applied to muscle relaxation using atracurium was performed in [9]. Nevertheless, this particular controller could easily be implemented as a simple PID without the need for fuzzy logic. Besides, it overlooks the potential for fuzzy logic controllers to provide a smooth and arbitrary non-linear control. This fact was the main driving behind the introduction of self-learning fuzzy controllers, which could modify the fuzzy rule base on-line so as to match the needs of each individual patient, which may change during the course of an operation [8, 10, 11].

More oriented control techniques incorporating on-line adaptation to individual patient's characteristics [12, 13, 14] extracted from the initial *bolus* given in the beginning of anaesthesia have also been developed. Parameters deduced from statistical techniques are used as predictors for the controller parameters, allowing the on-line autotuning of a PID controller. The robustness of these techniques in order to characterize the patients individual responses to the *bolus* has been firmly established [14].

Recently, adaptive switching supervisory control has been proposed to tackle the problem [15, 16]. In this approach, a broad bank of different models are considered along with an equal number of candidate controllers, each of them being tuned to one of the given models. A candidate model, and hence a controller, is selected by a supervisory in accordance with a logic which chooses the model associated to a certain cost function. An extensive simulation study proves the ability of the method to deal with this particular application, and the clinical cases obtained so far strongly validate this new approach.

However, attending to the characteristics of these systems, it is unlike that a single method could prove to be superior in every situation. Thus, extensive comparative studies between control strategies are essential.

Hipocrates is an advanced software tool developed in MATLAB for the control of neuromuscular blockade to be used on patients undergoing anaesthesia. In the surgery room the control system consists of a portable PC computer, a Datex AS/3 NMT sensor and a B|Braun compact perfusion pump. The package incorporates a variety of control strategies for the control of neuromuscular blockade by continuous infusion of the non-depolarising types of muscle relaxant drugs presently used in anaesthesia, namely *atracurium, cisatracurium, vecuronium* and *rocuronium*. *Hipocrates* may also be used as an advanced simulation tool for the test and comparison of different control strategies, under a wide range of situations. Therefore it provides an excellent environment for education and training purposes. It is reasonable to expect that this package and the described methodology will encourage the clinical application of closed-loop drug infusion systems, so that clinical staff and patients may receive the benefits of closed-loop drug therapy.

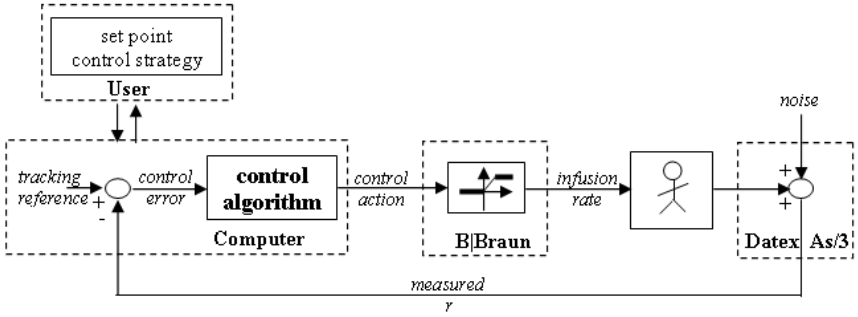

Figure 1. Automatic control scheme for a drug delivery system by continuous infusion.

2. Patients and Methods

2.1. An empirical model for neuromuscular blockade

The dynamic response of the neuromuscular blockade may be modelled by a linear pharmacokinetic model relating the drug infusion rate $u(t)$ $(\mu g\, kg^{-1}\, min^{-1})$, with the plasma concentration $c_p(t)$ $(\mu g\, ml^{-1})$ [23, 24], and a nonlinear model relating $c_p(t)$ to the induced pharmacodynamic response, $r(t)$ (%) [25]. The pharmacokinetic model for *atracurium* may be described by the following linear system of state equations,

$$\dot{x}_i(t) = -\lambda_i x_i(t) + a_i u(t) \quad i = 1, 2, \tag{1}$$

$$c_p(t) = \sum_{i=1}^{2} x_i(t) \tag{2}$$

where a_i $(kg\, ml^{-1})$, λ_i (min^{-1}) are patient dependent parameters. The pharmacodynamic effect for *atracurium* may be modelled by the Hill equation,

$$r(t) = \frac{100 C_{50}^s}{C_{50}^s + c_e^s(t)} \tag{3}$$

The variable $r(t)$, normalized between 0 and 100, measures the level of the neuromuscular blockade, 0 corresponding to full paralysis and 100 to full muscular activity. The plasma concentration $c_p(t)$ is related to $c_e(t)$ $(\mu g\, ml^{-1})$ by

$$\dot{c}_e(t) = -\lambda c_e(t) + \lambda c_p(t) \tag{4}$$

C_{50} ($\mu g\, ml^{-1}$), s and λ (min^{-1}) are also patient-dependent parameters.

The detailed analysis of a large set of clinical cases (Figure 2) indicates that the variability of the patient's responses is much wider than inferred by the pharmacokinetic/pharmacodynamic data available in the literature [24, 25]. The most obvious differences are the much larger lag and dispersion of the observed responses. An empirical model for the pharmacodynamic response of *atracurium* has been developed [12]. The alteration has been made on the linear part of the system by the inclusion of a first order system,

$$g(s) = \frac{1/\tau}{s + 1/\tau} \tag{5}$$

in a series connection. The time constant τ (min) is assumed to be a random variable independent of the remaining pharmacokinetic / pharmacodynamic parameters. Figure 3 shows the results for a family of N non-linear dynamic models, M_j, obtained assuming an uniform distribution for τ on the interval [0,3.5] minutes and a multidimensional log-normal distribution for the remaining parameters. This alternative model replicates well the patient's responses and has lead to further development of robust control strategies for clinical environment.

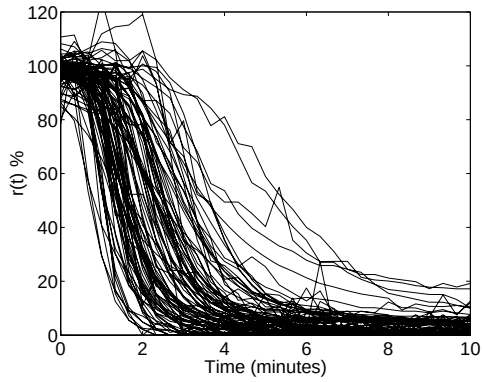

Figure 2. The responses of 100 patients induced by a *bolus* of 500 $\mu g\, kg^{-1}$ of *atracurium*. In a few cases high noise level is present in the measurement of r(t)%.

2.2. Methods for autocalibration of the controller

A digital PID controller incorporating several modifications to accommodate the characteristics of neuromuscular blockade was developed [22]. For clinical reasons the patient must undergo an initial *bolus* dose

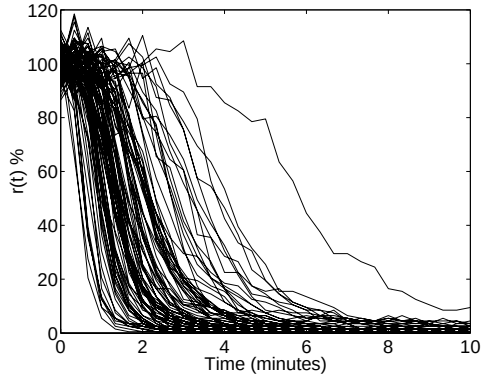

Figure 3. Simulated responses (100) induced by a *bolus* of 500 $\mu g\, kg^{-1}$ of *atracurium* with added measurement noise.

in order to induce total muscle relaxation in a very short period of time (usually shorter than 5 minutes). Since the responses of the patients to the initial *bolus* are fairly different, they may be used to improve the individual tuning of the controller. Methods for on-line characterization of the patient *bolus* response and for the on-line tuning of PID controller parameters to the individual patient dynamics have been developed [12, 13, 14]. The parameters of PID controller (namely the proportional gain, the derivative gain an the integral time constant) have been obtained from the L and R parameters (see Appendix) deduced from the Ziegler-Nichols step response method [26], applied to the empirical model bank [12]. The subsequent tuning of the controller to the dynamics of a patient undergoing surgery is performed by adjusting the R and L values using multiple linear regression techniques with predictor variables extracted from the observed initial *bolus* response.

Accordingly, let $\mathbf{\Psi}(p \times 1)$ denote the predictor variables extracted from the observed *bolus* response. Then, the controller parameters $\mathbf{\Phi}(n \times 1)$ are estimated from the regression equation,

$$\mathbf{\Phi} = \boldsymbol{\alpha}.\mathbf{\Psi} + \boldsymbol{\beta} + \boldsymbol{\varepsilon} \tag{6}$$

where $\boldsymbol{\alpha}(n \times p)$ and $\boldsymbol{\beta}(n \times 1)$ are matrices of unknown parameters to be determined and $\boldsymbol{\varepsilon}(n \times 1)$ is a vector of random error terms.

The parameters of the *bolus* response which has been found to perform well for that purpose are based on shape parameters, namely $T50$, S and P (Figure 4) and on principal component analysis (PCA) [14]. Table I summarizes the results obtained in terms of the % of variation explained by the linear regression model (6). $T50$ is the elapsed time between the *bolus* administration and the time the response $r(t)$ becomes less than 50%, S is a slope parameter, P is a persistence parameter,

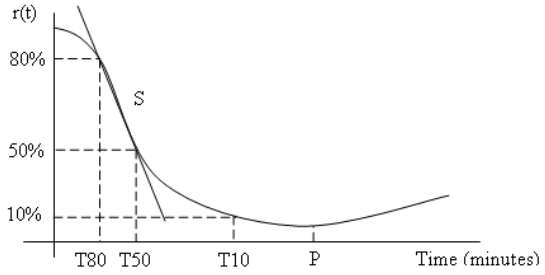

Figure 4. Parameters used to characterize the neuromuscular blockade response $r(t)$ induced by a *bolus* administered at $t = 0$.

since it describes the duration of the *bolus* effect on the patient and $(a_i)_{i=1}^{k}$ are the k principal components computed from the simulated response with and without added noise. The robustness of the on-line tuning method has been firmly established, namely in the presence of neuromuscular blockade measurement noise.

Table I. % of variation explained for linear regression models

	Without noise		**With noise**	
Predictors	**L**	**1/R**	**L**	**1/R**
T50 + S + P	95	70	94	69
a_1,...,a_3 + P	95	71	94	70

2.3. Multiple Model Switching Control

In order to tackle the high degree of uncertainty in neuromuscular blockade model knowledge, one possibility is to resort to switched multiple model control [15]. The basic structure of a supervisor based switched multiple model controller is seen in Figure 5, as described in [27, 28]. It consists of a bank of controllers C_1, ..., C_N, each one designed to match the plant models M_1, ..., M_N. This set of models is assumed to "cover" the possibilities of the real plant. In order to select which controller best matches the real plant, the principle according to which the best predictive performance model implies the best controller performance is applied. For evaluating the model predictive performance, the output

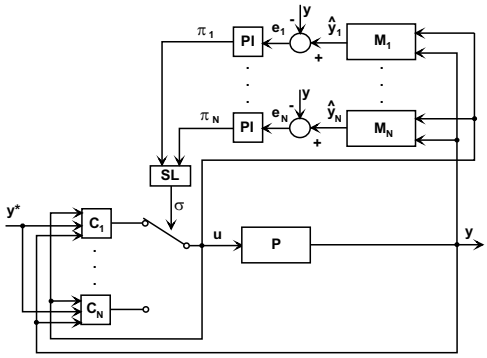

Figure 5. Supervisory switched multiple model controller.

$\hat{y}_i(t)$ of each model M_i is compared with the actual plant output $y(t)$ in order to build a prediction error given at each time t by

$$e_i(t) = \hat{y}_i(t) - y(t) \tag{7}$$

The PI blocks compute then the performance indexes $\pi_i = \int_0^t |e_i(t)|^2 dt$, $i = 1, ..., N$ which provide a measure of the prediction error power of each model. The switching logic block SL selects the index σ of the controller to apply to the plant. This selection is given by the value of i corresponding to the least value of π_i, but ensuring that, once a controller is applied to the plant, it remains so for a minimum amount of time τ_D (i.e. "dwell time" condition, which prevents high frequency commutation among controllers and ensures stability). A method for the implementation of on-line multiple model switching control has been proposed and evaluated [15]. In order to achieve good performance, restrictions amenable of practical implementation, based on robust stability criterion, are imposed [15].

3. Results

Hipocrates is a software tool [29, 30] for the control of neuromuscular blockade to be used on patients undergoing anaesthesia, as well as for simulation studies. The package has been developed in MATLAB using the current features on graphic user interfaces and covers two main objectives: control in a clinical environment and an advanced simulation tool for the test and comparison of different controllers under a variety of circumstances and muscle relaxant drugs, namely *atracurium, cisatracurium, vecuronium and rocuronium.*

At the present stage of development the package incorporates several noise reduction techniques coupled with three different control strategies:

- digital PID (with several modifications) [22]
- on-line auto-calibrated PID [12, 13]
- robust multiple model switching PID [15].

3.1. Control on Clinical Environment

The control system is easy to set up and to use in a clinical environment (Figure 6). It consists of:

- *a sensor*: the Datex AS/3 Neuromuscular Transmission monitor to measure the neuromuscular blockade level (control is based on the T1 response, i.e. the first EMG response).
- *a delivery system*: Perfusion compact B|BRAUN with Dianet interface, and
- *a computer*: PC compatible computer with two serial ports for connecting the NMT sensor and the perfusion pump.

The graphical interface includes a variety of different options namely those related with the operating mode, the set point, the control strategies and the filtering methods. Final report files (*.eps* and *.xls*) are automatically created. Figure 7 shows the control module interface for a real case using *Hipocrates* to control the neuromuscular blockade by continuous infusion of *atracurium* (fixed PID followed by autocalibrated PID through T50 value) and Figure 8 shows the correspondent *eps* report file.

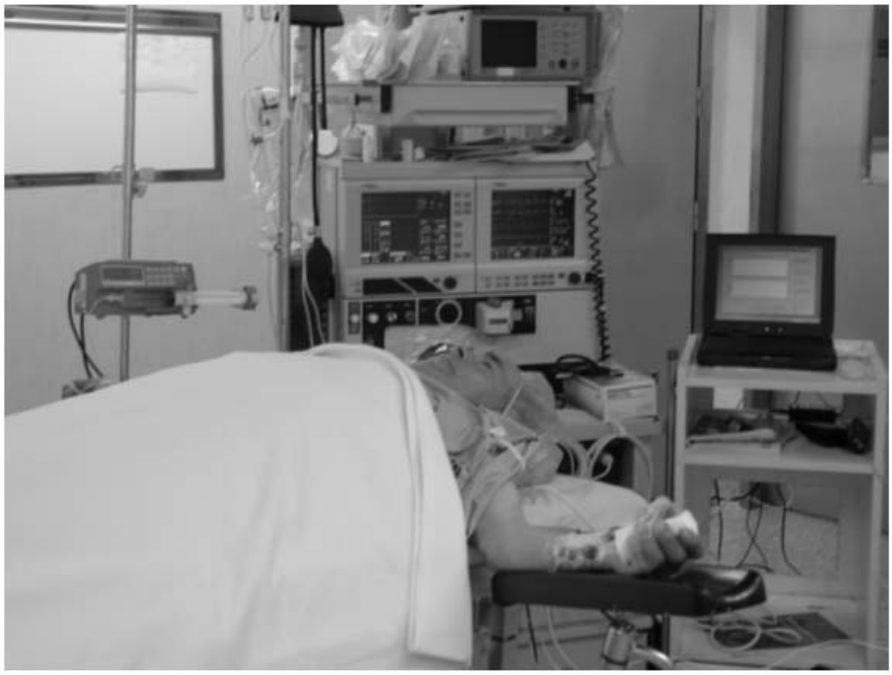

Figure 6. This photograph was taken at surgery room from Hospital Geral de Santo António, just before induction of anaesthesia. The computer (right side of the picture) is connected to the Datex AS3 NMT (center) and to the B|Braun perfusor (on the left side).

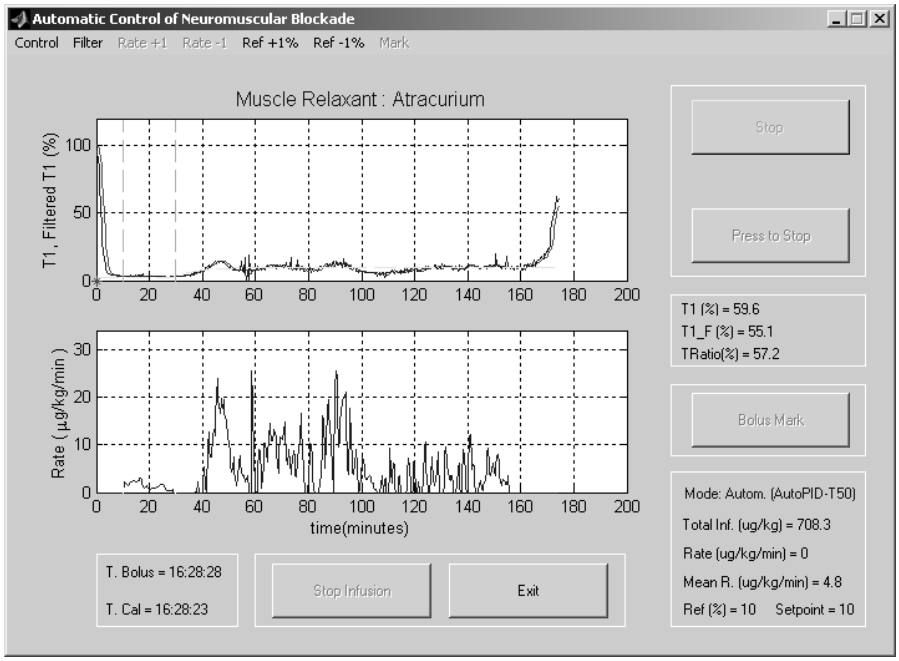

Figure 7. Control module interface (case ATR-22-May-2002 with fixed PID followed by autocalibrated PID through T50 value). The set point, the control strategy and the noise reduction technique can be selected and/or modified by the user through the toolbar and the graphic interface. The window shows all relevant information, namely the current values for T1=r(t)% (real and filtered), Tratio (T4/T1), infusion rate ($\mu g\, kg^{-1}\, min^{-1}$), the mean infusion rate ($\mu g\, kg^{-1}\, min^{-1}$), the total administered dose ($\mu g\, kg^{-1}$) and the set point (%).

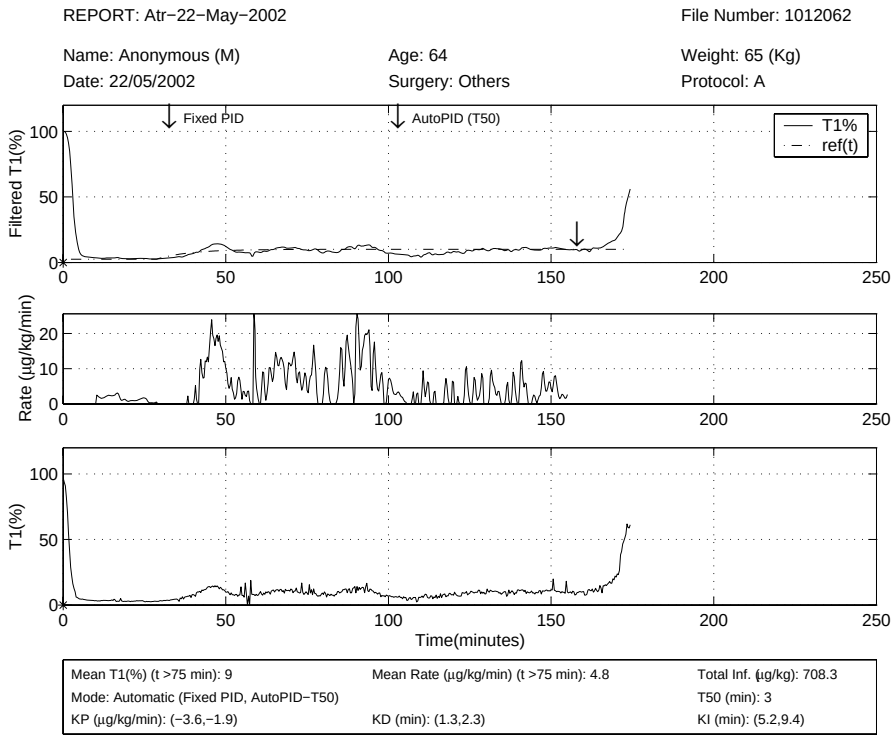

Figure 8. A global report (*.eps* file) is automatically created on exit of the control interface module.

3.2. Simulation tool

As a simulation tool the software incorporates sophisticated statistical generation of pharmacokinetic/pharmacodynamic models driven by flexible administration regimes (*bolus*, continuous infusion or a combination of both) [12]. Figures 9 and 10 illustrate two examples of the simulation module:

- manual control by administration of repeated *bolus* and continuous infusion (Figure 9)
- automatic control with added measurement noise on T1=r(t)%: initial *bolus* and automatic control of the continuous infusion with an autocalibrated PID controller (Figure 10).

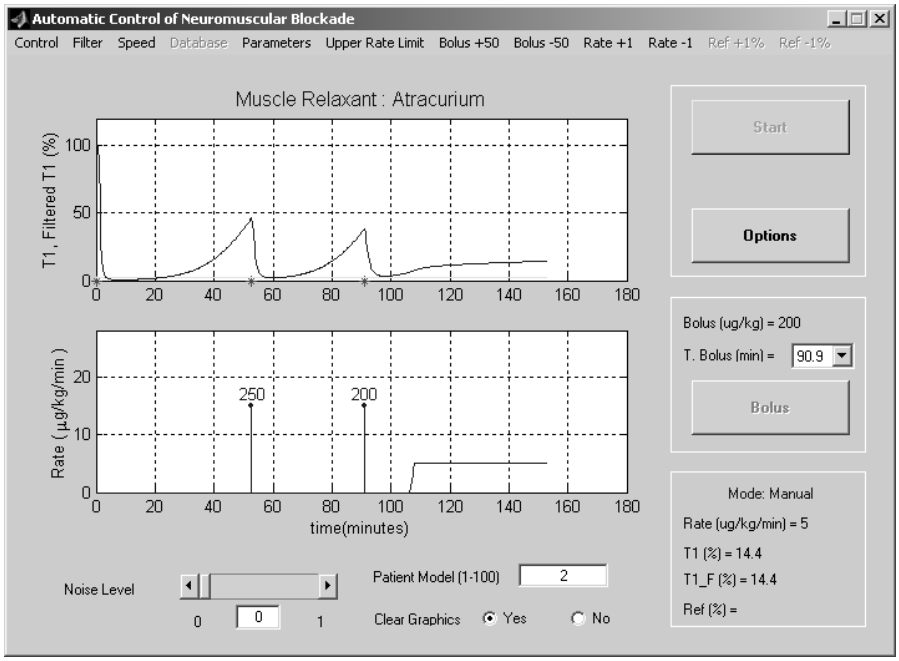

Figure 9. Simulation module interface under manual control strategy: administration of repeated *bolus* of *atracurium* (250 and 200 $\mu g\, kg^{-1}$) at t=53 and 91 minutes, after the initial one (500 $\mu g\, kg^{-1}$), followed by a constant infusion rate of 5 $\mu g\, kg^{-1}\, min^{-1}$ (t $>$ 105 minutes). The window shows the *bolus* administration times and values, the current value for constant infusion rate and T1=r(t)%.

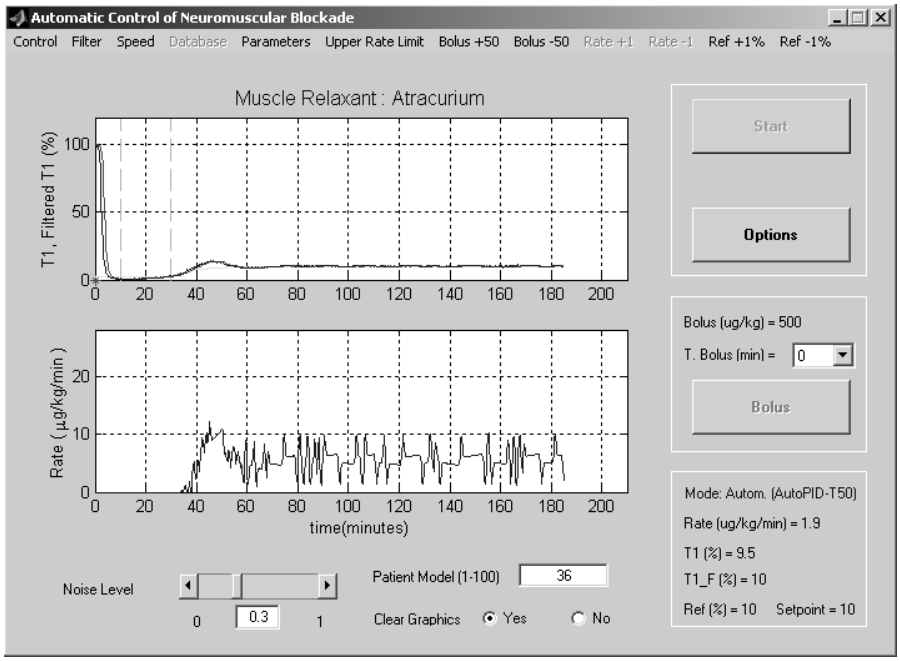

Figure 10. Simulation module interface under automatic control. The set point, the control strategy, the noise reduction technique, the muscle relaxant database, the individual model parameters and the measurement noise can be selected and/or modified by the user through the toolbar and the graphic interface. The window shows all relevant information, namely the current values for T1=r(t)% (real and filtered), infusion rate ($\mu g\, kg^{-1}\, min^{-1}$) and set point (%).

4. Conclusions

An automatic system (software package *Hipocrates*) for the control of neuromuscular blockade has been developed and validated for management under both inter and intraindividual variability and difficult or unexpected circumstances. It offers a highly friendly graphic interface and is easy to set up and to use in clinical environment. This control system, incorporating on-line patient-specific information procedures, provides robustness and adaptation to individual requirements, covering a wide and realistic range of situations. It can be used on patients undergoing surgery or as an advanced simulation tool for education and training purposes. A stand-alone version and user's manual may be requested to the authors. Presently *Hipocrates* is being used in Hospital Geral de Santo António, Porto, providing three different control strategies, namely digital PID, on-line auto-calibrated PID and robust multiple model switching PID.

Appendix

The digital PID controller can be implemented by the following form [26]:

$$u_n = g_c \left(1 + \frac{\Delta t}{c_i}\frac{z}{z-1} + \frac{c_d}{\Delta t}\frac{z-1}{z}\right) e_n \tag{8}$$

where $u(t)$ is the infusion rate and $e(t) = ref(t) - r(t)$ is the error, i.e. the difference between the desired level and the induced level of the neuromuscular blockade, $ref(t)$ and $r(t)$ respectively; Δt is the sampling period, $u_n = u(n\Delta t)$ and $e_n = e(n\Delta t)$. The controller parameters, namely the proportional gain g_c, the integral time constant c_i and the derivative time constant c_d are obtained from

$$\begin{aligned} g_c = \frac{1.2}{R * L} * \frac{1}{rd(r_0)} \quad & \mu\text{g kg}^{-1}\ \text{min}^{-1}, \\ c_i = 2 * L \quad & \text{min}, \\ c_d = L/2 \quad & \text{min} \end{aligned} \tag{9}$$

where L and R are deduced from the Ziegler-Nichols step response method, applied to the linear part of the combined pharmacokinetic/pharmacodynamic model, and $rd(r_0)$ is the partial derivative evaluated at the target value r_0,

$$rd(r_0) = \left.\frac{\partial r(t)}{\partial c_e(t)}\right|_{r=r_0}, \tag{10}$$

obtained from the Hill equation (3). Thus the controller gains are automatically adjusted to the specified target value by the gain scheduling technique.

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