Online Individualized Dose Estimation

Conceição Rocha
Faculdade de Ciências
Universidade do Porto
Rua Campo Alegre 687,
4169-007, Portugal
mnrocha@fc.up.pt
http://www.fc.up.pt

Teresa Mendonça
Faculdade de Ciências
Universidade do Porto
Rua Campo Alegre 687,
4169-007, Portugal
tmendo@fc.up.pt
http://www.fc.up.pt

M. Eduarda Silva
Faculdade de Economia
Universidade do Porto
Rua Dr. Roberto Frias,
4200-464, PORTUGAL
mesilva@fep.up.pt
http://www.fep.up.pt

Abstract— **The development of automated individualized drug dosage regimens, namely in general anaesthesia environment, has been a subject of interest in the last decades. The use of continuous intravenous drug administration aims at, accurately, maintaining the system at a desired target effect concentration level. Different methods have been proposed for the design of individualized dosage regimens. In this study individual drug dose design is achieved through the characterization of transient initial response induced by a bolus administration of drug. This approach is based on the statistical analysis of the data using Walsh-Fourier spectral analysis which provides information about patient dynamics, allowing the on-line drug dose design using multiple linear least squares and quantile regression technics. The proposed methodology is illustrated in the case where the effect measured on the patient corresponds to the neuromuscular blockade (NMB) level and the drug to the muscle relaxant *atracurium*.**

I. Introduction

The spread of automated technologies in clinical practice in almost every biomedical field leads to the search of robust and reliable automation methods. In particular, the development of automated individualized drug dosage regimens, namely in general anaesthesia environment, has been a subject of interest in the last decades.

The use of continuous intravenous drug administration aims at, accurately, maintaining the system at a desired target effect concentration level. Different methods have been proposed for the design of individualized dosage regimens depending on the characteristics of the clinical problem to be solved [Lago(1992)], [Bayard et al.(1994)].

Target Controlled Infusion (TCI) strategies, [Schraag(2001)], have been proposed to provide improved convenience and control during intravenous anaesthesia and are nowadays widely accepted. TCI is a feedforward control strategy that relies on the application of PK/PD population models to design the dose profile. Under the assumption that a reliable PK/PD population model is available to describe the patient characteristics, TCI devices calculate the drug dose to be administered such that a target level on the PD effect concentration will be reached.

Furthermore, these open-loop control devices do not compensate for mismatch between model and the patient dynamics, since they rely on a mean model approach for defining the individual dose regimen. Therefore, they are not completely adequate for drug administration, [Ting et al.(2004)].

A drug dosage regimen usually comprises a transient and a steady state phase. The transient phase corresponds to the induction of the desired effect usually by the administration of a initial bolus dose. It is reasonable to assume that the response of the patient to the bolus carries valuable information ([Silva et al(2002)]; [Silva et al(2005)]) that should be accounted both for the characterization of the individual behavior and for the design of so-called maintenance dose profile.

The major contribution of this study consists on the individual drug dose design through the characterization of transient initial response induced by a bolus administration of drug. This approach is based on the statistical analysis of the data using Walsh-Fourier spectral analysis. This method provides information about patient dynamics allowing the on-line drug dose design using multiple linear least squares and quantile regression technics.

The proposed methodology is illustrated in the case where the effect measured on the patient corresponds to the neuromuscular blockade (NMB) level and the drug to the muscle relaxant *atracurium*.

This paper is organized as follows: Section II presents a brief review in general TCI strategy; a description of the NMB model; an introduction to the the statistical methods and a description of the proposed methodology. Section III the results obtained by the application of the methodology to the NMB case study. Some comments and future work are presented in Section IV.

II. Individualized TCI strategy

The goal of the proposed methodology is to improve the commonly accepted TCI strategy. To that end, a statistical analysis of the patients response to the initial *bolus* response is carried out by Walsh-Fourier analysis, identifying *average periods*. Then, the neuro-muscular blockade level at those periods are used as predictor variables for the individual drug dose, u_{ss}, in multiple linear least squares and quantile regression models.

978-1-4244-5059-6/09/$26.00 ©2009 IEEE

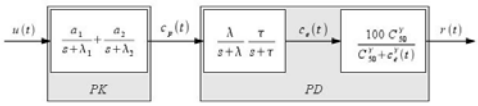

Fig. 1. Block diagram for neuromuscular blockade model using *atracurium*.

A. Target Controlled Infusion

TCI allows for a controlled infusion in such a manner as to attempt to achieve a user-defined drug concentration in a body compartment or tissue of interes,t [Absalom et al(2007)]. To accomplish that, the time course of infusion rates are predicted by validated PK population models. The PD behaviour of the drug in each patient is assessed by the anaesthetist from the patient's overall external physiological state and is then used to set the desired target concentration. Throughout the surgery, using a TCI system, the anaesthetist re-adjusts the target concentration as required on clinical grounds and based on his clinical experience and individual requirements of the patient. Hence, the feedforward TCI open-loop system is closed by the clinician.

B. NeuroMuscular Blockade

The dynamic response of NMB for several muscle relaxants may be modelled by a Wiener structure: a linear part followed by a non-linear static dynamic one. For *atracurium* the resulting block diagram [Weatherley et al(1983)] is shown in Fig. 1.

The linear PK part (Block 1 in Fig. 1) relates the drug infusion rate $u(t)$ $[\mu g\, kg^{-1}\, min^{-1}]$ with the plasma concentration $C_p(t)$ $[\mu g\, ml^{-1}]$, where
$\hat{\Theta}_{PK}$=$\{a_i\,[kg\, ml^{-1}],\ \lambda_i\,[min^{-1}]\}_{i=1,2}$ are patient dependent parameters.

The PD part has two linear blocks (Block 2 in Fig. 1) relating $C_p(t)$ and the effect concentration $C_e(t)[\mu g\, ml^{-1}]$, and a non-linear static Hill relationship (Block 3 in Fig. 1) between $C_e(t)$ and the blockade level $r(t)$ [%],

$$r(t) = f_{NL}(\hat{\Theta}_{PD}, C_e(t)) = \frac{100 C_{50}^{\gamma}}{C_{50}^{\gamma} + C_e^{\gamma}(t)} \qquad (1)$$

where $\hat{\Theta}_{PD} = \{\lambda\,[min^{-1}], C_{50}\,[\mu g\, ml^{-1}], \gamma\,(dimensionless), \tau\,[min^{-1}]\}$ are also patient-dependent.

At the beginning of a surgery, in the induction phase, it is usual to administrate a *bolus of atracurium* (typically $500\mu g\, kg^{-1}$), that may be described by $u_\delta = 500\delta(t)\mu g\, kg^{-1}$(where δ is the continuous time Dirac delta function).

Taking into account this parameterization and in order to cover a wide range of behaviours, a bank of nonlinear dynamic models $\mathcal{M}$=$\{M_i(\Theta^i_{PK}, \Theta^i_{PD})_{i=1,\ldots,500}\}$ was generated using the probabilistic model discussed in [Lago et al(1998)] assuming a multidimensional log-normal distribution for the eight PK/PD parameters and used throughout this study. Fig. 2 shows the NMB response and for each model in $\mathcal{M}$ subject to the initial *Bolus*.

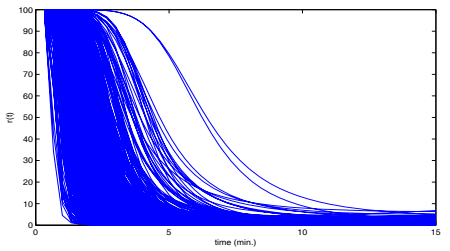

Fig. 2. Impulse response to *bolus* administration: neuromuscular blockade level for each of the 500 models in $\mathcal{M}$.

For each of these patient models, the constant infusion dose u_{ss} that should be given in order to drive the limiting value of NMB level to a prefixed reference (r^*), is obtained from the corresponding parameterization $\{\Theta_{PK}, \Theta_{PD}\}$:

$$\begin{aligned} &lim_{t\to\infty} r(t) = r^* \Rightarrow u(t) = u_{ss} H(t - t_0) \\ &u_{ss} = f_{NL}(\hat{\Theta}_{PD}, \hat{\Theta}_{PK}, r^*) = C_{50} \tfrac{((100/r^*)-1)^{1/\gamma}}{(a_1/\lambda_1)+(a_2/\lambda_2)} \end{aligned} \qquad (2)$$

where H is the Heaviside step function.

The reference level considered in this study id $r^* = 10\%$. However, for 24 models in bank $\mathcal{M}$, a valued of u_{ss} smaller than 4 was obtained form (2). Since these small values are not realistic from a clinical point of view, the 24 models are discarded. Thus, a bank of 476 models is used in this study.

C. 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 on the Walsh functions[Beauchamp(1975)], [Harmuth(1977)], [Kohn(1980)] which form a complete, ordered and orthonormed set of rectangular waves taking the values -1 and 1.

In general, one uses the Walsh or sequency order, which is comparable to the frequency order of the trigonometric functions. The sequency-ordered Walsh functions are denoted by $W(n,t)$, with $t \in [0,1[$ and $n = 1, 2, \ldots$. The n argument is designeted by *sequency* and represents the number of switches signs (zero-crossings) in the unit interval. [Harmuth(1977)] 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 of the data (which is the square of the Walsh-Fourier transform of the data) [Morettin(1981)], [Robinson(1972)], [Stoffer(1987)],

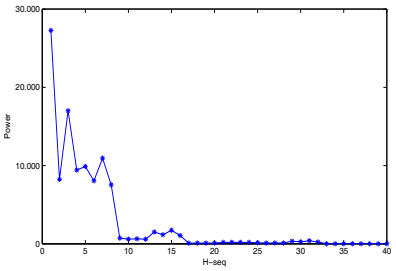

Fig. 3. Walsh periogram of neuro-muscular blockade.

Quantile 0.25

M	Predictors							%error Mean	%error Min	%error Max
1	v1	v2				v7	v8	7	0	27
5				v5	v6	v7	v8	7	0	27
9	v1				v6	v7	v8	7	0	27
13	v1	v2					v8	8	0	29
17		v2		v5			v8	8	0	29
21			v3	v5	v6	v7	v8	7	0	26
25				v5			v8	8	0	43
28	v1			v5				13.5	0	48

TABLE I

PREDICTORS AND CORRESPONDING MAPE FOR THE QUANTILE 0.25 REGRESSIONS. M DESIGNATES THE MODEL NUMBER.

[Stoffer(1991)]

$$I_W(\lambda_j) = \left[\frac{1}{\sqrt{N}}\sum_{n=0}^{N-1} x(n)W(n,\,\lambda_j)\right]^2, \qquad (3)$$

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". The Walsh periodogram given in 3 is modified to obtain the *Walsh-Harmuth periodogram*, by setting

$$I_H(\lambda_j) = I_W((2j-1)/N) + I_W(2j/N), \qquad (4)$$

with $j = 1, 2, \ldots, (N-2)/2$, where λ_j is the H-sequency.

Considering that during surgical intervention a patient attains different levels of neuro-muscular blockade,[Silva et al(2002)], [Silva et al(2005)], performed WFA in both simulated and clinical neuro muscular blockade data. Those authors found that the periodograms of the data present peaks corresponding to average periods of 2.7, 7.7, 10.7 and 14.3 minutes (aproximately) which provide individualized information on the patient's responses to the administration of a *bolus* of *atracurium*.

Here we investigate the relationship between the relaxation level at the average periods given by the WFA and the steady-state infusion level u_{ss}.

D. Quantile Regression

Quantile regression, [Koenker et al(1978)], was developed as an extension to the linear model for estimating rates of change not only in the conditional mean but also in all parts of the distribution of the response variable. Given a linear model relating a response variable Y to a predictor variable X, $Y = f(X,\beta) = \beta X$ the ordinary least squares (OLS) estimation of the conditional mean of the response variable Y conditional on X, $E(Y|X)$, is obtained by minimizing the a sum of squared residuals,

$$\sum_i (y_i - f(X,\beta))^2.$$

Similarly, the quantile of the response Y conditional on X can be obtained by minimizing a sum of asymmetrically weighted residuals,

$$\sum_i \rho_\tau(y_i - f(X,\beta)),$$

where ρ_τ is the tilted absolute value function for quantile τ, [Koenker et al(2001)]. Thus, to estimate the conditional median set $\tau = 1/2$ and then $\rho_{1/2}$ is the absolute value function. The minimization problem can be solved very efficiently by linear programming methods.

Quantile regression provides a more complete picture of the data than a single mean regression and can be particularly informative concerning the behaviour of the tail of the data distribution. Furthermore, quantile regression overcomes OLS axiom of homoscedasticity and is more robust to outliers which can distort OLS results significantly.

III. RESULTS

A. Regression models for the dose

In this section, the values of the bolus response at the Walsh-Fourier periods (WFA) are used as predictor variables for the dose u_{ss}. Quantile regression models, 0.25, 0.50 and 0.75 quantiles, are constructed. For comparison purposes linear regression models estimated by generalized least squares (GLS) method are also obtained. The predictor variables considered are:

$v1$	$v2$	$v3$	$v4$
$r(2.7)$	$r(7.7)$	$r(10.7)$	$r(14.3)$
$v5$	$v6$	$v7$	$v8$
$\sqrt{r(2.7)}$	$\sqrt{r(7.7)}$	$\sqrt{r(10.7)}$	$\sqrt{r(14.3)}$

where $r(t)$ represents the level of neuro-muscular blockade observed at time t. The regression models obtained, after performing the usual diagnostic and residual checks, are summarized in tables I to IV. Boxplots for the erros for the quantile 0.25 regression is represented in Fig. 4 as an illutration. Note that, apart from model 28, all the regression models contain $\sqrt{r(14.3)}$ as a predictor variable. The comparison between the several regression models is based on the mean absolute percentual error, $|\hat{u}_{ss} - u_{ss}|/u_{ss}$ (MAPE), which varies from 5.6% to 9.3%. Moreover, considering that during surgery a variation of the NMB level between 5% and 15% is clinically admissible, the number of predicted doses $\hat{u}_{ss}$ outside this interval is computed para each regression model. Quantile 0.25 regression models present the highest rate (12%) of predicted values outside the $[5\%, 15\%]$ range while quantile 0.75 regression model presents the lowest rate (5%).

Quantile 0.50

M	Predictors							% error Mean	Min	Max
2	v1	v2				v7	v8	6	0	23
6				v5	v6	v7	v8	6	0	31
10	v1				v6	v7	v8	6	0	36
14	v1	v2					v8	7	0	24
18		v2		v5			v8	7	0	25
22			v3	v5	v6	v7	v8	6	0	24
26				v5			v8	7	0	57

TABLE II

PREDICTORS AND CORRESPONDING MAPE FOR THE QUANTILE 0.50 REGRESSIONS. M DESIGNATES THE MODEL NUMBER.

Quantile 0.75

M	Predictors								% error Mean	Min	Max
3	v1	v2					v7	v8	8	0	29
7					v5	v6	v7	v8	7	0	37
11	v1					v6	v7	v8	7	0	35
15								v8	9	0	30
19					v5			v8	9	0	64
23	v1	v2	v3	v4	v5	v6	v7	v8	7	0	28

TABLE III

PREDICTORS AND CORRESPONDING MAPE FOR THE QUANTILE 0.75 REGRESSIONS. M DESIGNATES THE MODEL NUMBER.

GLS

M	Predictors								% error Mean	Min	Max
4	v1	v2					v7	v8	6	0	23
8					v5	v6	v7	v8	6	0	23
12	v1					v6	v7	v8	6	0	23
16	v1	v2						v8	9	0	62
20		v2			v5			v8	7	0	24
24	v1	v2	v3	v4	v5	v6	v7	v8	6	0	23
27					v5			v8	7	0	55

TABLE IV

PREDICTORS AND CORRESPONDING MAPE FOR THE GLS REGRESSIONS. M DESIGNATES THE MODEL NUMBER.

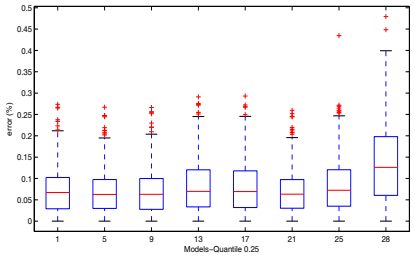

Fig. 4. Boxplots of $|\hat{u}_{ss} - u_{ss}|/u_{ss}$ for the quantile 0.25 regression models.

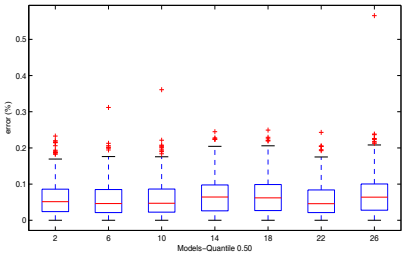

Fig. 5. Boxplots of $|\hat{u}_{ss} - u_{ss}|/u_{ss}$ for the quantile 0.50 regression models.

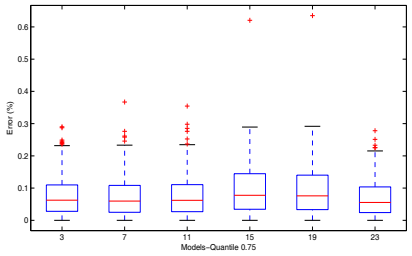

Fig. 6. Boxplots of $|\hat{u}_{ss} - u_{ss}|/u_{ss}$ for the quantile 0.75 regression models.

This results indicate that the regression models may be used to predict online the dose u_{ss}.

B. Aplication to clinical data

In this section, the analysis proposed above is applied to data collected during 17 cirurgical interventions. The data consists of the mean infusion dose given to each patient during the surgery, the starting time of infusion and the NMB observed in 20s intervals. For each patient, the WFA was performed and regression models estimated. The results obtained with the best regression model are presented in table V and the errors $u_{ss} - \hat{u}_{ss}$ are sumarized in Fig. 8. The NMB of pacients 12 to 17 present null values at times 7.7, 10.7 and 14.3, leading to an increase in the error.

The dose usually administered is the mean dose obtained from a population which is 5.78 $\mu g/kg/min$ if we consider the bank of models $\mathcal{M}$ as the population. Figure 8 represents boxplots of the errors commited using that mean dosage

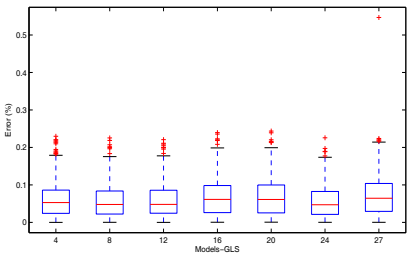

Fig. 7. Boxplots of $|\hat{u}_{ss} - u_{ss}|/u_{ss}$ for the GLS regression models.

Pacient	Infusion time	u_{ss}	$\hat{u}_{ss}$	error %	Model
1	123	9.3	9.80	5%	24 (GLS)
2	110	6.2	6.22	0%	13 (q(0.25))
3	128	4.8	4.91	2%	4 (GLS)
4	118	9.4	10.32	10%	1 (q(0.25))
5	173	5.2	5.03	4%	3 (q(0.75))
6	340	7.5	6.90	8%	7 (q(0.75))
7	114	4.5	4.52	1%	3 (q(0.75))
8	86	6.9	6.82	1%	15 (q(0.75))
9	344	4.2	4.00	4%	4 (GLS)
10	295	4.0	3.98	0%	25 (q(0.25))
11	356	5.8	5.78	0%	4 (GLS)
12	192	5.1	5.29	4%	28 (q(0.25))
13	201	5.4	5.34	1%	28 (q(0.25))
14	233	5.0	5.26	5%	28 (q(0.25))
15	222	6.3	5.42	14%	28 (q(0.25))
16	249	4.7	5.53	18%	28 (q(0.25))
17	224	6.5	5.56	14%	28 (q(0.25))

TABLE V

MEAN u_{ss} OBSERVED DURING SURGERY AND u_{ss} ESTIMATED BY REGRESSION MODEL FOR 17 PATIENTS.

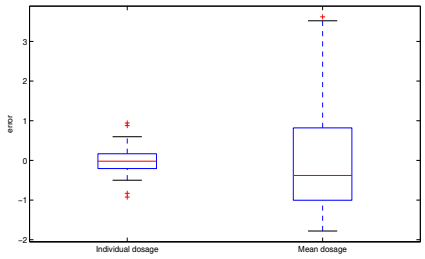

Fig. 8. $u_{ss} - \hat{u}_{ss}$- individual dosage and $u_{ss} - 5.78$ - mean dosage.

$u_{ss} - 5.78$ and the individualized dosage obtained from the regression models, $u_{ss} - \hat{u}_{ss}$, where u_{ss} is the observed mean drug dosage for the 17 pacients. Notoriously, the methodology proposed in this study leads to a more acurate drug dose regimen and an improved TCI.

IV. FINAL REMARKS

The clinical data used to illustrate the study was not collected to validate the methodology proposed here and therefore these results are merely preliminar. One question that was raised in this study and will be addressed in later work, regards the problem of choosing the best regression model for predicting the drug dose for a given patient. As far as this study goes there are several regression models that predict an individualized drug dose.

Acknowledgments

This work was supported in part by FCT and POCI2010 under Project POCI/MAT/6096/2004.

REFERENCES

[Absalom et al(2007)] A. R. Absalom and M. Struys. *Overview of Target Controlled Infusions and Total Intravenous Anaesthesia.* Academia Press,Gent, 2007.

[Bayard et al.(1994)] D. S. Bayard,M. H. Milman, and A. Schumitzky. Design of dosage regimens: a multiple model stochastic control approach. *Int. Journal of Bio-Medical Computing*, volume 36, pages 103–115, 1994.

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

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

[Koenker et al(1978)] R. Koenker and G. Bassett. Regression Quantiles. *Econometrica*, volume 46(1), pages 33–50,January, 1978.

[Koenker et al(2001)] R. Koenker and K. Hallock. Quantile Regression. *Journal of Economic Perspectives*, volume 15(4), pages 143–156, 2001.

[Kohn(1980)] R. Kohn. On the Spectral Decomposition of Stationary Time Series using Walsh Functions. *Advances in Applied Probability*, volume 12, pages 183–199, 1980.

[Lago(1992)] P. J. Lago. Open-loop stochastic control of pharmacokinetic systems: a new method for design of dosing regimens. *Comp. and Biom. Research*, volume 25, pages 85–100, 1992.

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

[Mendonça et al(1998)] T. Mendonça and P. Lago PID Control Strategies for the Automatic Control of Neuromuscular Blockade *Control Engineering Practice*, volume 6, pages 1225–1231, 1998.

[Morettin(1981)] P.A. Morettin. Walsh Spectral Analysis. *SIAM Review*, volume 23, pages 279–291, 1981.

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

[Schraag(2001)] S. Schraag. Theoretical basis of target controlled anaesthesia: history, concept and clinical perspectives. *Best Practice and Research Clinical Anaesthesiology*, volume 15(1), pages 1–17, 2001.

[Silva et al(2002)] M.E. Silva, T. Mendonça, I. Silva and H. Magalhães. On-line controller autocalibration based on parameter predictors: a case study. *Advances in Simulation, Systems Theory and Systems Engineering*, Editors Nikos E. Mastorakis, Vitaly V. Kluev, Djuro Koruga, WSEAS Press, pages 261–266, 2002.

[Silva et al(2005)] M.E. Silva, T. Mendonça, I. Silva and H. Magalhães. Statistical analysis of neuromuscular blockade response: contributions to an automatic controller calibration. *Computational statistics & Data Analysis*, volume 49(3), pages 955–968, 2005.

[Stoffer(1987)] D.S. Stoffer. Walsh-Fourier Analysis of discrete-valued Time Series. *Journal of the Time Series Analysis*, volume 8, pages 449–467, 1987.

[Stoffer(1991)] D.S. Stoffer. Walsh- Fourier Analysis and its Statistical Applications. *Journal American Statistical Association*, volume 86, pages 461–479, 1991.

[Ting et al.(2004)] C. H. Ting, R. H. Arnott, D. A. Linkens and A. Angel. Migrating from target-controlled infusion to closed-loop control in general anaesthesia, *Computer Methods and Programs in Biomedicine*, volume 75, pages 127–139, 2004.

[Weatherley et al(1983)] B. Weatherley, S. Williams, and S. Neill, Pharmacokinetics, Pharmacodynamics and Dose-Response Relationships of Atracurium Administered i.v. *British Journal of Anaesthesia*, volume 55, pages 39–45, 1983.

This Page Intentionally Left Blank