ALARM DETECTION METHODS FOR PHYSIOLOGICAL VARIABLES

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Abstract

The purpose of this work is to evaluate an adaptive controller which incorporates an alarm system, based on two different statistical methods: forecasting techniques and Walsh-Fourier spectral analysis (WFA). The resulting adaptive control system with an individual reference profile suitably tuned to the specific real case under control, contributes to the improvement of the overall reference tracking. The control of the neuromuscular blockade is used as case study.

1 Introduction

The development of automatic control systems for the continuous administration of drugs has been a subject of interest in the last decades and, in particular, for the control of the neuromuscular blockade during a surgical procedure. The non-depolarising types of muscle relaxant act by blocking the neuromuscular transmission, thereby producing muscle paralysis. The extent of muscle paralysis (or muscle relaxation) is then measured from an evoked EMG obtained at the hand by electrical external stimulation. A variety of different approaches to the design of an automatic control system of neuromuscular blockade has been proposed [7, 13, 18]. The design of these controllers is usually supported on a prototype for the nonlinear dynamical relationship between the muscle relaxant dose and the induced muscle paralysis. Such a prototype, which can be deduced from the available pharmacokinetic and pharmacodynamic data for the drug, merely describes the average characteristics of the response to the drug. However, in practice, a large variability of the individual responses to the infusion of the muscle relaxant is observed, [5, 10]. This variability suggests the need for an individual tuning of the controller according to the characteristics of the patient, [5, 10].

For clinical reasons, the patient must undergo an initial *bolus* dose to induce total muscle relaxation in a very short period of time (usually shorter than 5 minutes) and the automatic control system starts 10 minutes after the *bolus* administration. Therefore, the value of the reference is fixed at a low level during the first 30 minutes, after which the set-point is gradually raised in order to avoid sudden changes, as illustrated in Figure 1. It is shown in the literature, [10], that such reference profile is a better alternative to a constant one, leading to a substantial improvement of the controller performance. It reflects a compromise between the variability of the response to the initial *bolus*, the expected noise level in the measurement of neuromuscular blockade and clinical requirements. The response induced by the administration of an infusion rate is denoted by $r(t)$. This variable $r(t)$, normalised between 100% and 0%, measures the level of muscle relaxation, 0 corresponding to full paralysis and 100 to full muscular activity.

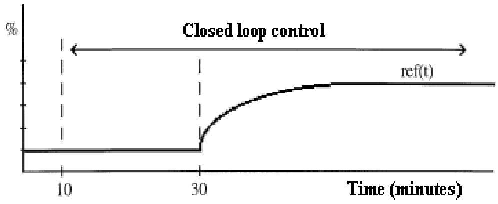

Figure 1. Graphic representation of the reference profile.

In order to accommodate the individual variability, methods for the on-line autocalibration of digital PID controller parameters for the administration of a muscle relaxant have been already proposed [5, 6, 10]. Regardless the control strategies adopted, the controller behaviour has been found satisfactory. However, the detailed analysis of the clinical cases reveals situations, as illustrated in Figure 2, characterized by the occurrence of a much longer effect of the initial *bolus*, resulting in an undesirable initial overshoot and oscillatory behaviour. It is then reasonable to assume that the reference profile should be time dependent on the effect of the initial *bolus* in order to improve the overall reference tracking. The duration of the individual *bolus* effect may be evaluated by the persistence parameter P, which also indicates the instant at which begins the

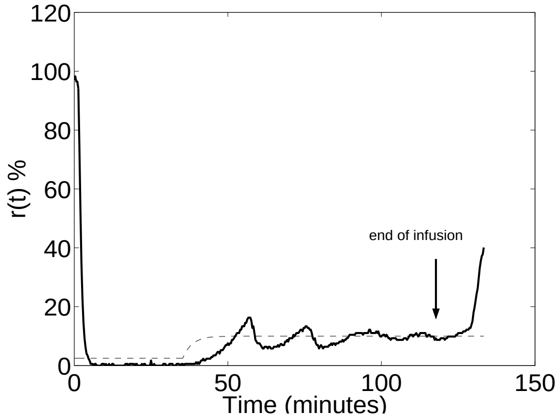

Figure 2. Clinical case. Plot of the neuromuscular blockade response and the fixed reference profile.

patient recovery.

The main purpose of this paper is to propose and evaluate an adaptive controller incorporating both a varying initial value for beginning of automatic control action and an individual reference profile, based on the estimation of the recovery time, P. Accordingly, the automatic control system incorporates an alarm system to estimate P, based on two different statistical methods: forecasting techniques and Walsh-Fourier spectral analysis. The performance of the resulting automatic control systems is assessed by a simulation study using a set of 500 models. This bank of models is generated according an empirical model for the response of the neuromuscular blockade induced by an initial *bolus* of *atracurium* assuming a multidimensional log-normal distribution for the eight pharmacokinetic/pharmacodynamic parameters, [5]. Also, for a better replication of the clinical environment, simulated measurement noise is added to each of the generated models.

2 Designing an adaptive reference trajectory

The design of a varying reference profile depends on the estimation of the recovery time P. Here two different methods are considered. One of the techniques consists in designing a naive alarm system for the neuromuscular blockade. The other methodology consists in predicting the parameter P by a linear regression using as predictors the neuromuscular blockade level at the time values corresponding to the average periods obtained by WFA.

2.1 Alarm system for neuromuscular blockade

The goal of an alarm system is to detect when a certain event, denominated by catastrophe, will take place. An alarm system, based on linear prediction of a stochastic process, where an alarm is given each time the predictor exceeds a critical level is designated as a naive alarm system or a naive catastrophe predictor, [17].

In this case study, the catastrophe is defined as the neuromuscular blockade upcrossing of a specified level, $\alpha\%$. Therefore, the alarm system provides an estimate of the recovery time, P, at an $\alpha\%$ critical neuromuscular blockade level, P_α, for α =2.5%, 5% and 10%.

The prediction of the process relies on the previous knowledge of a parametric model for the patient measurements of neuromuscular blockade. Therefore, identification techniques of linear models have been considered [8].

The neuromuscular blockade response, $r(t)$, is modelled using an AutoRegressive with eXogenous input, ARX, model of order (4,4)

$$\begin{aligned} r(t) = a_1 r(t-1) + a_2 r(t-2) + a_3 r(t-3) + a_4 r(t-4) + \\ b_0 u(t-1) + b_1 u(t-2) + b_2 u(t-3) + b_3 u(t-4) \end{aligned}$$

where $u(\cdot)$ is the input signal.

According to the inter and intra-variability from the patients responses to the administration of an initial *bolus*, on-line identification of the ARX model parameters based on input-output measurements is desirable and is achieved using the Kalman filter, [3], to estimate the time-varying parameters of the models and predict at time t the response at time $t+5$, $\hat{r}(t+5)$. If $\hat{r}(t+5) > \alpha$ then an alarm is given and P_α is estimated as $t+5$.

Table 1 presents the observed and estimated persistence parameter P_α (in minutes) for four simulated neuromuscular blockade response for α =2.5%, 5% and 10%.

	$P_{2.5}$	$\hat{P}_{2.5}$	P_5	$\hat{P}_5$	P_{10}	$\hat{P}_{10}$
Response 1	25.00	23.00	34.00	30.33	39.00	37.67
Response 2	28.00	22.33	33.67	32.33	38.00	37.33
Response 3	41.00	37.00	47.00	47.00	52.33	51.00
Response 4	24.33	19.67	30.33	28.00	36.33	32.00

Table 1. Observed and estimated persistence parameter.

The results presented in Table 1 show that the estimated persistence parameter, $\hat{P}_\alpha$, is close to the observed persistence parameter, P_α, for all critical relaxation level considered.

2.2 Walsh-Fourier spectral analysis

Walsh-Fourier spectral analysis (WFA) is a procedure used to analyse and characterize time series, specially when sharp discontinuities and changes of level occur in the data. The procedure is similar to the well known Fourier analysis, used to characterize periodic variation in a continuous signal.

The Walsh-Fourier analysis is based in the Walsh functions [1, 2, 4] which form a complete, ordered and orthonormed set of *rectangular waves* taking the values -1 and 1. The sequency-ordered Walsh functions are denoted by $W(n,t)$ where $n \in \mathbb{N}$ is denominated *sequency* and represents the number of switches signs (zero-crossings) in the unit interval and $t \in [0,1[$.

Let $x(0),\ldots,x(N-1)$ be $N = 2^p, p \in \mathbb{N}$, observations of a stochastic process. An estimator of the spectral density function (spectrum) of Walsh-Fourier [11, 12, 15, 16] is the *Walsh periodogram*, which is the square of the Walsh-Fourier transform of the data

$$I_W(\lambda_j) = \left[\frac{1}{\sqrt{N}} \sum_{n=0}^{N-1} x(n) W(n,\, \lambda_j)\right]^2 , \qquad (1)$$

where λ_j is a sequency of the form $\lambda_j = j/N,\ 1 \leq j \leq N-1$. One can plot $I_W(\lambda_j)$ versus λ_j to inspect for *peaks*. In the sequency domain, a peak indicates a *switch* each λ_j time points.

Considering that during the surgical intervention a patient attains different levels of neuromuscular blockade, it has been investigated how the Walsh-Fourier analysis can contribute to improve the neuromuscular blockade controller [14]. It has been found that the neuromuscular blockade levels at the average periods indicated by WFA have a high predictive power for the parameters of the controller and it has been also verified the robustness of the parameters prediction from WFA, in the presence of the high level noise that often contaminates the measurement of the muscle relaxation response [14]. Investigating the relationship between the persistence parameter P_α and the WFA average periods, it is found that P_α is highly correlated with the relaxation level at 14 minutes, $r(14)$ [14].

Therefore, the prediction of P_α by linear regression using as predictors the relaxation levels at WFA average periods is considered for different values of α and various sets of WFA periods. Table 2 summarize the predicting power of WFA results for the P_α parameter, in terms of the correlation coefficients.

	Without noise			**With noise**		
	$P_{2.5}$	P_5	P_{10}	$P_{2.5}$	P_5	P_{10}
r(14.0)	0.87	0.75	0.63	0.72	0.67	0.53
r(28.0)	0.85	0.88	0.87	0.76	0.84	0.84
r(1.6)+r(3.0)+r(7.0)+ r(12.0)+r(14.0)	0.89	0.83	0.77	0.77	0.72	0.60
r(1.6)+r(3.0)+r(7.0)+ r(12.0)+r(14.0)+r(28.0)	0.92	0.91	0.89	0.83	0.86	0.84

Table 2. Correlation coefficients.

It is found that the set of relaxation levels $W_{14} = \{r(1.6), r(3.0), r(7.0), r(12.0), r(14.0)\}$ constitute the best set of predictors, up to 14 minutes, for P_α. Moreover, it is found that the inclusion of $r(28.0)$ increases the correlation coefficient between the P_α and the predictors of the regression model.

3 Simulations Results

The ARX and WFA predictors of the persistence parameter are compared calculating the error

$$e_\alpha = P_\alpha - \hat{P}_\alpha \tag{2}$$

where P_α is true value of the parameter P for $\alpha = 5\%, 10\%$ and $\hat{P}_\alpha$ is the value estimated either by the predictor ARX process or by the linear regression with the set $W_{14} = \{r(1.6), r(3.0), r(7.0), r(12.0), r(14.0)\}$ of WFA average periods.

The boxplots of e_5, exhibited in Figure 3, indicate that the ARX method mostly overestimate P_α with a small dispersion of values, whilst the WFA method have a practically null mean error and presents a higher dispersion of values. However, the WFA method allows the estimation of the parameter P_α 14 minutes after the administration of the initial *bolus*.

Consider the simulated responses with $P_{10} > 28.0$ minutes and let $W_{28} = \{r(1.6), r(3.0), r(7.0), r(12.0), r(14.0), r(28.0)\}$ denote another set of WFA average periods. Figure 4 presents the boxplots of e_{10} for these simulated responses. $\hat{P}_{10}$ has been estimated by the predictor ARX process, as before, and by the linear regression with the set W_{28} of average periods. It can be seen a decreasing in the dispersion of error values, mostly for the WFA case.

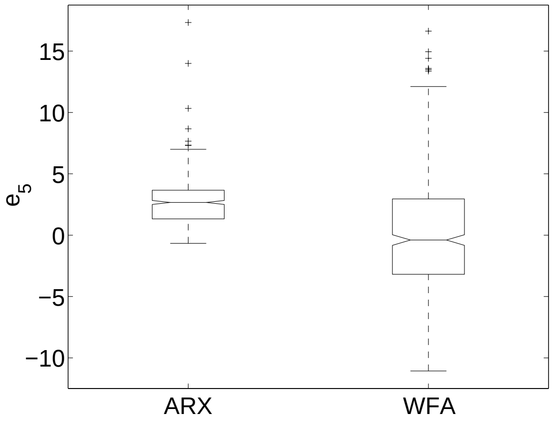

Figure 3. Boxplots of e_5.

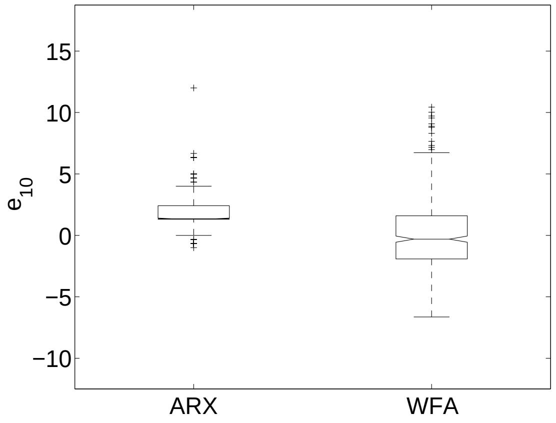

Figure 4. Boxplots of e_{10} for simulated responses with $P_{10} > 28.0$ minutes.

Consider, now, the simulated neuromuscular blockade response during automatic control infusion of *atracurium*, $r(t)$, represented in Figure 5 that mimics the clinical case illustrated in Figure 2.

Figures 6 and 7 present, respectively, the same simulated neuromuscular blockade response when the control action is delayed and starts at the instant when is predicted the up coming of the low level reference value: 38.0 minutes for the ARX approach and 37.0 minutes for the WFA case. It can be seen the improvement thus obtained in the reference tracking. Furthermore, the initial overshoot and the oscillatory behaviour have decreased.

The typical values for α (2.5%, 5% and 10%) used in this analysis are based on most of the real cases colleted so far and on clinical requirements. Even though the 5% level is considered as typical and therefore recomended in practice, it may be necessary to modify it depending on the individual real data colleted during the surgical procedure (for example, in some clinical cases, the *bolus* response may not reach a sufficiently low level).

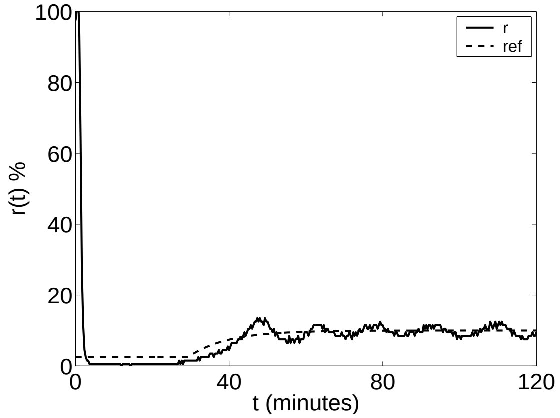

Figure 5. Simulated neuromuscular blockade response and reference when the control action starts at 30 minutes.

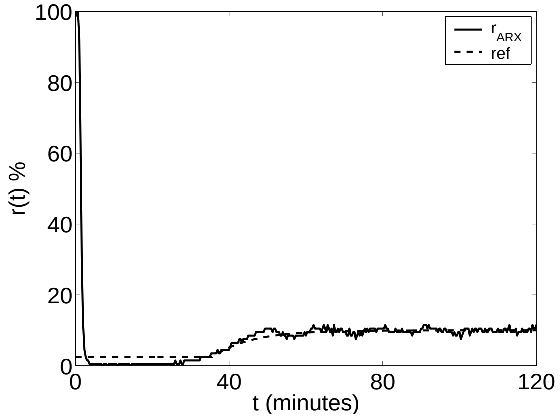

Figure 6. Simulated neuromuscular blockade response and reference when the control action starts at 38.0 minutes (ARX prediction of P_5).

4 Final Remarks

The problem of designing an adaptive controller of neuromuscular blockade which incorporates an alarm system is considered. The results show that the on-line prediction of the instant at which begins the patient's recovery from the initial *bolus*, either by ARX forecasting or WFA methodology, is a robust technique that can be used to improved the reference pursuit and to adapt the automatic control system to individual requirements.

Furthermore, the alarm system can easily be adapted to deal with other related situations, namely the detection of eventual changes in the dynamics of the system.

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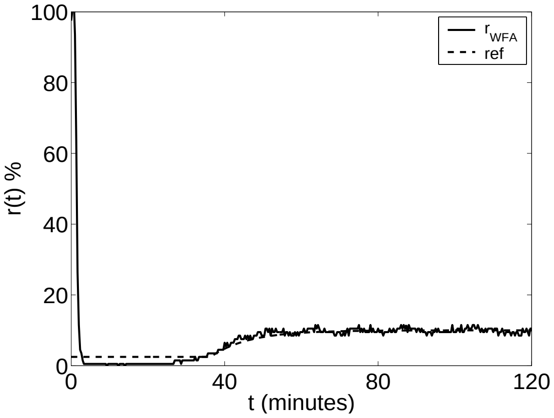

Figure 7. Simulated neuromuscular blockade response and reference when the control action starts at 37.0 minutes (WFA prediction of P_5).

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