Nature Inspired Varying Control for Neuromuscular Blockade

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Abstract

The real-time identification and control of biomedical systems has always been and still is a challenge. In order to follow the advances in anesthetic practice and respond to the new demands in drug effect assessment, the design of robust adaptive control based on the diversity of individual behaviour is considered. The synthesis procedure embodies methods for selecting a set of individual model stabilizing controllers and is used on a switching supervisory control. Based on the ideas introduced by (Hespanha and Morse, 2002), we implement a switching scheme for the control of the neuromuscular blockade of patients undergoing surgery. This approach uses a bank of stabilizing controllers each of them associated to a candidate model for the patient dynamics. Switching is made by means of a selection criterion based on an identification error. This scheme proves to have a good performance improving the tracking of the reference profile, even in the presence of measurement noise.

Index Terms

Switching, Linear systems, Hybrid systems, Neuromuscular blockade control, Control application

I. Introduction

The control of physical systems often involves a very high degree of uncertainty in the system dynamics, resulting from the individual behavior diversity. Mathematical models are increasingly used in such assessment, providing a description of interindividual sensitivity. One way of overcoming this problem is to use a system description based on multiple models in an attempt to mimic the diversity present in Nature. This technique has been considered by several authors, in order to obtain switching control schemes.

Model based switching control consists, roughly speaking, in designing a time-varying controller as follows. Given a process to control and a bank of candidate models for this process, a controller is tuned for each model in order to achieve the desired control goals. At each time instant a model is chosen, that best approximates the process in a suitable sense, and the corresponding controller is then made active. This gives rise to a switching (thus time-varying) control scheme as illustrated in Figure 1. In this Figure, ref denotes the reference, u denotes the control input, y the process output, d a bounded input disturbance, n a bounded measurement noise, and P is the process to be controlled. Assume that P is described by the transfer function H_P. We consider a bank $\mathcal{K} = \{K_j,\ j \in J\}$ of stabilizing proper controller transfer functions. $K(\sigma)$ is a time-variant controller constructed from the bank $\mathcal{K}$ in the following way. Based on the values of u and y, the selection procedure S yields at each time instant t the index $\sigma(t) \in J$ corresponding to the controller that should be active at that time. The signal $\sigma(.)$ is known as the *switching signal*. This scheme gives rise to different concrete control strategies according to the different classes of admissible controllers in the bank $\mathcal{K}$ and to the different selection procedures, see for instance (Morse, 1996) and (Narendra and Balakrishnan, 1997). Here the index set J is taken to be finite, $J = \{1, \ldots, N\}$ and it is assumed that each of the controllers K_j in the bank is tuned to solve the tracking problem for a linear time-invariant model M_j. Intuitively, if the process response is closer to the response of model M_j, one expects the controller K_j to perform better than the other ones. This motivates the implementation of a selection procedure S that corresponds to the minimization of a suitable function of the identification error $e_j := y - y_j$, where y_j denotes the response of M_j to the input u. A similar approach can be seen in (Neves *et al.*, 2002).

A crucial issue in this context is the stability of the overall switching system. Indeed, even in case each of the controllers K_j is stabilizing, the same does not necessarily hold for the resulting time-varying controller. In a recent paper (Hespanha and Morse, 2002) a procedure was proposed in order to solve this problem, based on the construction of adequate realizations for the process and the controller transfer functions.

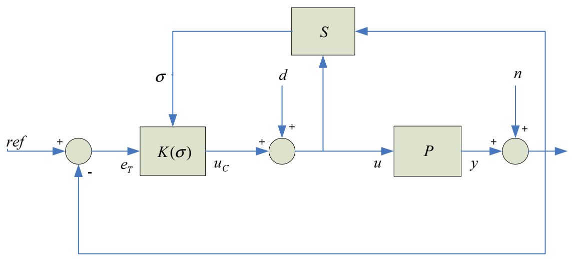

Fig. 1. Switching controller configuration

The main goal of this paper is to apply this procedure in a switching supervisory control of neuromuscular blockade, as an alternative method to the ones implemented (Magalhães, 2006; Gaivão *et al.*, 2006). The practical implementation issues for switching between stabilizing controllers are considered for the control of neuromuscular blockade of patients undergoing surgery. An extensive simulation study proves that this approach reveals to be robust, even in the presence of small perturbations and noise (Magalhães, 2006). Since the procedure is based on a bank of stabilizing controllers, methods will be proposed to select such a bank from a given set of candidates controllers.

II. Controller realization construction

The procedure proposed in (Hespanha and Morse, 2002) leads to the following algorithm. Given a bank $\mathcal{K}$ of controllers transfer functions and assuming that the process transfer function H_p is known:

1. Pick a controller $K^\star \in \mathcal{K}$.
2. Consider minimal realizations (A,B,C) and (F,G,H,J) for H_P and $K^\star$ respectively. Obtain X and Y such that $A+XC$ and $F+YH$ are asymptotically stable.
3. Define,

$$A_E := \begin{pmatrix} A+XC & 0 \\ 0 & F+YH \end{pmatrix}, \; B_E := \begin{pmatrix} B \\ -Y \end{pmatrix},$$

$$C_E := \begin{pmatrix} C & 0 \end{pmatrix}, \; D_E := \begin{pmatrix} -X \\ -G-YJ \end{pmatrix},$$

$$F_E := \begin{pmatrix} 0 & -H \end{pmatrix}, \; G_E = J$$

.

4. For each controller $K_j \in \mathcal{K}$, define the following transfer function,

$$S_j = (-Y_{\mathbf{C}} + X_{\mathbf{C}} K_j)(X_{\mathbf{P}} + Y_{\mathbf{P}} K_j)^{-1}, \tag{1}$$

with X_P, Y_P, X_C and Y_C given by

$$\begin{cases} X_{\mathbf{P}} = I - C_E(sI - A_E)^{-1} D_E \\ Y_{\mathbf{P}} = C_E(sI - A_E)^{-1} B_E \end{cases} \tag{2}$$

and

$$K_\star = X_{\mathbf{C}}^{-1} Y_{\mathbf{C}}$$

of $K_\star$, with

$$\begin{cases} X_{\mathbf{C}} = I + F_E(sI - A_E)^{-1} B_E \\ Y_{\mathbf{C}} = F_E(sI - A_E)^{-1} D_E + G_E \end{cases} . \tag{3}$$

5. Obtain stable realizations ($\bar{A}_j$,$\bar{B}_j$,$\bar{C}_j$,$\bar{D}_j$) for each S_j, more precisely:
   5.1 Pick any realization ($\tilde{A}_j$,$\tilde{B}_j$,$\tilde{C}_j$,$\tilde{D}_j$) for S_j with $\tilde{A}_j$ stable.
   5.2 For each $j \in J$ take Q_j symmetric and positive definite such that,

$$Q_j \tilde{A}_j + \tilde{A}_j^T Q_j = -I.$$

   5.3 Compute N_j such that $Q_j = N_j^T N_j$.
   5.4 Define:
   $\bar{A}_p = N_p \tilde{A}_p N_p^{-1}$,
   $\bar{B}_p = N_p \tilde{B}_p$,
   $\bar{C}_p = \tilde{C}_p N_p^{-1}$ and
   $\bar{D}_p = \tilde{D}_p$.

6. Define for each controller K_j the realization (F_j,G_j,H_j,J_j) given by,

$$F_p = \begin{pmatrix} A_E - B_E F_E + B_E \bar{D}_p C_E & B_E \bar{C}_p \\ \bar{B}_p C_E & \bar{A}_p \end{pmatrix},$$

$$G_p = \begin{pmatrix} -D_E + B_E(\bar{D}_p + G_E) \\ \bar{B}_p \end{pmatrix},$$

$$H_p = \begin{pmatrix} -F_E + \bar{D}_p C_E & \bar{C}_p \end{pmatrix} \quad and \quad J_p = \bar{D}_p + G_E.$$

7. Consider the realization $(A_E + D_E C_E, B_E, C_E)$ for the process transfer function H_P

The switching scheme to be implemented in the next section uses the realizations for the different controllers and for the process given in steps [6.] and [7.]. This guarantees that (no matter what is the adopted switching criterion) the resulting time-varying closed-loop system has a Lyapunov function and is hence stable, (Hespanha and Morse, 2002).

III. NEUROMUSCULAR BLOCKADE CONTROL BASED ON DIVERSITY

In this section we apply the previous algorithm to the problem of controlling the neuromuscular blockade by means of administration of *atracurium*. The dynamic response of the neuromuscular blockade may be modelled by a linear compartimental pharmacokinetic model relating the drug infusion rate $u(t)\left[\mu g\, kg^{-1}\, min^{-1}\right]$, with the plasma concentration $c_p(t)\left[\mu g\, ml^{-1}\right]$, and a nonlinear dynamic model relating $c_p(t)$ to the induced pharmacodynamic response, $r(t)$ (Weatherley *et al.*, 1983). The pharmacokinetic model may be described by the state equations,

$$\dot{x}_i(t) = -\lambda_i x_i(t) + a_i u(t) \qquad i = 1, 2 \tag{4}$$

$$c_p(t) = \sum_{i=1}^{2} x_i(t) \tag{5}$$

where (a_i, λ_i) are patient-dependent parameters.

The pharmacodynamic effect for atracurium may be modelled by the Hill equation,

$$r(t) = \frac{100 C_{50}^{\beta}}{C_{50}^{\beta} + c_e^{\beta}(t)} \quad . \tag{6}$$

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 the effect concentration $c_e(t)$ by

$$\dot{c}(t) = -\lambda c(t) + \lambda c_p(t). \tag{7}$$

C_{50}, β, λ are also patient-dependent parameters.

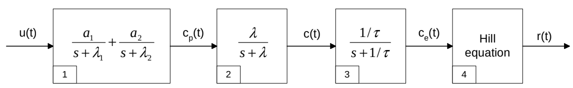

Fig. 2. Empirical pharmacokinetic/pharmacodynamic model

As it can be seen in Figure 2 the transfer function (Lago *et al.*, 1998) from u to c_e is given by

$$c_e(s) = g(s) \frac{\lambda}{s + \lambda} \left(\frac{a_1}{s + \lambda_1} + \frac{a_2}{s + \lambda_2} \right) \tag{8}$$

and the relationship between c_e and r remains described by the Hill equation 6.

Taking into consideration the specific characteristics of the system under control as well as clinical constraints, in the feedback control system, *atracurium* is administered through an inicial bolus followed by a continous infusion and the controller is coupled with a saturation function that can be represented by $\bar{u}(t) = max\,\{0, u(t)\}$. A bolus is a single dose B injected in a short period of time, usually represented by

$$u(t) = B\delta(t)\mu g\, kg^{-1},$$

where $\delta(t)$ is a Dirac δ function.

Our control objective is to achieve a desired level of the neuromuscular blockade, given by the Hill equation 6, specifically $r(t) = 10\%$, that we will denote ref_r. Inverting the Hill equation (6), one obtains the corresponding reference value ref_{c_e} for the effect concentration. Therefore we shall perform our control on the signal $c_e(t)$, in order to make it follow the reference value ref_{c_e}, and afterwards recover the corresponding value of $r(t)$.

For that purpose, we consider a family of linear models $\mathcal{M} = \{M_j : j = 1, \ldots, N\}$, of the form (8), that are intended to describe a wide range of clinical situations. The corresponding bank of continuous-time controllers consists of, $\mathcal{K} =$

$\{K_j : j = 1, \ldots, N\}\}$, such that each of them solves the desired tracking problem for the associated model M_j. Thus we are in the presence of a Model-Controller bank,

$$\{(M_j, K_j),\ j = 1, \ldots, N\}. \tag{9}$$

With the purpose of implementing the control scheme given by the Figure 1, the process P is assumed to be nominally described by a model $M^\star \notin \mathcal{M}$. The model-controller pair (M_j, K_j) for which K_j does not stabilize $M^\star$ is removed from the bank. This yields a restricted bank of stabilizing controllers $\bar{\mathcal{K}} \subset \mathcal{K}$, based on which the controller $K(\sigma)$ will be constructed.

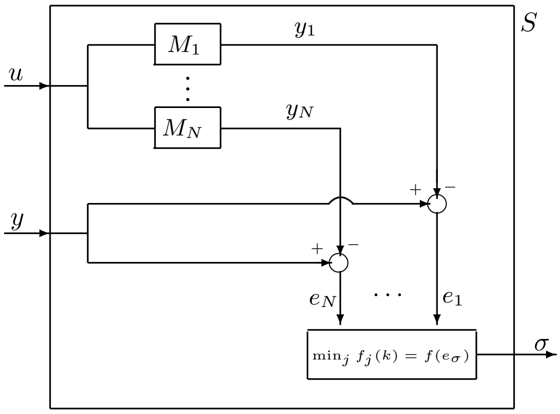

Fig. 3. Selection procedure.

The specification of the controller bank together with the controller selection procedure S yields a concrete control strategy. The selection procedure S can be seen in Figure 3 and is implemented as follows. At each instant t, the controller K_j to be chosen is the one associated with the model M_j for which $f_j(e_j) = \int_0^t w(\tau)|e_j|^2 d\tau$ is minimum, where $w(\tau)$ is a weight function of the form

$$w(\tau) = 100 - 100 * \exp\left(-\left(\frac{\tau - \alpha}{\beta}\right)^2\right),$$

with α and β positive constants. Each K_j is a modified PID controller of the form

$$K_j = g_c\left(1 + \frac{c_d s}{1 + \gamma s} + \frac{1}{c_i s}\right),$$

where γ is taken to be a small positive number (note that $\gamma = 0$ would give a PID). This adaptation is introduced in order to guarantee that the K_j's are proper transfer functions.

According to (Mendonça and Lago, 1998; Lemos *et al.*, 2005) each K_j proves to be suitable for practical implementation, fitting the restrictions imposed by the characteristics of this clinical environment application.

IV. Simulation Examples

In this section, we denote y as the process response considering the process described by $M^\star$. Moreover, we define $\bar{y}$ as,

$$\bar{y} = y + \phi d, \tag{10}$$

where $\phi(s)$ is a transfer function taking the form,

$$\phi(s) = \frac{(-19.27s + 3132)}{(s^2 + 10.5s + 24.72)},$$

and d is an impulse $\delta(t)$. We also define $\tilde{y}$ as,

$$\tilde{y} = y + n, \tag{11}$$

where n is a bounded Gaussian noise. In the present simulations we consider the following model-controller bank:

$$\{(M_j, K_j),\ j = 1, \ldots, 100\}, \tag{12}$$

and two distinct models M_{41} and M_{85} were chosen in order to simulate the real process P. The choice of these two models relies on the fact that both represent interesting and different features. Namely, M_{85} is one of the models from the bank that most present a transient response with an initial significant instability when controlled by a single stabilizing controller.

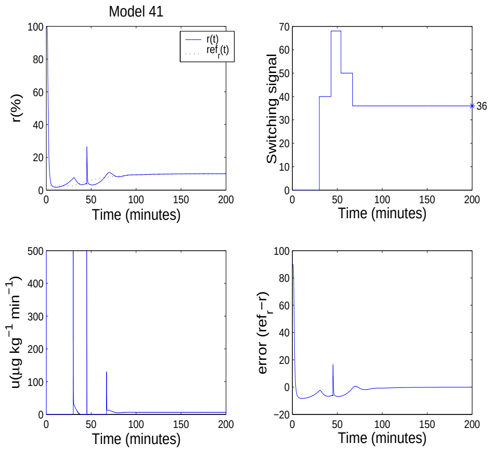

Fig. 4. Switching control for M_{41} using the stabilizing controller bank $\acute{\mathcal{K}}$. In these simulations conditions described by (i) were used and the control action was saturated at the level 0.

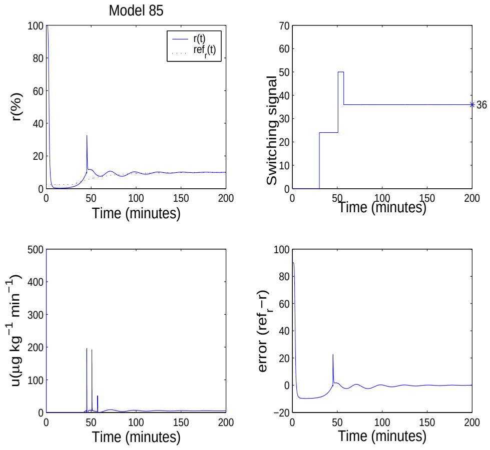

Fig. 5. Switching control for M_{85} using the stabilizing controller bank $\acute{\mathcal{K}}$. In these simulations conditions described by (i) were used and the control action was saturated at the level 0.

In order to implement the proposed control scheme, we consider the following restricted controller bank,

$$\acute{\mathcal{K}} = \{K_j : j \in \{15, 24, 36, 37, 39, 40, 47, 49, 50, 52, 56, 65, 68\}\} .$$

This single bank contains just stabilizing controllers for each of the models being considered, but note that both K_{41} and K_{85} were removed from $\acute{\mathcal{K}}$. For each model, the following distinct simulation conditions have been applied: (i) the model output is subject to a disturbance d given by (10) in the time instant $t = 45$, the control action begins 30 *minutes* after the standard initial *bolus* administration ($500\mu g\ kg^{-1}$) and the reference ref_r is time dependent (i.e. the value is initially fixed at a low level during the 30 *minutes* being gradually raised to the set point 10%, (Mendonça and Lago, 1998)); (ii) a bounded Gaussian noise $n(t)$ was superimposed to the output process in the interval $t \in [40, 85]$ and has the form (11), the control action begins at $t > 0$ since there is no *bolus* administration and the reference is a fixed value $ref_r = 10\%$. The simulation results are presented in Figures 4, 5, 6 and 7.

V. Conclusions

Using the ideas introduced in (Hespanha and Morse, 2002), we implemented a switching control scheme for the control of neuromuscular blockade based on a bank of stabilizing controllers. An extensive simulation study proves that this new approach reveals to be robust, even in the presence of small perturbations and noise. This new technique applied to the automatic control of neuromuscular blockade, has given good results and can be considered as a reliable approach to the problem.

References

Gaivão, J.P., E. Santos, T. Mendonça and P. Rocha (2006). Practical implementation issues for switching between stabilizing controllers. In: *Proc. 7th Portuguese Control Conference, CONTROLO06*. Lisbon, Portugal.

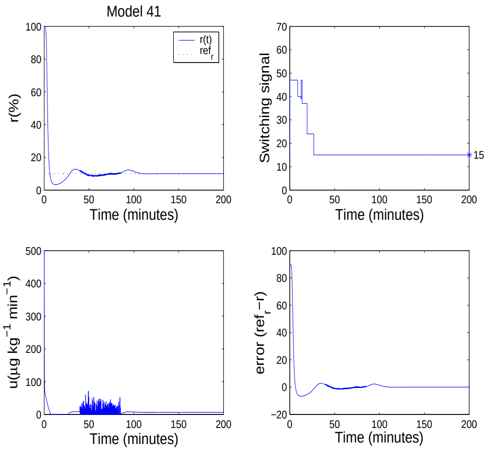

Fig. 6. Switching control for M_{41} using the stabilizing controller bank $\vec{\mathcal{K}}$. In these simulations conditions described by (ii) were used and the control action was saturated at the level 0.

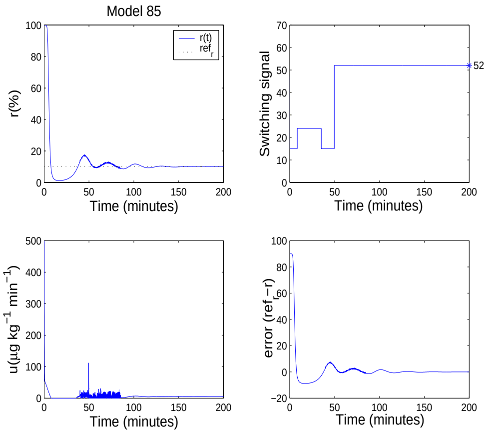

Fig. 7. Switching control for M_{85} using the stabilizing controller bank $\vec{\mathcal{K}}$. In these simulations conditions described by (ii) were used and the control action was saturated at the level 0.

Hespanha, J.P. and A. Stephen Morse (2002). Switching betwen stabilizing controllers. *Automatica* **38**(11), 1905–1917.

Lago, P., T. Mendonça and L. Gonçalves (1998). On-line autocalibration of a pid controller of neuromuscular blockade. *IEEE Conference on Control Applications*.

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

Magalhães, H.F. (2006). Contributions to the control of neuromuscular blockade. *PhD Thesis, Departamento de Matemática Aplicada, Faculdade de Ciências da Universidade do Porto*.

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

Morse, A.S. (1996). Supervisory control of families of linear set-point controllers -part 1: Exact matching. *IEEE Trans. Automat. Control* **41(10)**, 1413–1431.

Narendra, K.S. and J. Balakrishnan (1997). Adaptive control using multiple models. *IEEE Trans. Automat. Control* **42(2)**, 171–187.

Neves, A. J., P. Rocha and T. Mendonça (2002). A switching control scheme for improving reference tracking. In: *Proceedings of CONTROLO'2002, $5^t h$ Portuguese Conference on Automatic Control*. Aveiro, Portugal.

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