# RELEVANT CONTRIBUTIONS TO AN ADAPTIVE CONTROL SYSTEM FOR THE NEUROMUSCULAR BLOCKADE

Teresa Mendonça[1], M. Eduarda Silva[1], Isabel Silva[2] and Hugo Magalhães[1]
Dep. Matemática Aplicada, Fac. de Ciências, Univ. do Porto,
Rua do Campo Alegre 687, 4169-007 Porto, Portugal
Phone: +351-220100802, Fax: +351-220100809
E-mail: {tmendo, mesilva, imsilva, hfmagalh}@fc.up.pt
[1] UI&D Matemática e Aplicações, Universidade de Aveiro
Campus Universitário de Santiago, 3810-193 Aveiro, Portugal
[2] Dep. de Engenharia Civil, Fac. de Engenharia, Univ. do Porto,
Rua Dr. Roberto Frias, 4200-465 Porto, PORTUGAL

ABSTRACT: The aim of this paper is to illustrate how statistical techniques based on Walsh-Fourier spectral analysis (WFA) contributes to the design of an on-line adaptive control system for neuromuscular blockade that could be used successfully in a wide range of populations. It is found that neuromuscular blockade levels at the average periods indicated by WFA have a high predictive power for the parameters of the controller, providing additional information about the model. A classification algorithm, based on the observed values of neuromuscular blockade level at significant WFA periods, enables the on-line individual tuning of a time varying adaptive reference profile, hence decreasing the overshoot. The system provides strong robustness to inter and intra-individual variability of the patient's responses and adaptation to the individual requirements.

KEYWORDS: Control Systems in Medicine, Adaptive Control, On-Line Autocalibration, Regression Models, Walsh-Fourier Analysis.

## INTRODUCTION

Muscle relaxant drugs are currently given during surgical operations. The non-depolarising types of muscle relaxant act by blocking the neuromuscular transmission, thereby producing muscle paralysis. For clinical reasons the patient must undergo an initial *bolus* dose in order to induce total muscle relaxation in a very short period of time (usually shorter than 5 minutes). A variety of different approaches to the design of controllers for the automatic control of neuromuscular blockade has been proposed ([1], [2], [3]). The design of these controllers is usually based 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, 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. This variability suggests the need for an individual tuning of the controller according to the characteristics of the patient.

Methods for the on-line autocalibration of digital PID controller parameters for the administration of a muscle relaxant have been already proposed ([4], [5], [6]). The parameters of the PID controller (namely the proportional gain ($g_c$), the derivative gain constant ($c_d$) and the integral time constant ($c_i$)) have been obtained from the L and R parameters deduced from the Ziegler-Nichols step response method [7], applied to an empirical model for the muscle relaxant [4]. The subsequent tuning of the controller to the dynamics of a patient undergoing surgery is performed by adjusting the R and the L values using multiple linear regression techniques with predictor variables extracted from the observed initial *bolus* response.

The predictor variables used in this study are a set of shape parameters (SP) and a set of neuromuscular blockade levels at the average periods indicated by the Walsh-Fourier spectral analysis (WFA). It was found that WFA provides a characterization of the neuromuscular blockade response induced by an initial *bolus* at the beginning of anaesthesia, [8], leading to controller parameter prediction with high power. This findings are still apply for closed loop systems. The performance of the control systems calibrated by the R and L parameters estimated using SP and WFA is assessed. Furthermore, the WFA periods may be used to classify a bank of simulated models of neuromuscular blockade and subsequently to improve initial reference tracking.

## *BOLUS* RESPONSE DATA ANALYSIS

### EMPIRICAL MODEL

The dynamic response of the neuromuscular blockade may be modelled by a second order linear pharmacokinetic model relating the drug infusion rate, $u(t)$, to the plasma concentration, $c_p(t)$, and a nonlinear dynamic model relating $c_p(t)$ to the induced pharmacodynamic response, $r(t)$. 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. In this study the muscle relaxation drug used is the *atracurium* ([9], [10]). The pharmacodynamic effect for *atracurium* may be modelled by the Hill equation,

$$r(t) = \frac{100 C_{50}^{\beta}}{C_{50}^{\beta} + c_e^{\beta}(t)} \tag{1}$$

where the effect concentration, $c_e(t)$, is related to $c_p(t)$ by

$$\dot{c}_e(t) = k_{e0} c_p(t) - k_{e0} c_e(t) \tag{2}$$

where $k_{e0}$, $C_{50}$ and $\beta$ are also patient-dependent parameters. In order to accommodate the clinical data, the model for *atracurium* has been modified including on the linear part of the system a first order block, [4],

$$g(s) = \frac{1/\tau}{s + 1/\tau} \tag{3}$$

in a series connection. The time constant $\tau$ is assumed to be a random variable independent of the remaining pharmacokinetic/pharmacodynamic parameters. Therefore, the linear part of the resulting empirical model may be represented by the following transfer function from $u$ to $c_e$,

$$h_L(s) = \left( \frac{a_1}{s + \lambda_1} + \frac{a_2}{s + \lambda_2} \right) \frac{k_{e0}}{s + k_{e0}} \frac{1/\tau}{s + 1/\tau}. \tag{4}$$

This empirical model replicates well the characteristics of the patients responses, [4]. A set of 500 models, hereinafter referred as bank of models, are generated assuming a multidimensional log-normal distribution for the eight pharmacokinetic/pharmacodynamic parameters and used throughout this study. Also, for a better replication of the clinical environment, simulated measurement noise is added to each of the generated models. For this bank of models an automatic control system is designed, such that the value of the reference is initially fixed at a low level during the first 30 minutes, being gradually raised to the set-point (*ref*).

### *BOLUS* RESPONSE SHAPE PARAMETERS

The shape parameters (SP) represented in Figure 1 have been used to characterize the response induced by a *bolus* of muscle relaxant administered at t=0 minutes ([4], [6]). T80, T50 and T10 are elapsed times between the *bolus* administration and the time the response becomes less than 80%, 50% and 10%, respectively. S is a slope parameter and P is a persistence parameter, since it describes the duration of the *bolus* effect on the patient.

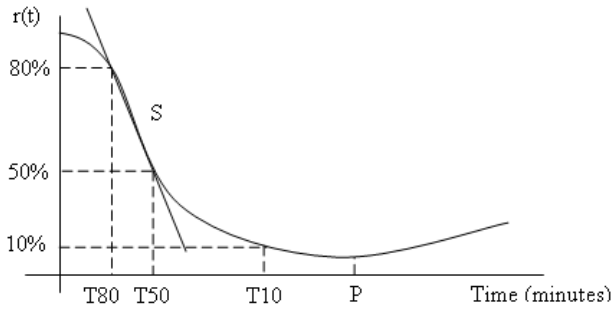


Figure 1: Shape parameters.

For each of the simulated models, with and without added noise, the parameters T80, T50, T10, S and P are obtained and used as predictors for the controller parameters L, R and $g_c$. The results are summarized in Table I, in terms of the % of variation explained by the multivariate regression model. A higher predictive power is obtained only when P is added to

the multivariate regression model. However, in a clinical situation the *bolus* response may not reach a sufficiently low level to allow the estimation of parameter P. Thus, although the parameter P is used in this study with simulated data, it cannot be directly used in a real situation.

| | Without noise | | | Without noise | | |
|---|---|---|---|---|---|---|
| **Predictors** | **L** | **1/R** | $g_c$ | **L** | **1/R** | $g_c$ |
| T50 | 87 | 42 | 7 | 87 | 42 | 7 |
| T50 + P | 94 | 70 | 69 | 93 | 69 | 65 |
| T50 + S | 87 | 49 | 22 | 87 | 45 | 15 |
| T50 + S + P | 95 | 70 | 69 | 94 | 69 | 65 |
| T80 + T50 + T10 + S | 90 | 61 | 59 | 89 | 57 | 52 |
| T80 + T50 + T10 + S + P | 95 | 73 | 74 | 94 | 69 | 70 |

Table I: % of variation explained for linear regression models.

*BOLUS* RESPONSE WALSH-FOURIER SPECTRAL ANALYSIS

Walsh-Fourier spectral analysis is a procedure used to analyse and characterize time series, especially 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 ([11],[12],[13]) which form a complete, ordered and orthonormed set of rectangular wave taking the values -1 and 1. The sequency-ordered Walsh functions are denoted by $W(n,t)$, with $t \in [0,1[$ and $n = 1, 2, \ldots$. The argument $n$ is denoted by *sequency* and represents the number of switches signs (zero-crossings) in the unit interval. [12] defines the term sequency (hereinafter represented by H-sequency) as one half the average number of zero crossings or sign changes that a function makes per unit time and defines the *average period* of oscillation (multiplicative inverse of *H-sequency*) as twice average separation, in time, between sign switches.

Let $x(0), \ldots, x(N-1)$ be $N$ observations of a stochastic process $\{X(n)\}$. An estimator of the spectral density function (spectrum) of Walsh-Fourier is the *Walsh periodogram* ([14], [15], [16], [17]), which is the square of the Walsh-Fourier transform of the data

$$I_W(\lambda_j) = \left[ \frac{1}{\sqrt{N}} \sum_{n=0}^{N-1} x(n) W(n,\, \lambda_j) \right]^2, \tag{5}$$

where $\lambda_j$ is a sequency of the form $\lambda_j = j/N$, $1 \leq j \leq N-1$. One can plot $I_W(\lambda_j)$ *versus* $\lambda_j$ to inspect for *peaks*. In the sequency domain, a peak indicates a *switch* each $\lambda_j$ time points. The Walsh periodogram given in (5) is modified to obtain the *Walsh-Harmuth periodogram*, by setting

$$I_H(\lambda_j) = I_W((2j-1)/N) + I_W(2j/N),$$

with $j = 1, 2, \ldots, (N-2)/2$, $N = 2^p, p \in \mathbb{N}$, where $\lambda_j$ is the H-sequency.

Considering that during a surgical intervention a patient attains different levels of neuromuscular blockade, it is investigated how the Walsh-Fourier analysis can contribute to improve the controller. It has been found, [8], that the average periods are correlated with SP for both the available real cases and the bank of simulated models (open loop).

Applying WFA to the bank of models in closed loop, it is found that the average periods are 1.0, 1.6, 2.6, 6.0, 12.0, 14.0, 17.0, 28.0, 34.0 and 42.0 minutes, approximately. Some of these periods coincide with the periods found for the open loop bank of models. Table II summarizes the predictive power of WFA results, in terms of the % of variation of L, R and $g_c$ for the closed loop simulations.

| | Without noise | | | With noise | | |
|---|---|---|---|---|---|---|
| **Predictors** | **L** | **1/R** | $g_c$ | **L** | **1/R** | $g_c$ |
| r(1.0) + r(1.6) + r(2.6) + r(6.0) + r(12.0) | 93 | 68 | 73 | 90 | 62 | 52 |
| r(1.0) + r(1.6) + r(2.6) + r(6.0) + r(12.0) + r(14.0) | 93 | 70 | 82 | 91 | 66 | 62 |
| r(1.6) + r(2.6) + r(6.0) + r(12.0) | 92 | 67 | 72 | 90 | 62 | 50 |
| r(1.6) + r(2.6) + r(6.0) + r(12.0) + r(14.0) | 93 | 70 | 81 | 91 | 65 | 61 |

Table II: % of variation explained for linear regression models (closed loop).

The inclusion of the relaxation level at 14.0 minutes, $r(14.0)$, in the set of predictors improves the quality of estimation of the controller parameter, specially for $g_c$. Further, it has been found, [8], that the persistence parameter P is highly correlated with $r(14.0)$. Therefore, $r(14.0)$ is a suitable candidate for replacing P in the multivariate regression model used for the on-line autocalibration of the controller parameters.

## CALIBRATING THE AUTOMATIC CONTROL SYSTEM

The additional information provided by the relaxation levels in the average periods of WFA suggests that the reference tracking may be improved if the control system, which is usually closed at 10 minutes, is recalibrated afterwards.
Thus, for the bank of models, a first calibration is done 10 minutes after the administration of the initial *bolus* using as predictors for L and R the set of SP and WFA relaxation levels indicated in Table III. Also, for each model of the bank, two calibrations, at 10 and 21 minutes, are performed with L and R estimated by using the set of predictors indicated in Table IV.

| | **10 minutes** |
|---|---|
| A1: | T50 + S |
| A2: | T50 + S + P |
| A3: | r(1.3) + r(1.6) + r(3.0) + r(7.0) |

Table III: Predictors used in the calibration at 10 minutes.

| | **10 minutes** | | **21 minutes** |
|---|---|---|---|
| B1: | T50 + S | $\rightarrow$ | T10 + T50 + T80 + S |
| B2: | T50 + S + P | $\rightarrow$ | T10 + T50 + T80 + S + P |
| B3: | r(1.3) + r(1.6) + r(3.0) + r(7.0) | $\rightarrow$ | r(1.3) + r(1.6) + r(3.0) + r(7.0) + r(14.0) |

Table IV: Predictors used in the calibrations at 10 and 21 minutes.

The performances of the resulting automatic control systems are compared through the reference tracking by evaluating the mean square error (MSE), in the steady-state (after 75 minutes), defined by

$$\text{MSE}(M) = \sum_{t=75}^{180} (ref - r_M(t))^2,$$

where $M = 1, \ldots, 500$ is a model in the bank, $r_M(t)$ is the relaxation level for the model $M$ at the time $t$ and $ref$ is the reference value. The MSEs thus obtained are represented in the boxplots of Figure 2.

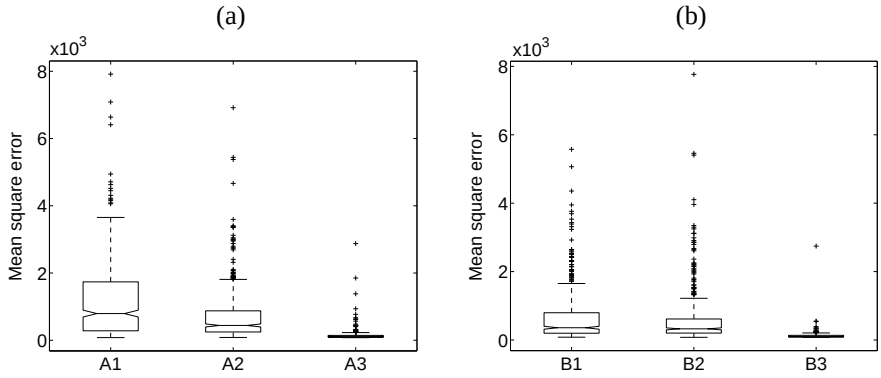


Figure 2: Boxplots of MSE for (a) one calibration at 10 minutes; (b) two calibrations, at 10 and 21 minutes.

Analysing Figure 2 it can be concluded that the use of the WFA relaxation levels as predictors for the controller parameters and the recalibration of the control system at 21 minutes leads to a noticeable decrease in the mean value as well as the variability of the MSE and, therefore, to a better reference tracking.

## CLASSIFICATION

The bank of models is classified using a classification program, the *K-Prototype*, based on the *K-Mean* algorithm for classification with the additional advantage of supplying the optimal number of existing classes in the data set evaluated

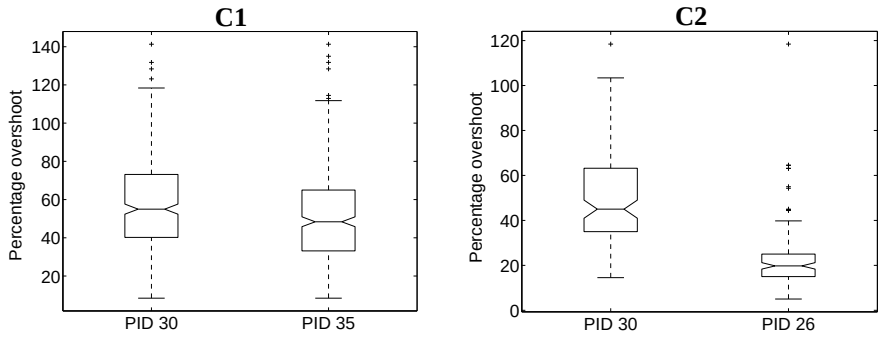

Figure 3: Boxplots of overshoot for the two classes, **C1** and **C2**.

([18], [19], [20], [21]).
This classification algorithm, using the observed values of neuromuscular blockade level at significant Walsh-Fourier periods $\{r(12.0), r(14.0), r(17.0), r(28.0)\}$, leads to an optimal classification of the model bank in two classes. This classification may be used to define an adaptive reference profile as opposed to the fixed reference profile, providing a substantial improvement of the control performance.
The adaptive reference profile for each class is obtained as the median of the duration of the *bolus* effect (relaxation level under 10%). Thus, for class **C1** the control action is set after 35 minutes whereas for class **C2** it is set at 26 minutes.
The performance of the two control systems (fixed reference profile *versus* class dependent reference profile) is compared calculating the overshoot (distance between the maximum value of the response and the reference value) for each model. The values thus obtained, represented in the boxplots of Figure 3, show a marked improvement in the overshoot, specially for **C2**.

## FINAL REMARKS

Neuromuscular blockade levels at the average periods indicated by WFA have a high predictive power for the parameters of the controller, both in open and closed loop situations and even in the presence of the high level noise that often contaminates the measurement of the muscle relaxation response.
The use of the WFA allows the construction of a control system which incorporates a recalibration of the controller parameters leading to an improved reference tracking. The results obtained so far indicate that WFA may be used to detect a time varying model.
Moreover, the initial reference tracking may also be improved with a decrease of the overshoot using an adaptive reference profile based on a classification of the models obtained from WFA.

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