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Observer design in switching control of neuromuscular blockade: clinical cases

Hugo Magalhães, João M. Lemos, Teresa Mendonça, Paula Rocha, Simão Esteves and José Gaivão

***Abstract*— This paper concerns the application of multiple model switched methods to the control of neuromuscular blockade of patients undergoing anaesthesia. Since the model representing the neuromuscular blockade process is subject to a high level of uncertainty due both to inter-patient variability and time variations, switched methods provide the adaptation capability needed to achieve the desired performance. The paper contributions are twofold: first, it is shown that, for the type of process control problem considered, the design of the associated observer must be carefully performed. Guidelines are provided for adequate selection of the characteristic polynomial defining the observer error dynamics. Second, clinical results using *atracurium* as blocking agent are reported in order to illustrate the use of the proposed control structure in actual clinical practice.**

I. INTRODUCTION

Feedback control for drug dosing in clinical pharmacology is receiving increasing attention [1]. Significant examples are provided by the closed-loop control of the cardiovascular function and automated anaesthesia [1]. During surgical procedures patients are usually under general anaesthesia, defined as the lack of response and recall to noxious stimuli, reflected in loss of conscience, pain insensitivity and muscle paralysis. Several approaches to the neuromuscular blockade control problem as well as an introduction to this issue can be seen in [2]–[4]. Muscle relaxant drugs are frequently given during surgical operations. The non-depolarising types of muscle relaxant act by blocking the neuromuscular transmission (NMT), thereby producing muscle paralysis. The level of muscle relaxation is measured from an evoked EMG at the hand by electrical stimulation of the adductor policies muscle to supramaximal train-of-four stimulation of the ulnar nerve. In a clinical environment the measurement of the neuromuscular blockade level corresponds to the first single response ($T_1\%$) calibrated by a reference twitch, obtained by defining a supramaximal stimulation current. This measuring process is prone to the occurrence of outliers, a problem dealt with in [5]. The control of the neuromuscular blockade provides a good illustration of the main features and inherent constraints associated with the control of physiological variables. It is characterized by a very high degree of uncertainty in the dynamics of the system due both to inter-patient variability as well as time variations. This suggests that multiple-models based control techniques would provide a suitable solution [6], [7]. Such a scheme (incorporating several modifications in order to accommodate the specific characteristics of the problem) has been developed in [8], using multiple controllers constructed from a bank of models which replicate the observed variability of the dynamic responses to the muscle relaxant [9]. In [10] restriction techniques (controller localization) relying on a robustness condition have been proposed. These techniques yield good results but suffer from the major drawback of assuming a strong assumption on the plant dynamics.

The main contribution of this paper consists in showing that, for neuromuscular blockade control using switched multiple models, if the design of the associated observer is correctly done, the algorithm is able to stabilize all the possible plant dynamic outcomes within the range covered by the bank of models/controllers. Guidelines are provided for adequate selection of the characteristic polynomial defining the observer error dynamics. Furthermore, clinical results using *atracurium* as blocking agent are reported in order to illustrate the use of the proposed control structure in actual clinical practice.

II. NEUROMUSCULAR BLOCKADE MODEL

The dynamic response of the neuromuscular blockade for *atracurium* may be modelled as follows [4], [9]. A linear pharmacokinetic model, described by the following linear system of state equations

$$\begin{cases} \dot{x}_1(t) = -\lambda_1 x_1(t) + a_1 u(t) \\ \dot{x}_2(t) = -\lambda_2 x_2(t) + a_2 u(t) \\ c_p(t) = \sum_{i=1}^{2} x_i(t), \end{cases} \tag{1}$$

relates the drug infusion rate $u(t)$ $[\mu g\, kg^{-1}\, min^{-1}]$ with the plasma concentration $c_p(t)$ $[\mu g\, ml^{-1}]$, where x_i $(i = 1, 2)$ are state variables (implicitly defined by (1)) and a_i $[kg\, ml^{-1}]$, λ_i $[min^{-1}]$ $(i = 1, 2)$ are patient dependent parameters. The physiological basis of the model described by equation (1) consists of assuming two plasma compartments (central and peripheric) both communicating with each other. A linear second order model, described by the cascade of two first order systems, written as

$$\begin{aligned} \dot{c}(t) &= -\lambda\, c(t) + \lambda\, c_p(t) \\ \dot{y}(t) &= -1/\tau\, y(t) + 1/\tau\, c(t), \end{aligned} \tag{2}$$

is assumed to relate $c_p(t)$ with the concentration in the effect compartment, $y(t)$ $[\mu g\, ml^{-1}]$. Here, $c(t)$ is an intermediate

H. Magalhães, T. Mendonça and J. Gaivão are with the DMA, FCUP, Rua do Campo Alegre, 687, 4169-007 Porto, Portugal. {hfmagalh,tmendo, jose.gaivao}@fc.up.pt

J.M. Lemos is with the INESC-ID/IST, Rua Alves Redol, 9, 1000-029 Lisboa, Portugal. jlml@inesc.pt

P. Rocha is with the DM, UA, Campo de Santiago, 3810-193 Aveiro, Portugal. procha@mat.ua.pt

Simão Esteves is with the Anestesiology Department, Hospital Geral de Santo António, Largo Prof. Abel Salazar, 4050 Porto, Portugal.

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variable and λ $[min^{-1}]$, τ $[min]$ are patient dependent parameters. It is remarked that standard models developed for *atracurium* [11] do not consider equation (2). As shown in [9], the inclusion of this equation corresponding to a first order approximation of the τ delay $e^{-\tau s}$ allows a better replication of the observed experimental responses. Finally the pharmacodynamic effect, that relates $y(t)$ to the induced pharmacodynamic response, $r(t)$ [%], may be modelled by the Hill equation [11],

$$r(t) = 100C_{50}^{\gamma}/(C_{50}^{\gamma} + y^{\gamma}(t)),$$

where the parameters C_{50} $[\mu g\, ml^{-1}]$ and γ (adimensional) are also patient-dependent. 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.

III. Switching control

In recent years adaptive control approaches based on supervisory switching control have been proposed to deal with systems presenting high level of uncertainty. This section describes the basic structure of switching control and presents a solution to overcome robustness issues related to the implementation of such a control scheme. It is assumed that a discretization procedure has taken place, and hence from now on the variable t represents discrete time instants.

A. Basic structure

The basic structure of a supervisor based switched multiple model controller is shown in Figure 1, as described in [6], [7], [10]. In Figure 1, r denotes the sensor measure, ref denotes the reference, e_c the control error and P the plant to be controlled. A bank of controllers $C_j, j = 1, ..., N$ is designed to match the plant models M_j. This set of models is assumed to "cover" all the possibilities of the actual plant P. In order to select at each time instant which controller best matches P, the following principle is applied: the model with the best performance implies the best controller. One possibility for evaluating the model performance is to compare the output r_j of each model M_j with the process output r. Another possibility is to construct estimators E_j based on each of the models M_j, see subsection III-B.

In either case an error e_j is produced, which is measured through a performance index (PI) π_j, $j = 1, ..., N$, computed by

$$\pi_j(t) = \sum_{k=0}^{t} \lambda_{\pi}^{t-k} e_j^2(k), \quad 0 < \lambda_{\pi} \leq 1$$

where λ_{π} is the forgetting factor. 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 j corresponding to the least value of π_j. An integrator common to all blocks ensures smooth transition between different controllers [6] $\big($discrete control transfer function $C_j(z) = \bar{C}_j(z)\frac{z\Delta t}{z-1}$, Δt sampling time$\big)$. Outlier removal is performed with a Bayesian filter, according to the techniques described in [5].

B. Observer Dynamics

As done in [6], the estimate $\hat{y}_j(t)$ of $y(t)$ is made by including an observer polynomial.

Let the linear part of each model M_j be represented by the ARX model

$$A_j(q^{-1})y_j(t) = B_j(q^{-1})u(t) + \bar{e}_j(t), \tag{3}$$

in which

$$A_j(q^{-1}) = 1 + \sum_{i=1}^{n_a} a_{j,i}q^{-i}, \;\; B_j(q^{-1}) = \sum_{i=1}^{n_b} b_{j,i}q^{-i}$$

are polynomials in the unit delay operator q^{-1}. A_j is a monic polynomial of degree n_a and B_j is a polynomial of degree n_b, for all $j = 1, ..., N$. In order to associate to (3) a state space model, define $(n_b > 1)$

$$s_j(t) = \\ [y_j(t) \; \ldots \; y_j(t - n_a + 1) \;\; u(t-1) \; \ldots \; u(t - n_b + 1)]^T.$$

For $n_b = 1$, $s_j(t) = [y_j(t) \; \ldots \; y_j(t - n_a + 1)]$. In the case of an ARX model, *i.e.* when the disturbance acting on (3) is white noise, $s_j(t)$ is a (nonminimal) state associated to (3), whose evolution is described by the state-space model

$$\begin{array}{rcl} s_j(t+1) & = & \Phi_j s_j(t) + \Gamma_j u(t) + G\bar{e}(t+1) \\ y_j(t) & = & Hs(t) \end{array} \tag{4}$$

in which

$$\Phi_j = \\ \left[\begin{array}{cccccc} -a_{j,1} & \ldots & -a_{j,n_a} & b_{j,2} & \ldots & b_{j,n_b} \\ & I_{n_a-1} & 0_{n_a-1\times 1} & & 0_{\substack{n_a-1 \\ \times n_b-2}} & 0_{n_a-1\times 1} \\ 0 & \ldots & 0 & 0 & \ldots & 0 \\ & 0_{\substack{n_b-2 \\ \times n_a-1}} & 0_{n_b-2\times 1} & & I_{n_b-2} & 0_{n_b-2\times 1} \end{array}\right],$$

$$\Gamma_j = [b_{j,1} \;\; 0_{1\times n_a-1} \;\; 1 \;\; 0_{1\times n_b-2}]^T,$$

with the "1" in Γ_j in the n_a+1th position $(n_b > 1)$ and $G = [1 \;\; 0_{1\times n_a+n_b-2}]^T, H = [1 \;\; 0_{1\times n_a+n_b-2}]$. Consider now the problem of designing a state observer to (4) or equivalently, a prediction to (3). For that sake add $A_o y_j(t) - A_j y_j(t)$ to both sides of (3) to conclude that the model may be represented by

$$y_j(t) = (A_o - A_j)\frac{1}{A_o}y_j(t) + \frac{B_j}{A_o}u(t) + \frac{1}{A_o}\bar{e}_j(t),$$

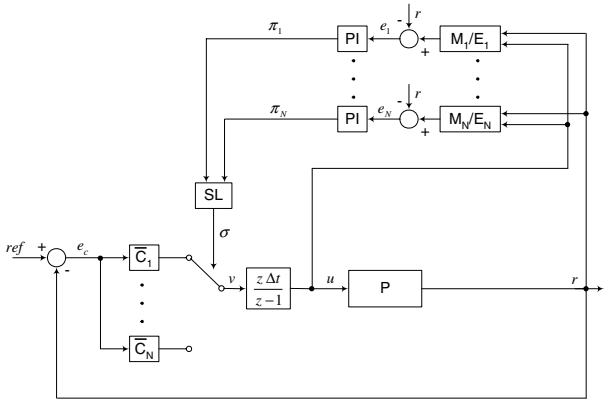

Fig. 1. Switched multiple model control strategy.

where $A_o(q^{-1}) = 1 + \sum_{i=1}^{n_a} a_{o,i} q^{-i}$ is a stable monic polynomial with the same degree as the A_j's, which will hereafter be referred as the "observer polynomial". Define an estimator E_j for the plant by

$$\hat{y}_j(t) = (A_o - A_j)\frac{1}{A_o} y(t) + \frac{B_j}{A_o} u(t). \tag{5}$$

The idea behind this is that if the process model would coincide with M_j, y would coincide with y_j. Therefore

$$y(t) \; - \; \hat{y}_j(t) = y_j(t) \; - \; \hat{y}_j(t) = \frac{1}{A_o}\bar{e}_j(t)$$

and the estimate $\hat{y}_j$ would be asymptotically accurate.

The estimator (5) can be interpreted in terms of a state observer as follows. Define

$$\eta(t) \;\; = \;\; \frac{1}{A_o(q^{-1})} y(t), \tag{6}$$

$$\nu(t) \;\; = \;\; \frac{1}{A_o(q^{-1})} u(t). \tag{7}$$

With the state defined by

$$x_\eta(t) = [\eta(t) \;\; \eta(t-1) \;\; \ldots \;\; \eta(t-n_a+1)]^T,$$

the state-space realization of (6) is seen to be

$$x_\eta(t) = \bar{\Phi}_o x_\eta(t-1) + \bar{\Gamma}_o y(t), \tag{8}$$

where

$$\bar{\Phi}_o = \begin{bmatrix} -a_{o,1} & -a_{o,2} & \ldots & -a_{o,n_a} \\ & I_{n_a-1} & & 0_{n_a-1\times 1} \end{bmatrix},$$

$$\bar{\Gamma}_o = [1 \;\; 0_{1\times n_a-1}]^T.$$

For (7), a similar reasoning holds. The state defined by

$$x_\nu(t) = [\nu(t) \;\; \nu(t-1) \;\; \ldots \;\; \nu(t-n_a+1)]^T$$

yields

$$x_\nu(t) = \bar{\Phi}_o x_\nu(t-1) + \bar{\Gamma}_o u(t). \tag{9}$$

In turn, defining the state of the reconstructor as

$$s_f(t) = \left[x_\eta(t)^T \;\; x_\nu(t)^T\right]^T,$$

equation (8) together with (9) yield

$$s_f(t) = \Phi_o s_f(t-1) + \Gamma_{oy} y(t) + \Gamma_{ou} u(t), \tag{10}$$

in which

$$\Phi_o = \begin{bmatrix} \bar{\Phi}_o & 0_{n_a\times n_a} \\ 0_{n_a\times n_a} & \bar{\Phi}_o \end{bmatrix},$$

$$\Gamma_{oy} = \left[\bar{\Gamma}_o^T \;\; 0_{1\times n_a}\right]^T, \;\; \Gamma_{ou} = \left[0_{1\times n_a} \;\; \bar{\Gamma}_o^T\right]^T.$$

From (5)

$$\hat{y}_j(t) = H_{j,o} s_f(t-1),$$

with $H_{j,o}$ given by

$$H_{j,o} = [a_{o,1} - a_{j,1} \ldots a_{o,n_a} - a_{j,n_a} \;\; b_{j,1} \ldots b_{j,n_b} \;\; 0_{1\times n_a - n_b}].$$

The advantage of using the state-space model (10) consists in the fact that it readily provides a shared state realization, *i.e.*, a state-space realization in which the state is common to all models M_j/E_j in Figure 1. The vector $s_f(t)$ corresponds to a filtering of $s_j(t)$ by the observer dynamics. This dynamics may be chosen in order to provide the controller with robustness properties with respect to unmodelled plant dynamics.

IV. Results

To achieve a high level of neuromuscular blockade in a short time, a *bolus* of *atracurium* is always administered in the beginning of a surgery. After the administration of the *bolus*, the level of the neuromuscular blockade increases very quickly (the variable r, that measures muscular activity decreases), and full muscle paralysis is induced in a few minutes. Following that initial period, the control objective is to follow a specific reference profile with a final target value $ref \equiv ref_0$. The value of the reference profile is initially fixed at a low level (typically 2.5%) during the first 30 minutes. It is then gradually increased to the final value (typically 10%). A bank of $N = 100$ non-linear dynamic models $M_j, j = 1, \ldots, N$ with the same structure as described in section II was generated using the probabilistic model for *atracurium* [9]. Furthermore, for each M_j, a PID controller $C_j, j = 1, \ldots, N$ was tuned using the dominant-pole placement rule [12]. The choice of $N = 100$ for the number of models/controllers and their distribution was motivated by experimental observations, which suggest that possible outcomes are suitably covered.

An extensive simulation study using each model of the bank for mimicking the real plant P was conducted. This study, based on the mean square error (MSE) and initial overshoot value, proved the superior performance of the designed controller when A_o roots $r_i^o \in [0.65, 0.95], i = 1, \ldots, n_a = 4$ (order of the neuromuscular blockade model). Note that for simplicity all roots of A_o were considered equal. Figure 2 shows the MSE as a function of the roots r_i^o of the observer polynomial A_o for the worst case observed, *i.e.*, for $P = M_{69}$. As an illustrative example, Figure 3 displays the results for $P = M_{69}$ with roots of A_o at $\{0.92, 0.92, 0.92, 0.92\}$.

Figures 4 and 5 show two clinical results with observer dynamics where the roots of A_o are $\{0.85, 0.85, 0.85, 0.85\}$ and $\{0.92, 0.92, 0.92, 0.92\}$, respectively. In the first clinical case, a change in the overall characteristics is observed at $t \approx 100$ *min*, possibly due to an increase in the noise level. In spite of presenting a slight oscillatory response, a good performance was obtained by the control system (MSE=4.9). In the latter case, a very good performance in terms of the reference tracking was obtained (MSE=0.4).

V. Conclusions

The control of neuromuscular blockade during anaesthesia, through the continuous infusion of a muscle relaxant, is characterized by a very high degree of uncertainty in the dynamics of the system, due both to inter-patient variability as well as time variations. In order to deal with these features multiple model based switching control was used and the effect of the inclusion of observer dynamics was

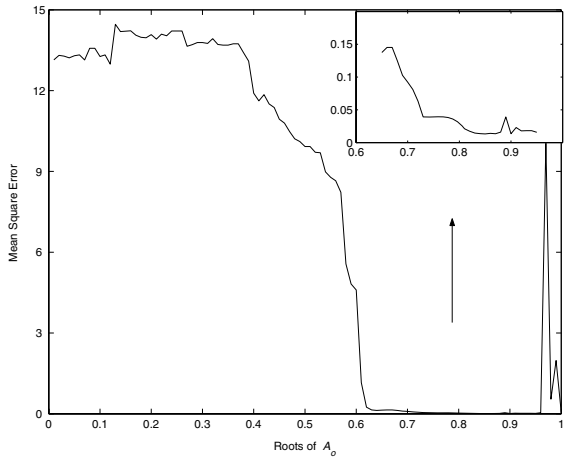

Fig. 2. Mean square error (MSE) for $P = M_{69}$ as a function of the roots r_i^o of the observer polynomial A_o. Upper right corner shows a zoom of the MSE for $0.65 \leq r_i^o \leq 0.95$.

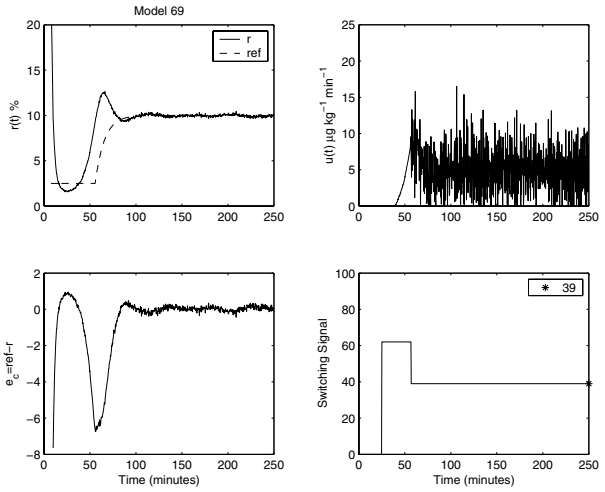

Fig. 3. Results obtained for $P = M_{69}$ with observer dynamics where the roots of A_o are $\{0.92, 0.92, 0.92, 0.92\}$.

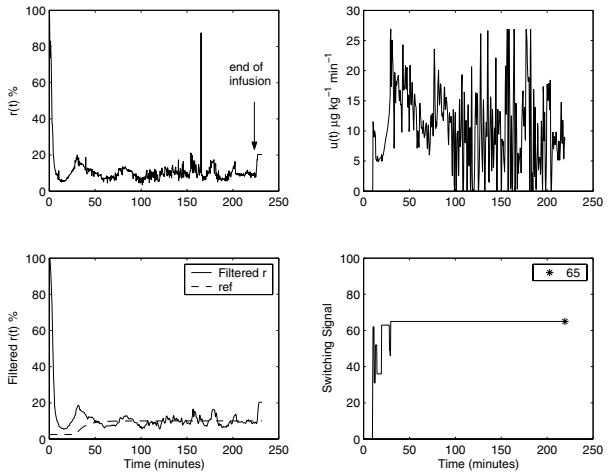

Fig. 4. Clinical results obtained with observer dynamics where the roots of A_o are $\{0.85, 0.85, 0.85, 0.85\}$.

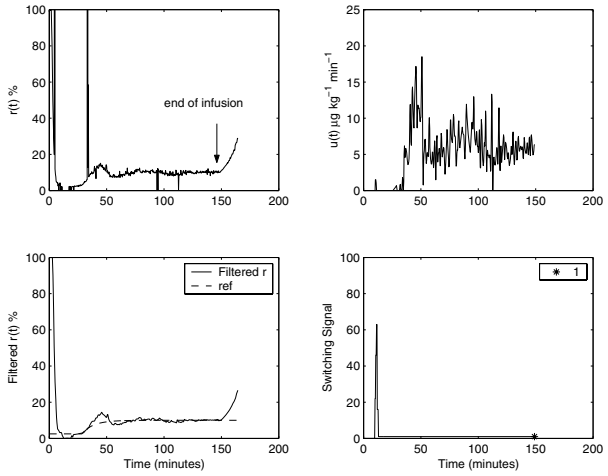

Fig. 5. Clinical results obtained with observer dynamics where the roots of A_o are $\{0.92, 0.92, 0.92, 0.92\}$.

considered. The good results obtained either in the reported simulation study or in the few clinical cases collected so far suggest an extensive clinical evaluation in order to validate the robustness and superior performance of the observer design in switching control. Furthermore, the use of other neuromuscular blockade drugs would be surely worth to try along with the choice of A_o patient dependent roots.

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