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Statistical analysis of neuromuscular blockade response: contributions to an automatic controller calibration

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Abstract

Muscle relaxant drugs are currently given during surgical operations. The design of controllers for the automatic control of neuromuscular blockade benefits from an individual tuning of the controller to the characteristics of the patient. A novel approach to the characterization of the neuromuscular blockade response induced by an initial *bolus* at the beginning of anaesthesia is proposed. This approach is based on the statistical analysis of the data using principal components and Walsh–Fourier spectral analysis. These methods provide information about the patients dynamics, allowing the on-line autocalibration of the controller, using multiple linear regression techniques. Observed and simulated data are used to compare different approaches to the characterization of the *bolus* response.

Keywords: Control application; On-line autocalibration; Principal components analysis; Regression models; Walsh–Fourier analysis; Wiener models

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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-depolarizing 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 for the neuromuscular blockade has been proposed (Linkens, 1994; Schilden and Olkkola, 1991; Wait et al., 1987). 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 (Lago et al., 1998; Mendonça and Lago, 1998). This variability suggests the need for an individual tuning of the controller according to the characteristics of the patient (Lago et al., 1998; Mendonça and Lago, 1998).

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 min). It is reasonable to assume that the response of the patient to the *bolus* carries valuable information that should be accounted for in the design of an automatic control system for the neuromuscular blockade, thus resulting in an improved tuning of the controller to the patients individual dynamics and dosage requirements.

Methods for the on-line autocalibration of a digital PID controller parameters for the administration of a muscle relaxant have been already proposed (Lago et al., 1998, 2000; Mendonça and Lago, 1998). The parameters of the PID controller (namely the proportional gain, the derivative gain and the integral time constant) have been obtained from the L and R parameters deduced from the Ziegler–Nichols step response method (Franklin, 1994), applied to the pharmacokinetic/pharmacodynamic model for the muscle relaxant. The subsequent tuning of the controller to the dynamics of a patient undergoing surgery is performed by adjusting multiple linear regression models of L and R^{-1} on explanatory or predictor variables extracted from the observed *bolus* response. Here, three different approaches to the characterization of the observed *bolus* response are considered. The *bolus* response is analysed using two statistical techniques: principal components analysis (PCA), and Walsh–Fourier spectral analysis (WFA), thus obtaining predictor variables for the controller parameters. The descriptions of the *bolus* response proposed here, PCA and WFA, are compared with an alternative method based on the *bolus* response shape parameters, SPA (Lago et al., 1998, 2000; Mendonça and Lago, 1998).

2. Bolus response data analysis

In this section, the neuromuscular blockade model is presented and three different approaches are used to characterize the observed *bolus* response.

2.1. Empirical model

The dynamic response of the neuromuscular blockade may be modelled by a Wiener structure (Lago et al., 1998; Weatherley et al., 1983). It is composed by a linear compartmental pharmacokinetic model relating the drug infusion rate $u(t)$ ($\mu g\,kg^{-1}\ min^{-1}$), to the plasma concentration $c_p(t)$ ($\mu g\ ml^{-1}$), 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* (Ward et al., 1983; Weatherley et al., 1983). The pharmacokinetic model may be described by the state equations,

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

where a_i ($kg\,ml^{-1}$) and λ_i (min^{-1}) ($i = 1, 2$) are the pharmacokinetic patient-dependent parameters, $u(t)$ is the quantity of drug administered by time unit, $x_i(t)$ ($i = 1, 2$) are the state variables and $c_p(t)$ is the plasma concentration. The pharmacodynamic effect for *atracurium* may be modelled by the Hill equation

$$r(t) = \frac{100 C_{50}^{\beta}}{C_{50}^{\beta} + c_e^{\beta}(t)}, \tag{2}$$

where the effect concentration $c_e(t)$ ($\mu g\,ml^{-1}$) is related to $c_p(t)$ by

$$\dot{c}_e(t) = k_{e0} c_p(t) - k_{e0} c_e(t), \tag{3}$$

where k_{e0} (min^{-1}), C_{50} ($\mu g\,ml^{-1}$) and β are also patient-dependent parameters. Fig. 1(a) illustrates the responses induced on 85 patients by the administration of a *bolus* of 500 $\mu g\,kg^{-1}$ of *atracurium* in the beginning of the surgery. 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,

$$g(s) = \frac{1/\tau}{s + 1/\tau} \tag{4}$$

in a series connection. The time constant τ (min) is assumed to be a random variable independent of the remaining pharmacokinetic / pharmacodynamic parameters (Lago et al., 1998).

Therefore, the linear part of the resulting empirical model may be represented by the following transfer function from u to c_e.

$$h_L(s) = \left(\frac{a_1}{s + \lambda_1} + \frac{a_2}{s + \lambda_2} \right) \frac{k_{e0}}{s + k_{e0}} \frac{1/\tau}{s + 1/\tau}. \tag{5}$$

The neuromuscular relaxation level is simulated assuming an uniform distribution for τ and a multidimensional log-normal distribution for the seven pharmacokinetic/pharmacodynamic

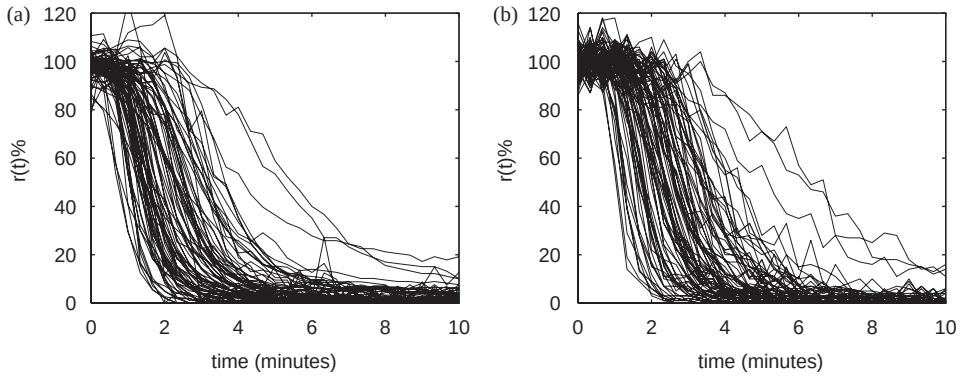

Fig. 1. The responses induced by a *bolus* of 500 $\mu g\,kg^{-1}$ of *atracurium* on 85 patients undergoing surgery (a), and simulated responses (100 models) induced by a *bolus* of 500 $\mu g\,kg^{-1}$ of *atracurium* with added measurement noise (b).

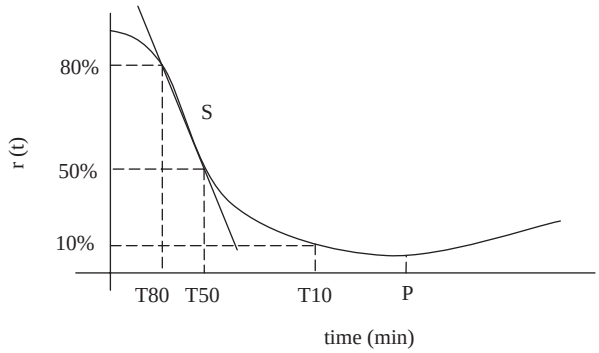

Fig. 2. Parameters used to characterize the neuromuscular blockade response induced by a *bolus* of a muscle relaxant administered at $t = 0$ min.

parameters and used throughout this study. Also, for a better replication of the clinical environment, simulated measurement log-normal noise is added to each of the generated models. Fig. 1(b) illustrates 100 responses simulated the empirical model (Eqs. (2) and (5)) using an uniform distribution for τ on the interval [0, 3.5] min. As illustrated, the empirical model replicates well the characteristics of the patients responses in Fig. 1(a).

2.2. Bolus response shape parameters

A method to characterize the *bolus* response based on shape parameters obtained on-line, has been proposed (Lago et al., 1998; Mendonça and Lago, 1998; Lago et al., 2000). The diagram on Fig. 2 represents the shape parameters used to characterize the response induced by a *bolus* of muscle relaxant administered at $t = 0$ min. $T80$, $T50$ and $T10$ are elapsed times between the *bolus* administration and the time the response $r(t)$ 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. 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 used in a real situation.

2.3. Bolus response PCA

Principal Components Analysis is a statistical procedure which is performed in order to simplify the description of a set of correlated variables. In the present situation, those variables are the m time consecutive measurements, $r(1), \ldots, r(m)$, of the muscle relaxation response induced by the *bolus* of muscle relaxant given in the beginning of anaesthesia. The measurements are taken every δt seconds on the interval $[0, (m-1).\delta t]$ ($\delta t = 20$ sec is a typical value). Let $\mathbf{r}$ be the random vector $\mathbf{r} = [r(1), \ldots, r(m)]^T$ with mean $\mathbf{r}_0$ and correlation matrix $\mathbf{\Sigma}$.

Each principal component is a linear combination of these variables. The coefficients of these linear combinations are chosen such that they define orthogonal directions of maximum variability and are obtained as the eigenvectors, $\boldsymbol{v}_1, \ldots, \boldsymbol{v}_m$, of $\mathbf{\Sigma}$. Considering only the k most significant eigenvalues, $\theta_1, \ldots, \theta_k$, the vector $\mathbf{r}$ is projected on a lower dimensional space without loosing much information, as follows

$$\mathbf{r} \approx \mathbf{r}_0 + \boldsymbol{v}\mathbf{a}, \tag{6}$$

where

$$\mathbf{a} = \boldsymbol{v}^{\mathrm{T}}(\mathbf{r} - \mathbf{r}_0), \tag{7}$$

and $\boldsymbol{v} = [\boldsymbol{v}_1, \ldots, \boldsymbol{v}_k]$.

The proportion of the total variation in the original data explained by the first k components is given by

$$p_k = \frac{\sum_{j=1}^{k} \theta_j}{\sum_{j=1}^{m} \theta_j}.$$

Consider the 100 simulated responses induced by a *bolus* of 500 $\mu g\,kg^{-1}$ of *atracurium* without added noise, represented in Fig. 3(a). Performing PCA on this data, it is found that the proportions of the total variation explained by the first 3, 5 and 10 principal components are $p_3 = 98.5\%$, $p_5 = 99.8\%$ and $p_{10} = 100\%$, respectively. Thus, for practical purposes it is considered that the muscle relaxation response can be accurately represented by the first three principal components. The projections of each simulated response on this lower dimensional space is obtained from equation (6) for $k = 3$. Fig. 3(b) illustrates the projections for the set of 100 simulated responses represented in Fig. 3(a).

2.4. Bolus response WFA

Walsh-Fourier spectral analysis is a procedure used to analyze and characterize time series, specially when sharp discontinuities and changes of level occur in the data. The

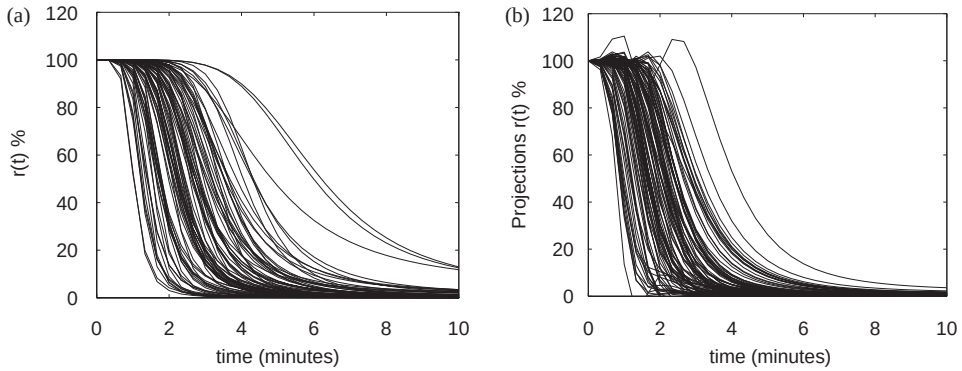

Fig. 3. Simulated responses (100 models) induced by a *bolus* of 500 $\mu g\,kg^{-1}$ of *atracurium* without added noise (a) and projections of these simulated responses using 3 principal components (b).

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 which form a complete, ordered and orthonormed set of *rectangular waves* taking the values -1 and 1 (Beauchamp, 1975; Harmuth, 1977; Kohn, 1980). The Walsh functions may be ordered in the so-called *Walsh or sequency* order, which is comparable to the frequency order of sines and cosines. The sequency-ordered Walsh functions are denoted by $W(n,t)$, where $t \in [0,1[$ and $n = 1, 2, \ldots$, the *sequency*, represents the number of times that the function switches signs in the unit interval.

Let $\{X(t)\}$ be a stationary stochastic process, with zero mean and absolutely summable autocovariance function, $R(k)$. The *Walsh–Fourier spectral density function* of $X(t)$ is defined as (Morettin, 1981; Robinson, 1972; Stoffer, 1987, 1991)

$$f(\lambda) = \sum_{\tau=0}^{\infty} \Gamma(\tau)\, W(\tau,\ \lambda), \quad 0 \leqslant \lambda < 1, \tag{8}$$

where $\Gamma(j)$ is the *logical covariance* defined by

$$\Gamma(j) = \frac{1}{N} \sum_{k=0}^{N-1} R(j \oplus k - k), \quad 1 \leqslant j < N, \tag{9}$$

with $\oplus$ being the dyadic sum (Robinson, 1972). Let $x(0), \ldots, x(N-1)$ be N observations of the process. An estimator of the spectral density is the *Walsh periodogram* of the data

$$I_W(\lambda_j) = \left[\frac{1}{\sqrt{N}} \sum_{n=0}^{N-1} x(n)\, W(n,\ \lambda_j) \right]^2, \tag{10}$$

where λ_j is a sequency of the form $\lambda_j = j/N,\ 1 \leqslant j \leqslant N-1$. 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".

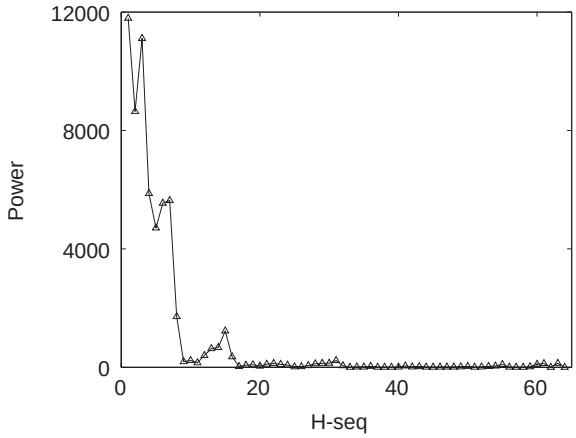

Fig. 4. Walsh periodogram of one of the patients.

Table 1
Correlation coefficients

	Without noise		With noise		Real data	
	r (1.7)	r (3.0)	r (1.7)	r (3.0)	r (3.0)	r (7.0)
T50	0.86	0.94	0.85	0.93	0.90	0.77

Considering that during the surgical intervention a patient attains different levels of neuromuscular blockade, we investigate how the WFA, can contribute to improve the controller. Accordingly, the Walsh periodogram of the induced neuromuscular blockade, $r(t)$, is evaluated on data collected during surgery: 34 clinical trials with neuromuscular blockade induced by a *bolus* of *atracurium*, measured during, approximately, 42 min, in a total of 128 samples. The periodograms thus obtained present peaks in the neighbourhood of the sequencies $\frac{3}{128}$, $\frac{7}{128}$ and $\frac{15}{128}$ which correspond to *average periods* (Harmuth, 1977) of 14.2, 6.1 and 2.8 min, respectively. In Fig. 4 the Walsh periodogram of one of the real cases is exhibited.

To investigate the relationship between the relaxation level at the *average periods* given by the WFA and the shape parameters $T10$, $T50$, $T80$, S and P), the correlation coefficients are computed, for simulated models with and without added noise and for the set of real data available, and found significant. Table 1 presents the correlation coefficients between $T50$ and the relaxation level at some of the *average periods*, which are highly significant (p-value < 0.001), thus establishing a clear relationship between these parameters and validating the use of $T50$ to characterize the individual dynamic model (Lago et al., 1998, 2000; Mendonça and Lago, 1998).

3. Regression models for the controller parameters

In this section, multiple linear regression models for each of the controller parameters, L and R^{-1}, on the explanatory (or predictor) variables extracted from the observed *bolus* response are constructed as follows. Consider a set of N independent observations $(\phi_i, \psi_{i1}, \ldots, \psi_{ip})$, $i = 1, \ldots, N$ where ϕ_i represents the observed value of the controller parameter, either L or R^{-1}, and the ψ_{ij} represent the observed values of the explanatory or predictor variables. Here the explanatory or predictor variables considered are: the shape parameters (SPA), the principal components (PCA) and the values of the *bolus* response at the Walsh–Fourier periods (WFA). Preliminary data analysis indicates that a multiple linear regression model is adequate.

Let $\mathbf{\Phi}(N \times 1)$ represent the vector of the controller parameter variables, assumed uncorrelated. Let $\mathbf{\Psi}$ be a $N \times (p+1)$ matrix of observed constants extracted from the *bolus* response,

$$\mathbf{\Psi} = \begin{bmatrix} 1 & \psi_{11} & \ldots & \psi_{1p} \\ 1 & \psi_{21} & \ldots & \psi_{2p} \\ \ldots & \ldots & \ldots & \ldots \\ 1 & \psi_{N1} & \ldots & \psi_{Np} \end{bmatrix}, \tag{11}$$

and let $\boldsymbol{\alpha}$ denote a $((p+1) \times 1)$ vector of unknown parameters. Then, the controller parameters and the *bolus* response are related by the equation,

$$\mathbf{\Phi} = \mathbf{\Psi}\ \boldsymbol{\alpha} + \boldsymbol{\varepsilon}, \tag{12}$$

where $\boldsymbol{\varepsilon}$ is a vector of uncorrelated random variables, normally distributed with mean 0 and variance σ^2. The observations on $\mathbf{\Phi}$ and $\mathbf{\Psi}$ are obtained from a set of $N = 500$ simulated models for the neuromuscular blockade response, without and with added noise, as introduced in Section 2.1. The multiple regression models are then fitted by least squares. The variables to be included in the model, are chosen by a stepwise selection method (Draper and Smith, 1981) and the usual residual checks are performed for all the regression models. In the following sections, the regression models presented are obtained from the simulated data without added noise. In the last section, to compare the different approaches, the worst case is considered: simulated data (neuromuscular blockade level) with added noise.

3.1. Regression on the shape parameters

In this section, the shape parameters are used as explanatory variables for the controller parameters. Linear regression models of L and R^{-1}, on $T50$, $T10$, $T80$, S and P are computed and summarized in Table 2 with the corresponding mean square error (MSE) and R^2, the percentage of variation in the data explained by the model.

The parameter $T50$ alone explains 87% of the variation of L and 42% of the variation of R^{-1}. These values are increased with the inclusion of the variables S and P, $T10$ and $T80$ as explanatory variables. Similar conclusions can be drawn when the observations are obtained in the presence of noise.

Table 2
Linear regression models on the shape parameters

Without noise			
	Model	R^2	MSE
SP1	$\hat{L} = 1.199 + 1.171\ T50$	87	0.125
SP2	$\hat{L} = -0.184 + 1.303\ T50 + 0.039\ P$	94	0.060
SP3	$\hat{L} = 0.591 + 1.092\ T50 + 0.007S + 0.047P$	95	0.048
SP4	$\hat{L} = 0.984 - 2.482\ T80 + 4.729\ T50 - 0.975\ T10$	90	0.098
SP5	$\hat{L} = 0.402 - 0.717\ T80 + 1.679\ T50 + 0.007S + 0.051P$	95	0.047
SP6	$\hat{R}^{-1} = 135.529 + 37.033\ T50$	42	1168.358
SP7	$\hat{R}^{-1} = 263.978 + 24.786\ T50 - 3.582\ P$	70	610.963
SP8	$\hat{R}^{-1} = 239.010 + 13.990\ T50 + 0.721\ S$	49	1028.655
SP9	$\hat{R}^{-1} = 271.716 + 485.487\ T80 - 579.857\ T50 + 128.376\ T10 + 0.741\ S$	61	790.814
SP10	$\hat{R}^{-1} = 319.767 + 383.120\ T80 - 392.637\ T50 + 64.762\ T10 + 0.316\ S$ $-3.415\ P$	73	560.076

3.2. Regression on principal components

For each of the simulated models, the *bolus* response is observed for the first 10 min, in a total of 30 observations. The principal components of $\mathbf{r} = [r(1), r(2), \ldots, r(30)]$ are obtained and used as explanatory variables in a multiple regression model for the variables L and R^{-1} (the controller parameters). The models thus obtained are summarized in Table 3 with the corresponding MSE and R^2.

The first 3 principal components explain 85% of the variation of L and 47% of the variation of R^{-1}. This percentage of explained variation increases with the inclusion of more principal components as expected, attaining a value of 92% for L and 66% for R^{-1}, with the first 10 principal components. The inclusion of the shape parameter P as one of the explanatory variables improves the fit of the regression models, PC2, PC4, PC6, PC8, PC10, PC12. The conclusions remain the same when observations with added noise are considered.

3.3. Regression on Walsh–Fourier periods

Table 4 summarizes the regression models obtained when the explanatory variables are the relaxation levels at the WFA average periods. The neuromuscular blockade level at the average periods found by WFA of the *bolus* response explain 93% of the variation of L and 69% of the variation of R^{-1}. A model with a smaller mean square error is found when the parameter P is added as an explanatory variable. When the analysis is carried out considering data with added noise the conclusions are similar.

Table 3
Linear regression models on the PCA

	Without noise		
	Model	R^2	MSE
PC1	$\hat{L} = 3.468 - 0.008a_1 - 0.002a_2 + 0.013a_3$	85	0.144
PC2	$\hat{L} = 2.077 - 0.010a_1 - 0.003a_2 + 0.015a_3 + 0.048\,P$	95	0.051
PC3	$\hat{L} = 3.468 + 0.004a_2 - 0.008a_3 - 0.002a_4 + 0.013a_5$	86	0.143
PC4	$\hat{L} = 2.062 - 0.002a_2 - 0.010a_3 - 0.003a_4 + 0.015a_5 + 0.048\,P$	95	0.050
PC5	$\hat{L} = 3.468 - 0.121a_2 + 0.172a_3 - 0.032a_4 + 0.013a_5 - 0.004a_6$ $+0.004a_7 - 0.008a_8 - 0.002a_9 + 0.013a_{10}$	92	0.076
PC6	$\hat{L} = 2.301 - 0.051a_2 + 0.045a_3 - 0.010a_8 - 0.003a_9 + 0.014a_{10}$ $+0.040\,P$	95	0.048
PC7	$\hat{R}^{-1} = 207.288 - 0.333a_1 + 0.424a_3$	47	1084.168
PC8	$\hat{R}^{-1} = 307.118 - 0.159a_1 + 0.283a_3 - 3.415\,P$	71	599.759
PC9	$\hat{R}^{-1} = 207.288 + 1.172a_1 - 0.485a_2 - 0.333a_3 + 0.424a_5$	49	1035.771
PC10	$\hat{R}^{-1} = 305.549 + 0.806a_1 - 0.162a_3 + 0.286a_5 - 3.361\,P$	71	584.472
PC11	$\hat{R}^{-1} = 207.288 + 8.316a_2 - 12.031a_3 + 2.638a_4 - 1.070a_5$ $+1.172a_6 - 0.485a_7 - 0.333a_8 - 0.066a_9 + 0.424a_{10}$	66	699.776
PC12	$\hat{R}^{-1} = 291.317 + 3.230a_2 - 2.886a_3 + 0.859a_6 - 0.186a_8 + 0.306a_{10}$ $-2.874\,P$	72	574.500

Table 4
Linear regression models on the WFA average periods

	Without noise		
	Model	R^2	MSE
WF1	$\hat{L} = 1.448 + 0.008\mathrm{r}(0.7) + 0.010\mathrm{r}(1.3) + 0.005\mathrm{r}(1.7) + 0.025\mathrm{r}(3.0)$ $+0.108\mathrm{r}(7.0) - 0.445\mathrm{r}(14.0)$	93	0.065
WF2	$\hat{L} = 0.179 + 0.008\mathrm{r}(0.7) + 0.010\mathrm{r}(1.3) + 0.006\mathrm{r}(1.7) + 0.025\mathrm{r}(3.0)$ $+0.082\mathrm{r}(7.0) - 0.161\mathrm{r}(14.0) + 0.036\,P$	95	0.048
WF3	$\hat{L} = 2.094 + 0.016\mathrm{r}(1.3) + 0.027\mathrm{r}(3.0) + 0.104\mathrm{r}(7.0) - 0.445\,\mathrm{r}(14.0)$	93	0.067
WF4	$\hat{L} = 0.816 + 0.014\mathrm{r}(1.3) + 0.003\mathrm{r}(1.7) + 0.026\mathrm{r}(3.0)$ $+0.081\mathrm{r}(7.0) - 0.161\mathrm{r}(14.0) + 0.036\,P$	95	0.049
WF5	$\hat{R}^{-1} = 100.659 + 0.573\mathrm{r}(0.7) + 0.429\mathrm{r}(1.7) + 0.288\mathrm{r}(3.0)$ $-1.417\mathrm{r}(7.0) + 30.568\mathrm{r}(14.0)$	69	638.302
WF6	$\hat{R}^{-1} = 180.072 + 0.593\mathrm{r}(0.7) + 0.350\mathrm{r}(1.7) + 0.307\mathrm{r}(3.0)$ $+13.138\mathrm{r}(14.0) - 2.243\,P$	72	569.560
WF7	$\hat{R}^{-1} = 153.535 + 0.504\mathrm{r}(1.7) + 0.232\mathrm{r}(3.0) - 1.277\mathrm{r}(7.0) + 30.365\mathrm{r}(14.0)$	68	647.796
WF8	$\hat{R}^{-1} = 233.641 + 0.425\mathrm{r}(1.7) + 0.261\mathrm{r}(3.0) + 13.354\mathrm{r}(14.0) - 2.212\,P$	72	579.985

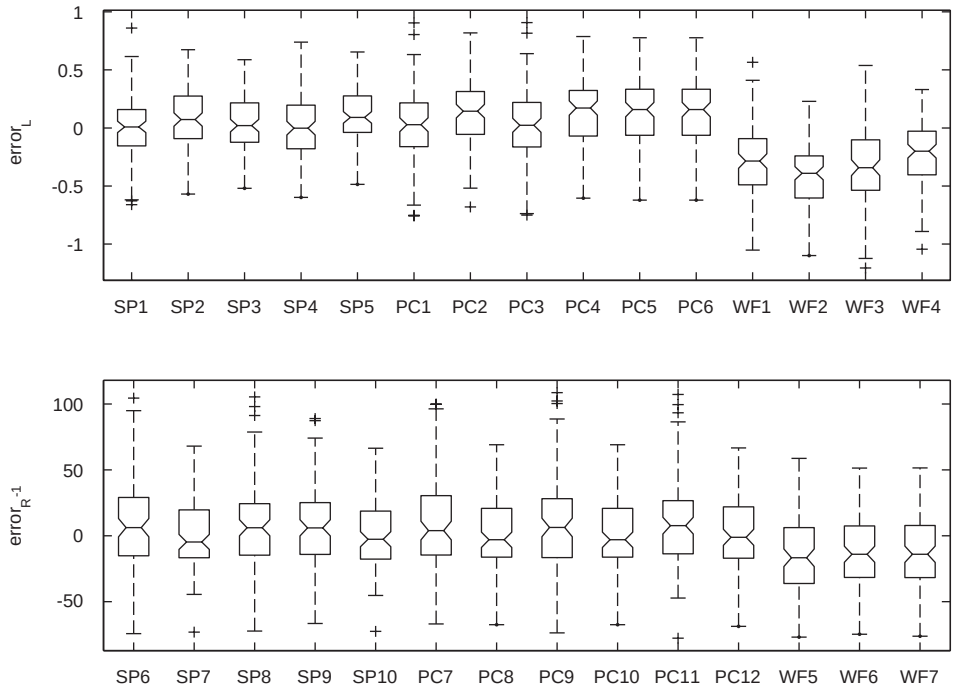

Fig. 5. Boxplots of the errors, $error_L$ and $error_{R^{-1}}$ obtained from 100 simulated neuromuscular blockade level models with added noise.

3.4. Choosing the controller parameters predictors

In this section the regression models obtained so far are compared in terms of their predicting performance. Thus, a new set of 100 responses are simulated from the empirical model (Eqs. (2) and (5)) and the values of the parameters L and R^{-1} of a PID controller are obtained by the Ziegler–Nichols step response method as described in Section 1. For each of the simulated models, with and without added noise, the shape parameters $T80$, $T50$, $T10$, S and P are computed. Moreover, PCA and WFA are accomplished and estimates for the controller parameters, L and R^{-1}, are obtained. The three different approaches are compared through the prediction error, computed as the difference between the observed and the estimated or predicted values for L and R^{-1}, $error_L$ and $error_{R^{-1}}$, respectively.

The results presented in Section 3.4 refer to the worst case, which is when the data is observed with noise.

Fig. 5 represents the boxplots of $error_L$ and $error_{R-1}$. Concerning parameter L, the errors that present a higher dispersion are those obtained from the models with the PCA and WFA regressors. Also L is, generally, underestimated by SP and PCA and overestimated by WFA. Now, consider the prediction of parameter R^{-1}. Observing the boxplots in Fig. 5 it is notorious that the inclusion of parameter P as a predictor variable in the multiple regression model, produces errors with a smaller mean and smaller variance, models SP7,

Table 5
Multiple regression models with regressor P replaced by regressor $r(14.0)$

	With noise		
Model	R^2	MSE	
SP4	$\hat{L} = 1.130 + 1.920\ T50 - 0.458\ T10$	89	0.105
SP5	$\hat{L} = 0.223 + 0.565\ T80 + 0.454\ T50 + 0.176\ T10 + 0.004S + 0.044\ P$	94	0.059
M1	$\hat{L} = 1.210 + 1.273\ T50 - 0.253$ r(14.0)	91	0.087
PC1	$\hat{L} = 3.468 + 0.008a_1 - 0.002a_2 + 0.013a_3$	85	0.145
PC2	$\hat{L} = 2.129 + 0.010a_1 - 0.003a_2 + 0.015a_3 + 0.045\ P$	94	0.057
M2	$\hat{L} = 3.719 + 0.010a_1 - 0.004a_2 + 0.014a_3 - 0.310$ r(14.0)	91	0.092
WF3	$\hat{L} = 2.127 + 0.015$r(1.3) $+ 0.029$r(3.0) $+ 0.067$r(7.0) $- 0.335$r(14.0)	90	0.096
WF4	$\hat{L} = 0.689 + 0.013$r(1.3) $+ 0.004$r(1.7) $+ 0.026$r(3.0) $+0.079$r(7.0) $- 0.117$r(14.0) $+ 0.040\ P$	94	0.056
SP9	$\hat{R}^{-1} = 208.877 + 76.627\ T80 - 123.180\ T50 + 52.049\ T10 + 0.418\ S$	57	880.635
SP10	$\hat{R}^{-1} = 276.985 + 27.283\ T80 + 0.103\ S - 3.439\ P$	69	627.804
M3	$\hat{R}^{-1} = 205.484 + 85.045\ T80 - 80.426\ T50 + 16.118\ T10 + 0.436\ S$ $+21.472$r(14.0)	64	738.834
PC7	$\hat{R}^{-1} = 207.288 + 0.316a_1 + 0.424a_3$	46	1090.990
PC8	$\hat{R}^{-1} = 304.874 + 0.128a_1 + 0.287a_3 - 3.282\ P$	70	618.584
M4	$\hat{R}^{-1} = 187.053 + 0.099a_2 + 0.307a_3 + 24.981$ r(14.0)	63	749.225
WF5	$\hat{R}^{-1} = 153.924 + 0.503$r(1.7) $+ 0.299$r(3.0) $+ 25.173$ r(14.0)	62	767.205
WF7	$\hat{R}^{-1} = 248.650 + 0.383$r(1.7) $+ 0.359$r(3.0) $+ 10.223$r(14.0) $- 2.585\ P$	71	601.216

SP10, PC8, PC10, PC12, WF6, WF7. However, this parameter is not suitable for practical implementation since in some cases the *bolus* response may not reach a sufficiently low level. Investigating the relationship between P and the Walsh–Fourier periods, it is found that P is correlated with $r(14.0)$: correlation coefficients of 0.82 and 0.71 for data without added noise and with added noise, respectively (p-values < 0.001).

Since $r(14.0)$ is easily observed, it is investigated the effect of replacing P by $r(14.0)$ in the multiple linear regression models. Analysing Table 5 , models M1, M2, M3, M4, it is found that the fit of the models, measured by MSE and R^2, does not decrease much.

To assess the performance of the models in predicting L and R^{-1}, boxplots for $error_L$ and $error_{R^{-1}}$ are presented in Fig. 6. The inclusion of $r(14.0)$ as explanatory variable decreases the variability of the errors, leading to more accurate predictions.

In a clinical environment a high level noise often contaminates the measurement of the muscle relaxation response, as illustrated in Fig. 1. The robustness of the controller parameters prediction, in the presence of noise in the *bolus* response measurement, has been investigated in detail. All the predictors have been found to be very insensitive to the presence of noise, the periods of the WFA achieving the best results. Therefore, it can be concluded that the on-line prediction of the controller parameters from the patient *bolus* response is a robust technique suitable for use in a clinical environment.

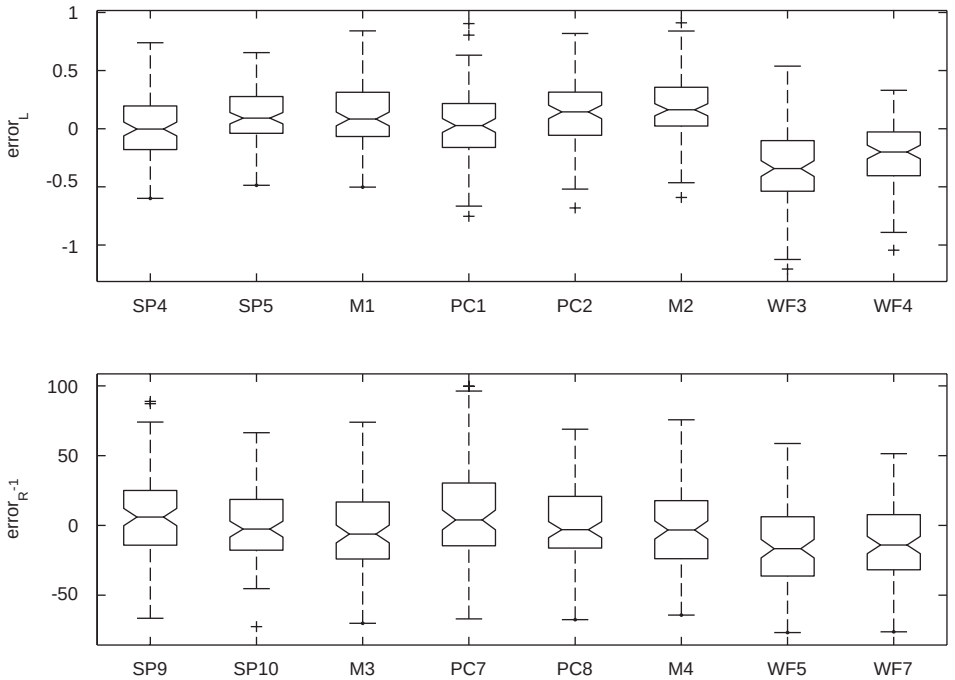

Fig. 6. Boxplots of the errors (100 models with noise).

4. Final remarks

Here, the problem of inferring patients individualized information from the response induced by an initial *bolus* dose given in the beginning of anaesthesia is considered. This individualized information is very important for the design of improved on-line autocalibrated automatic controllers of muscle relaxation. Two different statistical techniques are used to analyse and characterize the *bolus* response data: principal components analysis and Walsh–Fourier spectral analysis. Parameters deduced from the analysis are then used as predictors for the controller parameters, allowing the on-line autotuning of a PID controller. Results are illustrated using realistic dynamic models that mimic not only the large variability of patients responses to the administration of *atracurium*, but also the large level of measurement noise which occurs in a clinical environment. The robustness of the PCA and WFA for characterizing the patients individual responses to the *bolus* has been firmly established.

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References

Beauchamp, K.G., 1975. Walsh Functions and Their Applications. Academic Press, New York.

Draper, N.R., Smith, H., 1981. Applied Regression Analysis. Wiley, New York.

Franklin, G.F., 1994. Feedback Control of Dynamic Systems. Addison-Wesley, Reading, MA.

Harmuth, H.F., 1977. Transmission of Information by Orthogonal Function. Springer, Berlin.

Kohn, R., 1980. On the spectral decomposition of stationarity time series using Walsh functions. Adv. in Appl. Probab. 12, 183–199.

Lago, P., Mendonça, T., Gonçalves, L., 1998. On-line autocalibration of a PID controller of neuromuscular blockade. In: Proceedings of the 1998 IEEE International Conference on Control Applications. Trieste, Italy, pp. 363–367.

Lago, P., Mendonça, T., Azevedo, H., 2000. Comparison of on-line autocalibration techniques of a controller of neuromuscular blockade. In: Proceedings of IFAC Modeling and Control in Biomedical Systems. Karlsburg-Greisfswald, Germany, pp. 263–268.

Linkens, D.A., 1994. Intelligent Control in Biomedicine. Taylor & Francis, London.

Mendonça, T., Lago, P., 1998. Control strategies for the automatic control of neuromuscular blockade. Control Eng. Pract. 6, 1225–1231.

Morettin, P.A., 1981. Walsh spectral analysis. SIAM Rev. 23, 279–291.

Robinson, G.S., 1972. Logical convolution and discrete Walsh and Fourier power spectra. IEEE Trans. Audio Electroacoust. AU-20, 271–280.

Schilden, H., Olkkola, K.T., 1991. Use of a pharmacokinetic-dynamic model for the automatic feedback control of *atracurium*. Eur. Clin. Pharmacol. 40, 293–296.

Stoffer, D.S., 1987. Walsh–Fourier analysis of discrete-valued time series. J. Time Ser. Anal. 8, 449–467.

Stoffer, D.S., 1991. Walsh–Fourier analysis and its statistical applications. J. Amer. Statist. Assoc. 86, 461–479.

Wait, C., Goat, V., Blogg, C., 1987. Feedback control of neuromuscular blockade: a simple system for the infusion of anaesthesia. Anesthesia 42, 1212–1217.

Ward, S., Neill, A., Weatherley, B., Corall, M., 1983. Pharmacokinetics of *atracurium* besylate in healthy patients (after a single i.v. *bolus* dose). Br. J. Anaesth. 55, 113–118.

Weatherley, B., Williams, S., Neill, S., 1983. Pharmacokinetics, pharmacodynamics and dose–response relationships of *atracurium* administered i.v. Br. J. Anaesth. 55, 39s–45s.