On-line controller autocalibration based on parameter predictors: a case study

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Abstract: In this paper, a method for the on-line autocalibration of a controller, based on statistical regression techniques, is presented. The control of neuromuscular blockade is used as a case study. The method relies on the information about the patients dynamics, inferred from the response induced by the initial bolus dose given in the beginning of anaesthesia. A new approach to the characterization of the bolus response based on Walsh-Fourier spectral analysis is considered. A detailed comparison of alternative descriptions is presented.

Key-Words: Control Application, On-line Autocalibration, PCA, Regression models, Walsh-Fourier, Wiener models.

1. 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. The extent of muscle paralysis (or muscle relaxation) is measured from an evoked EMG obtained at the hand by electrical external stimulation. A variety of different approaches to the design of controllers for the automatic control of neuromuscular blockade has been proposed [6, 10, 13]. 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, only describes the average characteristics of the response to the drug. Therefore, given the large interindividual variability of the responses, it provides a quite poor description of individual responses. In the vast majority of situations the controllers have fixed parameters, therefore the large variability of the individual responses to the infusion of the drug are simply accommodated by the intrinsic properties of a closed control loop. In spite of leading ultimately to a fixed-parameter controller, some of the techniques explicitly incorporate in the controller design a measure of the statistical variability of the patients responses, thus leading to a more robust control [7].

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). The detailed analysis of a large number of clinical results [4, 7] clearly indicates that the response of the patients to the administration of a muscle relaxant reveals a very large (and unexpected) non uniformity of responses. Such characteristic is not always predicted from the available pharmacokinetic and pharmacodynamic data, that although predicting a large interindividual variability of the responses, points to a much more uniform behaviour. This remark strongly suggests

the need for an individual tuning of the controller to the characteristics of the patient.

It is reasonable to assume that the response of the patient to the bolus given at the beginning of anaesthesia carries valuable information on the dynamics of the patients response to the infusion of the relaxant. Therefore, the characteristics of the bolus response should be accounted in the design of an automatic control system of neuromuscular blockade, thus resulting in an improved tuning of the controller parameters to the patients individual dynamics and dosage requirements.

Here, a new approach to the characterization of the individual dynamic based bolus response is proposed and the results compared with alternatives methods proposed. [4, 5].

2. The on-line estimation of the controller parameters by multiple regression

Methods for the on-line autocalibration of a digital PID controller parameters for the administration of a muscle relaxant had been already proposed [4, 5, 7]. 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, applied to the pharmacokinetic/pharmacodynamic model for the muscle relaxant. The subsequent tuning of the controller to the dynamics of a patient undergoing surgery was performed by adjusting the R and the L values using multiple linear regression techniques.

The applicability of the method relies on the fulfilment of two conditions: the availability of a probabilistic description for a pharmacokinetic/pharmacodynamic model for the drug and some individualised response of the patient, such as the response to the bolus of the relaxant usually given in the beginning of anesthesia.

Let $\mathbf{\Phi}_k\,(k = 1 : N)$ be the $(n \times 1)$ vector of the parameters of the controller for model k. For every model $\mathbf{\Theta}_k$ the bolus response is also obtained and a set of p variables describing such response are deduced from it. Let $\mathbf{\Psi}_k\,(k = 1 : N)$ be the $(p \times 1)$ vector of those variables. A linear regression model relating the variables $\mathbf{\Psi}$ and $\mathbf{\Phi}$ is assumed,

$$\mathbf{\Phi} = \alpha.\mathbf{\Psi} + \beta + \varepsilon \qquad (1)$$

where ε is a $(n \times 1)$ vector of random error terms and $\alpha\,(n \times p)$ and $\beta\,(n \times 1)$, are matrices of unknown parameters to be determined. This is a well known statistical procedure. Details on the estimation of α and β may be found in the reference manuals of the statistical package used, which usually incorporates tests for the adequacy of the linear model and parsimony tests (some of the p components of vector $\mathbf{\Psi}$ may be redundant and therefore should be eliminated). Post hoc analysis of the residuals ε should be made. Where a clear nonnormality is found, transformation of the components of $\mathbf{\Phi}$ should be considered.

The tuning of the controller parameters to a particular patient undergoing surgery is a simple procedure: it requires the extraction of the predictor variables $\mathbf{\Psi}$ from the observed bolus response and the estimation of the controller parameters $\mathbf{\Phi}$ from the regression equation,

$$\mathbf{\Phi} = \alpha.\mathbf{\Psi} + \beta \qquad (2)$$

Regarding the predictor variables, several approaches may be considered based on the bolus response.

Figure 1 illustrates the response induced by a bolus of a muscle relaxant administered in the beginning of the anaesthesia. The variable $r(t)$, normalised between 100% and 0% measures the level of muscle relaxation, 100% corresponding to full muscular activity and 0% to full paralysis. The diagram shows a set of parameters, that may be obtained on-line, and have been used to characterize the bolus response [4, 7]. $T80$, $T50$ 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.

The tuning of the PID controller was performed by a linear regression of L and R^{-1} on $T50$ [4]. A more complete description of the bolus response based on principal component analysis led to an alternative regression approach [5]. In the next section, we consider a Walsh-Fourier analysis (WFA) of the bolus response to determine significant periods and use them as predictor variables.

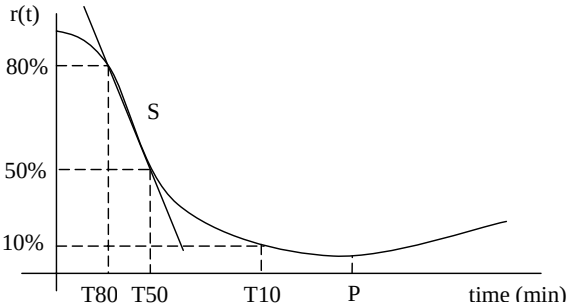

Fig. 1. Parameters used to characterize the muscle relaxation response induced by a bolus of a relaxant at $t = 0$.

3. Walsh-Fourier Spectral Analysis of the Bolus Response

Walsh-Fourier spectral analysis is a procedure used to analyse and characterize time series, specially when sharp discontinuities and changes of levels 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 which form a complete, ordered and orthonormed set of *rectangular waves* taking the values -1 e 1 [1, 2, 3]. 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 [8, 9, 11, 12]

$$f(\lambda) = \sum_{\tau=0}^{\infty} \Gamma(\tau)\, W(\tau,\, \lambda),\ \text{com}\ \ 0 \leq \lambda < 1 \qquad (3)$$

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

$$\Gamma(j) = \frac{1}{N} \sum_{k=0}^{N-1} R(j \oplus k - k), \quad 1 \leq j < N, \qquad (4)$$

with $\oplus$ being the dyadic sum [9]. Given N observations, $x(0), x(1), \ldots, x(N-1)$, of the process, an estimator of the spectral density is the Walsh periodogram of the data

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

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 muscular relaxation, we investigate how the Walsh-Fourier analysis can contribute to improve the controller. Accordingly, the Walsh periodogram of the muscle relaxation, $r(t)$, is evaluated on data collected during surgery (34 clinical trials with neuromuscular blockade induced by atracurium bolus). It is verified that the periodograms present peaks in the neighbourhood of the sequencies 3/128, 7/128 and 15/128 which correspond to *average periods* [2] of 14.2 minutes, 6.1 minutes and 2.8 minutes, respectively. In Figure 2 is exhibited the Walsh periodogram of one of the patients.

In the following section, the relationship between this *average periods* given by the Walsh-Fourier spectral analysis and the shape parameters (*T10, T50, T80, S and P*), used to tune the PID controller, is discussed. Moreover, it is investigated the use of the *average periods*, to improve the estimation of the controller parameters. Finally, a comparison with the regression of R and L using principal components of the response induced by a bolus of $500 \mu g k g^{-1}$ as predictors is performed.

4. A case study: the administration of atracurium

Figure 3 illustrates the responses induced by the administration of a bolus of 500 $\mu g k g^{-1}$ of atracurium on 85 patients. The variability of the responses is much wider than that predicted by the pharmacokinetic and pharmacodynamic data for atracurium [14, 15]. Therefore, to accomodate the clinical data, an improved empirical dynamic model, Wiener [1] structure based, for atracurium has been developed [4].

A large number of simulated models (N=500 models) have been generated. As illustrated in Figures 4 and 5, the empirical model replicates well the characteristics

[1]The Wiener models, consisting of a linear dynamic element followed in series by a static non-linear element, are considered to be ideal for representing a wide range of non-linear processes.

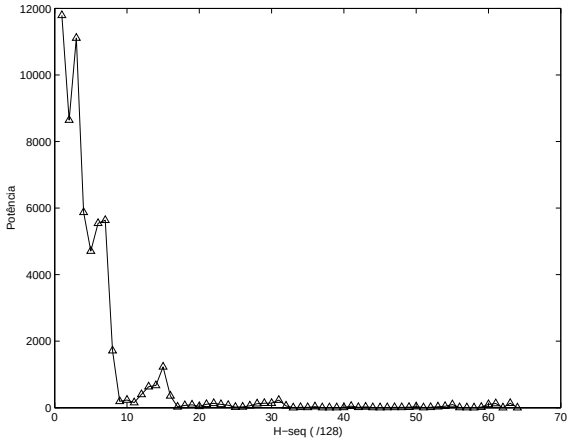

Fig. 2. Walsh periodogram of one of the patients.

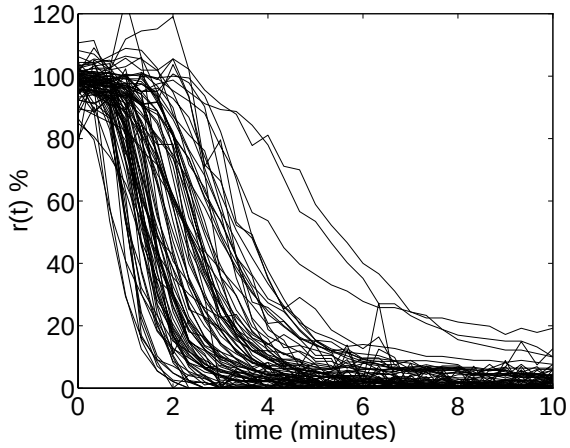

Fig. 3. The responses induced by a bolus of 500 $\mu g kg^{-1}$ of atracurium on 85 patients undergoing surgery.

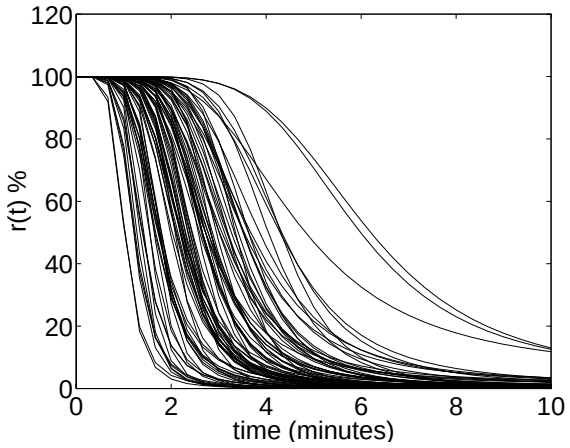

Fig. 4. Simulated responses induced by a bolus of 500 $\mu g\, kg^{-1}$ of atracurium. A multidimensional log-normal distribution for the pharmacokinetic/pharmacodynamic parameters has been assumed.

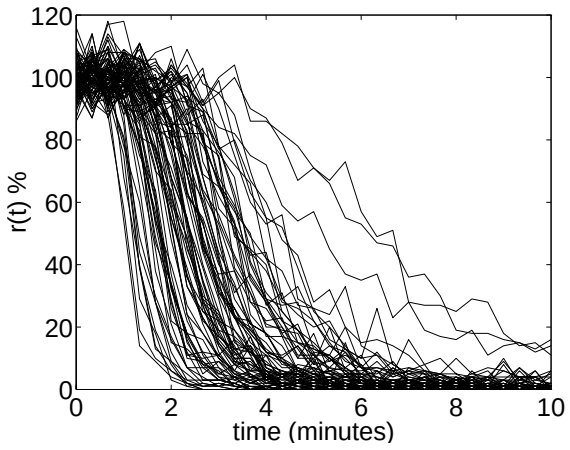

Fig. 5. The simulated responses with simulated measurement noise.

of the patients responses. Figure 5 illustrates the same simulated responses of Figure 4 with added simulated measurement noise.

For each of the simulated models, the values for L and R of a PID controller have been obtained, as well as the parameters $T80$, $T50$, $T10$, S and P. Moreover, PCA and WFA analysis are accomplished and estimates of the controller parameters, L and R, are obtained using the three different approaches. Tables 1 and 2 present a summary of the results, using 128 sample points corresponding to approximately 42 minutes.

Table 1 presents the correlation coefficient between the *average periods* and their multiples given by the Walsh-Fourier spectral analysis and the parameter $T50$, for simulated models with and without noise and for the set of real data available. The correlation establishes a clear relationship between these parameters, validating the use of $T50$ to characterize the individual dynamic model [4, 7].

Table 2 summarizes the predictive power of $T50$, PCA and WFA, in terms of the % of variation of L and of R^{-1}. It is found that the predictive power of muscle relaxation levels at the average periods found by WFA of the bolus response is the highest, since they explain 93% of the variation of L and 69% of the variation of R^{-1}. These results are comparable with those obtained with PCA analysis. A higher predictive power is obtained only when the parameter P is added to the mul-

	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

Table 1. Correlation coefficients.

tivariate regression model. However, since this parameter is not suitable for practical implementation (in some cases the bolus response may not reach a sufficiently lower level), the PCA and the relaxation level at the WFA periods of the bolus response can be considered the best predictors for L and R^{-1}.

In a clinical environment a high level noise often contaminates the measurement of the muscle relaxation response, as illustrated in Figure 3. 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.

	Without noise		With noise	
Predictors	**L**	**1/R**	**L**	**1/R**
T50	87	42	87	42
T50 + r (14.0)	93	64	91	60
T50 + r (3.0) + r (7.0) + r (14.0)	93	69	91	61
T50 + r (0.7) + r (1.7) + r (3.0) + r (14.0)	89	68	91	63
T50 + r (0.7) + r (1.3) + r (1.7) + r (3.0) + r (14.0)	90	69	92	63
T50 + P	94	70	93	42
T50 + P + r (1.3)	95	70	94	69
$a_1, \ldots, a_{10}$	92	66	86	49
$a_1, \ldots, a_{10}$ + P	95	72	95	70
r (0.7) + r(1.3) + r (1.7) + r (3.0) + r(7.0) + r (14.0)	93	69	91	63
r (1.3) + r (1.7) + r (3.0) + r(7.0) + r (14.0)	90	69	92	63

Table 2. % of variation explained for linear regression models

5. Conclusions

The present study compares and evaluates statistical regression techniques based on different features of the patients response to the administration of a muscle relaxant. The individualized information inferred from the response induced by the initial bolus dose given in the beginning of anaesthesia, is of great utility for the design of improved on-line autocalibrated automatic controllers of muscle relaxation. The bolus response has been characterized by shape parameters, by parameters deduced from principal component analysis and by parameters deduce from a Walsh-Fourier spectral analysis. The tuning of the PID controller was achieved by multiple regression techniques. 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 Walsh-Fourier analysis for characterizing the patients individual responses to the bolus has been firmly established.

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References:

[1] Beauchamp, K.G. "Walsh Functions and their applications", *Academic Press*, (1975).

[2] Harmuth, H.F. "Transmition of Information by Orthogonal Function", *Springer-Verlag*, (1977).

[3] Kohn, R. "On the Spectral Decomposition of Stationarity Time Series using Walsh Functions', *Advances in Applied Probability*, **12**, pp. 183-199, (1983).

[4] Lago, P. and T. Mendonça and L. Gonçalves. "On-line Autocalibration of a PID Controller of Neuromuscular Blockade", *Proceedings of the 1998 IEEE International Conference on Control Applications*, pp. 363–367, Trieste, Italy, (1998).

[5] Lago, P. and T. Mendonça and H. Azevedo. "Comparision of On-line Autocalibration Techniques of a Controller of Neuromuscular Blockade", *Proceedings of IFAC Modeling and Control in Biomedical Systems*, pp. 263–268, Karlsburg-Greisfswald, Germany, (2000).

[6] Linkens, D.A.. *Intelligent Control in Biomedicine*, Taylor and Francis, (1994).

[7] Mendonça, T. and P. Lago. "Control Strategies for the Automatic Control of Neuromuscular Blockade", *Control Engineering Practice*, **6**, pp. 1225–1231, (1998).

[8] Morettin, P.A. " Walsh Spectral Analysis" *SIAM Review*, **23**, pp. 279-291, (1981).

[9] Robinson, G.S. “Logical Convolution and Discrete Walsh and Fourier Power Spectra”, *IEEE Transactions on Audio and Electroacoustics*, **AU-20**, pp. 271-280, (1972).

[10] Schilden, H. and K.T.Olkkola. “Use of a pharmacokinetic-dynamic model for the automatic feedback control of Atracurium”, *Eur. Clin. Pharmacol.*, **40**, pp. 293–296, (1991).

[11] Stoffer, D.S. “Walsh-Fourier Analysis of discrete-valued Time Series”, *Journal of the Time Series Analysis*, **8**, pp. 449-467, (1987).

[12] Stoffer, D.S. “Walsh- Fourier Analysis and its Statistical Applications”, *Journal American Statistical Association*, **86**, pp. 461-479, (1991).

[13] Wait, C. and B. Neil and C. Blogg. “Feedback control of neuromuscular blockade”, *Anesthesia*, **42**, pp. 1212–1216, (1987).

[14] Ward, S. and A. Neill and B. Weatherley and M. Corall. “Pharmacokinetics of Atracurium besylate in healthy patients (after a single i.v. bolus dose)”, *British Journal of Anaesthesia*, **55**, pp. 113–116, (1983).

[15] Weatherley, B. and S. Williams and E. Neill. “Pharmacokinetics, Pharmacodynamics and Dose-Response Relationships of Atracurium Administered i.v.”, *British Journal of Anaesthesia*, **55**, pp. 39s–45s, (1983).