Prediction error identification of minimally parameterized Wiener models in anesthesia

Margarida Martins da Silva

Division of Systems and Control, Department of Information Technology, Uppsala University, Box 337, SE-751 05 Uppsala, Sweden; Dep. Matemática, Faculdade de Ciências da Universidade do Porto, Rua do Campo Alegre, 4169-007 Porto, Portugal; Center for Research & Development in Mathematics and Applications, Dep. Matemática, Campus Universitário de Santiago, 3810-193 Aveiro, Portugal (e-mail: margarida.silva@it.uu.se, margarida.silva@fc.up.pt).

Abstract: Patient modeling is a necessary step towards the achievement of successful control strategies that guarantee adequate drug dosing in patients subject to anesthesia. In this paper, Prediction Error Method algorithms for the identification of Wiener models describing the effect of drugs in those patients are derived. The proposed methods are general for cases where the effect of drugs in the human body is modeled by pharmacokinetic/pharmacodynamic models. In order to exemplify the performance of the proposed Prediction Error Method algorithms a database with real records collected from patients undergoing general anesthesia is used. The two parameters of a SISO Wiener model describing the effect of the muscle relaxant atracurium in the NeuroMuscular Blockade are identified. Regarding the Depth of Anesthesia, the four parameters of a MISO Wiener model describing the joint effect of the hypnotic propofol and the opioid remifentanil in the Bispectral Index are also identified. The results show that the identified parameters give rise to predicted output signals that follow the main trends of the real signals, discarding the noise that highly corrupts the measurements. This fact supports the use of these minimally parameterized models to model the aforementioned systems since they correctly describe the real dynamics of the systems.

Keywords: Identification algorithms, Prediction Error Method, Wiener models, biomedical systems, NeuroMuscular Blockade, Bispectral Index, anesthesia.

1. INTRODUCTION

This paper presents Prediction Error Method (PEM) algorithms for the identification of minimally parameterized Wiener models in anesthesia. The proposed algorithms are general for cases where the relationship between the amount of drug that is given to a certain patient and the observed effect is modeled by a Wiener structure, Wigren (1993): a linear mixing dynamics of the drug followed by a static nonlinearity describing the measured effect. This is the case of most Pharmacokinetic/Pharmacodynamic (PK/PD) cascaded models, Derendorf and Meibohm (1999).

The choice of the model to describe the PK/PD effect of drugs in the human body may strongly influence the performance of control strategies for automatic drug administration, specially the ones that are intrinsically model-based. This idea goes in line with the parsimony principle of system identification theory and is strongly correlated with the new models and identification strategies proposed in this paper.

During general anesthesia, two variables that must be controlled, among others, and that are usually described as Wiener models are the NeuroMuscular Blockade (NMB) and the Depth of Anesthesia (DoA). While the NMB quantifies the level of muscle paralysis as consequence of the administration of muscle relaxants, the DoA is related with the loss of consciousness due to hypnotics and opioids administration. In the clinical practice, the NMB is usually quantified from one evoked electromyogram (EMG) at the hand of the patient, Mendonça et al. (2009), and ranges from 100% (“normal” state) to 0% (complete paralysis). For the DoA assessment, the most widely accepted index in the focal point of anesthesia research nowadays is the electroencephalogram(EEG)-derived Bispectral Index (BIS), Sigl and Chamoun (1994), scaled from 97.7 (awake EEG) to 0 (electrical silence), Johansen and Sebel (2000).

The first contribution of this paper is hence to present PEM identification algorithms for minimally parameterized Wiener models for the NMB and the BIS. It should be stressed that the use of minimally parameterized models, Silva et al. (2011, 2010a), is in the core of the developed
Fig. 1. Block diagram of the NMB SISO Wiener model.

The signal $y_a$ is not available for measurement.

PEM identification strategies. The second contribution is
to analyze the performance of the proposed PEM algo-
rithms in two databases of real records collected in the
surgery room.

The paper is organized as follows. Section 2 presents the
minimally parameterized models and the prediction error
algorithms for both the NMB (in section 2.1) and the BIS
(in section 2.2). Section 3 shows the identification results
obtained after running the prediction error algorithms in
NMB and BIS records collected in patients undergoing
general anesthesia. Section 4 draws the conclusions.

2. THE MINIMALLY PARAMETERIZED MODELS
AND THE PEM ALGORITHMS

This section presents the minimally parameterized Wiener
models that are used in this paper: a Single Input Single
Output (SISO) model for the NMB and a Multiple Input
Single Output (MISO) model for the BIS. Due to the
cascade structure of the Wiener models it is generally not
possible to identify the linear dynamics independently of
the static nonlinearity, Wigren (1993). This is so because,
from an input-output perspective, only the product of the
static gains of the two cascaded blocks is important. Hence,
since independent parameterizations of the two blocks are
used, in order to reach a unique system parameterization,
the static gain must be fixed in one of the blocks. The
linear dynamic block is chosen for this purpose. The
differential static gain is then estimated by the parameters
to be adapted in the nonlinear block. The parameter vector
$\theta$ is hence partitioned as $\theta = [\theta_1^T \theta_2^T]^T$ where $\theta_1$
accounts for the parameters to be identified in the linear block and
$\theta_2$ accounts for the parameters to be identified in the
nonlinear block of the Wiener model. The PEM algorithms
for simultaneous identification of the linear dynamics and
static nonlinearity are derived at the end of each one of the
following two subsections for both the NMB and the
BIS.

2.1 The NeuroMuscular Blockade

The minimally parameterized model: The SISO Wiener
model describing the effect of the muscle relaxant atrac-
curium in the NMB (Fig. 1), Silva et al. (2011), is here
characterized.

In frequency domain, the linear dynamics is modeled in
continuous-time by

$$\tilde{Y}_a^*(s, \theta_1) = \frac{k_1 k_2 k_3 \alpha^3}{(s + k_1 \alpha)(s + k_2 \alpha)(s + k_3 \alpha)} U_a(s), \quad (1)$$

where $\tilde{Y}_a^*(s, \theta_1)$ is the Laplace transform of the continuous-
time output $\tilde{y}_a(t, \theta_1)$ of the linear dynamic block of the
model; and $U_a(s)$ is the Laplace transform of the input
signal $u_a(t)$ (atracurium infusion rate). Here the param-
eter $\theta_1 = \alpha$ to be identified describes the variability of
inter-patients’ dynamics. Aiming for the best modeling,
the constants $k_i, \{i = 1, 2, 3\}$ are chosen as 1, 4, and 10,
respectively, as in Silva et al. (2011).

In order to implement the proposed NMB model structure
in the identification algorithm, the continuous-time represen-
tation (1) was sampled using the zero-order hold method, Aström
and Wittenmark (1984), with frequency equal to 1/3 min$^{-1}$. This choice is due to the fact that,
in the surgery environment, data from NMB is acquired
every 20 seconds. The corresponding discrete-time model
then becomes

$$\tilde{y}_a(t, \theta_1) = B(q^{-1}, \theta_1) A(q^{-1}, \theta_1) u_a(t), \quad (2)$$

where $\tilde{y}_a(t, \theta_1)$ is the output of the linear dynamic block
of the model; $u_a(t)$ is the piecewise-constant input signal;
and $q^{-1}$ denotes the backward shift operator.

The static nonlinearity is mathematically represented by
the Hill equation, Weatherley et al. (1983), as

$$\tilde{y}(\theta_n, \tilde{y}_a(t, \theta_1)) = \frac{100 C_{50}^2}{C_{50}^2 + (\tilde{y}_a(t, \theta_1))^\gamma}. \quad (3)$$

Here the parameter $\theta_n = \gamma$ to be identified adapts the
shape or static differential gain of (3); $\tilde{y}(\theta_n, \tilde{y}_a(t, \theta_1))$
is the output of the nonlinearity; and $C_{50}$ is a normalizing
constant that is kept constant during simulations, as in
Silva et al. (2011).

The PEM algorithm: The PEM determines

$$\theta = [\theta_1^T \theta_2^T]^T = [\alpha \gamma]^T \quad (4)$$

so that the prediction error

$$\varepsilon(t, \theta) = y(t) - \tilde{y}(\theta_n, \tilde{y}_a(t, \theta_1)) \quad (5)$$

becomes as small as possible. Note that $y(t)$ is the mea-
sured output (NMB) and $\tilde{y}(\theta_n, \tilde{y}_a(t, \theta_1))$ is the predicted
output based on the parameter vector $\theta$.

The negative gradient $\psi(t, \theta)$ of the prediction error $\varepsilon(t, \theta)$
with respect to the parameter vector that is needed to the
PEM algorithms is given by

$$\psi(t, \theta) = -\frac{\partial \varepsilon(t, \theta)}{\partial \theta}^T$$

$$= \frac{\partial \tilde{y}(\theta_n, \tilde{y}_a(t, \theta_1))}{\partial \theta} \frac{\partial \tilde{y}_a(t, \theta_1)}{\partial \alpha} \frac{\partial \tilde{y}(\theta_n, \tilde{y}_a(t, \theta_1))}{\partial \gamma}. \quad (6)$$

The criterion to be minimized in the search, Söderström
and Stoica (1989), is

$$V(\theta) = \frac{1}{N} \sum_{t=1}^{N} \varepsilon^2(t, \theta), \quad (7)$$

where $N$ is the total number of data points.

The minimization of (7) is performed using the numerical
Newton-Raphson algorithm, Söderström and Stoica
(1989),

$$\hat{\theta}^{(k+1)} = \hat{\theta}^{(k)} - \beta \left( \frac{\partial^2 V(\hat{\theta})}{\partial \theta^2} \right)^{-1} \frac{\partial V(\hat{\theta})}{\partial \theta}, \quad (8)$$

where $\hat{\theta}^{(k)}$ denotes the $k$th iteration in the search and $\beta$
is a diagonal matrix used to control the step length. The
derivatives of $V(\theta)$ can be found as:
\( V'(\theta) = -\frac{2}{N} \sum_{t=1}^{N} \varepsilon^T(t, \theta) \psi^T(t, \theta) \), \hspace{1cm} (9)

\( V''(\theta) = \frac{2}{N} \sum_{t=1}^{N} \psi(t, \theta) \psi^T(t, \theta) - \frac{2}{N} \sum_{t=1}^{N} \varepsilon^T(t, \theta) \frac{\partial}{\partial \theta} \psi^T(t, \theta) \approx \frac{2}{N} \sum_{t=1}^{N} \psi(t, \theta) \psi^T(t, \theta) \). \hspace{1cm} (10)

The approximation in (10) is justified in Söderström and Stoica (1989) and is supported by the fact that, at the global minimum point, \( \varepsilon(t, \theta) \) becomes asymptotically white noise which is independent of \( \psi(t, \theta) \).

Regarding the linear block of the Wiener model, a projection algorithm is needed to keep the model asymptotically stable. For this purpose, the poles of the transfer function (1) are monitored at every iteration step by the use of the following projection algorithm for the parameter \( \alpha \):

\[ \alpha^{(k+1)} = \begin{cases} \alpha^{(k+1)}, & \text{if } \alpha^{(k+1)} > \delta > 0 \\ \alpha^{(k)}, & \text{if } \alpha^{(k+1)} \leq \delta \end{cases} \] \hspace{1cm} (11)

For the nonlinear block (3), it is necessary to assure that \( \gamma \) does not reach negative values. The following projection algorithm was used for the parameter \( \gamma \):

\[ \gamma^{(k+1)} = \begin{cases} \gamma^{(k+1)}, & \text{if } \gamma^{(k+1)} > \delta > 0 \\ \gamma^{(k)}, & \text{if } \gamma^{(k+1)} \leq \delta \end{cases} \] \hspace{1cm} (12)

Both updates are hence stopped if the new parameter estimates are outside the feasible region.

The PEM for the identification of the NMB can be summarized using the formulas defined above:

for \( k = 0 \) to \( K \)

\[ \dot{\theta} = \dot{\theta}^{(k)} \Leftrightarrow \begin{bmatrix} \hat{\theta}_T \\ \hat{\theta}_n \end{bmatrix} = \begin{bmatrix} \hat{\theta}_T^{(k)} \\ \hat{\theta}_n^{(k)} \end{bmatrix} \]

\[ \hat{y}_n(t, \hat{\theta}_n) = B(q^{-1}, \hat{\theta}_n) u_n(t) \]

\[ \hat{y}(\hat{\theta}_n, \hat{y}_n(t, \hat{\theta}_n)) = \frac{100 \, C_{50}^\gamma}{C_{50}^\gamma + (\hat{y}_n(t, \hat{\theta}_n))^{\gamma}} \]

\[ \varepsilon(t, \hat{\theta}) = y(t) - \hat{y}(\hat{\theta}_n, \hat{y}_n(t, \hat{\theta}_n)) \]

\[ \frac{\partial \hat{y}(\hat{\theta}_n, \hat{y}_n(t, \hat{\theta}_n))}{\partial \hat{\theta}_n}(t, \hat{\theta}_n) = \frac{-100 \, C_{50}^\gamma \hat{y}_n(t, \hat{\theta}_n)^{\gamma-1}}{(C_{50}^\gamma + \hat{y}_n(t, \hat{\theta}_n)^{\gamma})^2} \]

\[ \frac{\partial \hat{y}_n(t, \hat{\theta}_n)}{\partial \alpha} = \frac{\hat{y}_n(t, \hat{\theta}_n)|_{\hat{\alpha}=\hat{\alpha}+\Delta \hat{\alpha}} - \hat{y}_n(t, \hat{\theta}_n)}{\Delta \hat{\alpha}} \]

\[ \frac{\partial \hat{y}(\hat{\theta}_n, \hat{y}_n(t, \hat{\theta}_n))}{\partial \gamma} = \frac{100 \, C_{50}^\gamma \log(C_{50}^\gamma) - 100 \, C_{50}^\gamma}{(C_{50}^\gamma + \hat{y}_n(t, \hat{\theta}_n)^{\gamma})^2} \times \left( \log(C_{50}^\gamma) C_{50}^\gamma + \log(\hat{y}_n(t, \hat{\theta}_n)) \hat{y}_n(t, \hat{\theta}_n)^\gamma \right) \]

2.2 The Bispectral Index

The minimally parameterized model: The MISO Wiener model describing the joint effect of the hypnotic propofol and the opioid remifentanil in the BIS (Fig. 2), Silva et al. (2010a), is characterized here.

As explained in Silva et al. (2010a), a third-order continuous-time model is proposed for the linear dynamics of both propofol and remifentanil.

Propofol linear dynamics is hence modeled in continuous-time by

\[ \hat{Y}_p(s, \theta_l) = \frac{\gamma}{s + \gamma} \left( s + d_1 \right) \left( s + d_2 \right) \left( s + d_3 \right) U_p(s) \] \hspace{1cm} (13)

where \( \hat{Y}_p(s, \theta_l) \) is the Laplace transform of the continuous-time output \( \hat{y}_p(t, \theta_l) \) of the linear dynamic block of the model for propofol and \( U_p(s) \) is the Laplace transform of the input signal \( u_p(t) \) (propofol infusion rate). The pole location \( \chi \) is selected as the parameter to be identified in (13).

Remifentanil linear dynamics is similarly modeled in continuous-time by

\[ \hat{Y}_r(s, \theta_r) = \frac{l_1 l_2 l_3 \eta^3}{(s + l_1 \eta)(s + l_2 \eta)(s + l_3 \eta)} U_r(s) \] \hspace{1cm} (14)

where \( \hat{Y}_r(s, \theta_r) \) is the Laplace transform of the continuous-time output \( \hat{y}_r(t, \theta_r) \) of the linear dynamic block of the model for remifentanil and \( U_r(s) \) is the Laplace transform of the input signal \( u_r(t) \) (remifentanil infusion rate). The pole location \( \eta \) is selected as the parameter to be identified in (14).
The constants $d_i$ and $l_i$, $i = 1, 2, 3$ were chosen as $d_1 = 1, d_2 = 9, d_3 = 10$ and $l_1 = 1, l_2 = 2, l_3 = 3$, having been determined by the use of batch identification over a different database of real BIS data, Silva et al. (2010b). Consequently, the parameter vector $\theta_t$ becomes $\theta_t = [\chi \eta]^T$.

In order to implement the proposed model structure in the PEM algorithm, the continuous-time representations of (13) and (14) were sampled using the zero-order hold method, Aström and Wittenmark (1984), with frequency of 1/12 min$^{-1}$. This value is dependent on the sampling rate of the measurement devices of BIS. Consequently, the discrete-time outputs of the linear dynamic blocks for propofol and remifentanil are, respectively,

$$
\hat{y}_p(t, \theta_t) = \frac{D(q^{-1}, \theta_t)}{C(q^{-1}, \theta_t)} u_p(t),
$$

and

$$
\hat{y}_r(t, \theta_t) = \frac{G(q^{-1}, \theta_t)}{F(q^{-1}, \theta_t)} u_r(t).
$$

Using as starting point the standard model of Minto et al. (2000) that describes the effects of the interaction between propofol and remifentanil in the BIS, a new formulation for the nonlinearity was proposed in Silva et al. (2010a):

$$
\hat{y}(\theta_n, \hat{y}_p(t, \theta_t), \hat{y}_r(t, \theta_t)) = \frac{y_0}{1 + \left(\frac{\hat{y}(t, \theta_t)}{EC_{SO_p}} + m \frac{\hat{y}_p(t, \theta_t)}{EC_{SO_p}}\right)\zeta}.
$$

Here $\theta_n = [m \zeta]^T$; $m$ and $\zeta$ are the parameters to be identified in the nonlinearity; $EC_{SO_p}$ and $EC_{SO_r}$ are propofol and remifentanil normalizing constants, respectively, that were chosen in Silva et al. (2010a); and $y_0 = 97.7$ is the baseline value for BIS.

The PEM algorithm: The PEM determines $\theta$ so that the prediction error

$$
\varepsilon(t, \theta) = y(t) - \hat{y}(\theta_n, \hat{y}_p(t, \theta_t), \hat{y}_r(t, \theta_t))
$$

becomes as small as possible. Note that $y(t)$ is the measured output (BIS) and $\hat{y}(\theta_n, \hat{y}_p(t, \theta_t), \hat{y}_r(t, \theta_t))$ is the predicted output based on the parameter vector $\theta$.

The gradient of the prediction error $\varepsilon(t, \theta)$ is given by

$$
\psi(t, \theta) = -\left[\frac{\partial \varepsilon(t, \theta)}{\partial \theta}\right]^T = \begin{bmatrix}
\frac{\partial \hat{y}(\theta_n, \hat{y}_p(t, \theta_t), \hat{y}_r(t, \theta_t))}{\partial \hat{y}_p(t, \theta_t)} & \frac{\partial \hat{y}(\theta_n, \hat{y}_p(t, \theta_t), \hat{y}_r(t, \theta_t))}{\partial \hat{y}_r(t, \theta_t)} & \frac{\partial \hat{y}(\theta_n, \hat{y}_p(t, \theta_t), \hat{y}_r(t, \theta_t))}{\partial \chi} & \frac{\partial \hat{y}(\theta_n, \hat{y}_p(t, \theta_t), \hat{y}_r(t, \theta_t))}{\partial \eta} & \frac{\partial \hat{y}(\theta_n, \hat{y}_p(t, \theta_t), \hat{y}_r(t, \theta_t))}{\partial m}
\end{bmatrix}. \tag{19}
$$

The quadratic criterion (7) is used, being minimized by the Newton-Raphson algorithm (8). The derivatives of $V(\theta)$ are calculated using (9) and (10).

The restriction on the update of the estimates of $\chi$ and $\eta$ are the same as to $\alpha$ for the NMB in (11). The argument supporting this choice is the same as before. Similarly, $m$ and $\zeta$ follow the same projection algorithm of $\gamma$ in (12). According to Minto et al. (2000), the interaction between propofol and remifentanil is supradditive. As consequence, it is assumed that $m$ in (17) is lower bounded by zero. For $\zeta$ the argument is the same as for $\gamma$ in (12). Both updates are hence stopped if the new parameter updates are outside the feasible region.

The PEM for the identification of BIS can be summarized using the formulas defined above:

for $k = 0$ to $K$

$$
\hat{\theta} = \hat{\theta}^{(k)} \Leftrightarrow \left[\hat{\theta}_p^T \hat{\theta}_n^T\right]^T = \left[\hat{\theta}_p^{(k)} T \hat{\theta}_n^{(k) T}\right]^T,
$$

$$
\hat{y}_p(t, \hat{\theta}_t) = \frac{D(q^{-1}, \hat{\theta}_t)}{C(q^{-1}, \hat{\theta}_t)} u_p(t),
$$

$$
\hat{y}_r(t, \hat{\theta}_t) = \frac{G(q^{-1}, \hat{\theta}_t)}{F(q^{-1}, \hat{\theta}_t)} u_r(t).
$$

$$
\hat{y}(\hat{\theta}_n, \hat{y}_p(t, \hat{\theta}_t), \hat{y}_r(t, \hat{\theta}_t)) = \frac{y_0}{1 + \left(\frac{\hat{y}(t, \hat{\theta}_t)}{EC_{SO_p}} + m \frac{\hat{y}_p(t, \hat{\theta}_t)}{EC_{SO_p}}\right)\zeta}.
$$

$$
\varepsilon(t, \hat{\theta}) = y(t) - \hat{y}(\hat{\theta}_n, \hat{y}_p(t, \hat{\theta}_t), \hat{y}_r(t, \hat{\theta}_t))
$$

$$
\frac{\partial \hat{y}_p(t, \hat{\theta}_t)}{\partial \chi} = \frac{\hat{y}_p(t, \hat{\theta}_t)|_{\chi = \hat{\chi} + \Delta \hat{\chi}} - \hat{y}_p(t, \hat{\theta}_t)}{\Delta \hat{\chi}}
$$

$$
\frac{\partial \hat{y}_r(t, \hat{\theta}_t)}{\partial \eta} = \frac{\hat{y}_r(t, \hat{\theta}_t)|_{\eta = \hat{\eta} + \Delta \hat{\eta}} - \hat{y}_r(t, \hat{\theta}_t)}{\Delta \hat{\eta}}
$$

$$
\psi(t, \hat{\theta}) = \begin{bmatrix}
-y_0 \hat{m} \hat{\zeta} \left(\frac{\hat{y}_p(t, \hat{\theta}_t)}{EC_{SO_p}} + \hat{m} \frac{\hat{y}_p(t, \hat{\theta}_t)}{EC_{SO_p}}\right)^{\hat{\chi} - 1} \frac{\partial \hat{y}_p(t, \hat{\theta}_t)}{\partial \chi}
\end{bmatrix}^T
$$

$$
-y_0 \hat{m} \hat{\zeta} \left(\frac{\hat{y}_r(t, \hat{\theta}_t)}{EC_{SO_r}} + \hat{m} \frac{\hat{y}_r(t, \hat{\theta}_t)}{EC_{SO_r}}\right)^{\hat{\eta} - 1} \frac{\partial \hat{y}_r(t, \hat{\theta}_t)}{\partial \eta}
$$

$$
-y_0 \hat{m} \hat{\zeta} \left(\frac{\hat{y}_p(t, \hat{\theta}_t)}{EC_{SO_p}} + \hat{m} \frac{\hat{y}_p(t, \hat{\theta}_t)}{EC_{SO_p}}\right)^{\hat{\chi} - 1} \left(1 + \left(\frac{\hat{y}_p(t, \hat{\theta}_t)}{EC_{SO_p}} + \hat{m} \frac{\hat{y}_p(t, \hat{\theta}_t)}{EC_{SO_p}}\right)^{\hat{\chi}}\right)^2
$$

$$
-y_0 \log \left(\frac{\hat{y}_p(t, \hat{\theta}_t)}{EC_{SO_p}} + \hat{m} \frac{\hat{y}_p(t, \hat{\theta}_t)}{EC_{SO_p}}\right) \hat{y}_p(t, \hat{\theta}_t) + \hat{m} \frac{\hat{y}_p(t, \hat{\theta}_t)}{EC_{SO_p}} \hat{\zeta}
$$

$$
\left(1 + \left(\frac{\hat{y}_p(t, \hat{\theta}_t)}{EC_{SO_p}} + \hat{m} \frac{\hat{y}_p(t, \hat{\theta}_t)}{EC_{SO_p}}\right)^{\hat{\chi}}\right)^2
$$

\[5618\]
\[
V'(\hat{\theta}) = -\frac{2}{N} \sum_{t=1}^{N} \epsilon^T(t, \hat{\theta}) \psi^T(t, \hat{\theta})
\]
\[
V''(\hat{\theta}) \approx \frac{2}{N} \sum_{t=1}^{N} \psi(t, \hat{\theta}) \psi^T(t, \hat{\theta})
\]
\[
\hat{\theta}(k+1) = \hat{\theta}(k) - ... \text{ using the parameter estimates given by the PEM,}
\]
capture the main behavior of the real signals, discarding
\[
\text{end}
\]
Note that a numerical differentiation is used because the mathematical expressions for the derivatives of (15) and (16) with respect to \( \chi \) and \( \eta \) become very complicated. The steps \( \Delta \chi \) and \( \Delta \eta \) used for the differentiation are selected to be sufficiently small.

3. RESULTS

In order to evaluate the performance of the developed identification methods, the PEM algorithms were applied to all real records in the NMB and BIS databases.

3.1 Real databases: clinical data

The NMB database has 60 records of patients subjected to general anesthesia during abdominal interventions where the NMB was controlled in closed-loop, Mendonça et al. (2004). The muscle relaxant atracurium was intravenously administered to the patients to keep the NMB around 10\% after the induction phase. For the induction a bolus of 500 \( \mu \text{g.kg}^{-1} \) was used. Patients were 32 male, 28 female, 60±16 years, 67.9 ± 11.8 kg.

The BIS database has 25 records of patients subjected to general anesthesia during abdominal interventions. During surgery the DoA was manually controlled by the anesthetist by the administration of propofol and remifentanil and having as target a BIS between 40 and 65 during maintenance. Patients were 10 male, 15 female, 61 ± 16 years.

3.2 Identification results

For the NMB records, \( K = 20000 \), \( \beta \) has 0.1 and 1 as the diagonal elements (to allow different convergence rates to \( \alpha \) and \( \gamma \) in the parameter vector \( \theta \)) and \( \hat{\theta}^{(0)} = [0.5 \ 2.0]^T \). It should be noted that for both the NMB and BIS cases, the number of iterations \( K \) was chosen to ensure convergence of the parameter estimates.

A representative example of the obtained results after applying the PEM algorithm described in section 2.1 to the NMB records is shown in Fig. 3. It is clear from the upper plot that the predicted signal \( \hat{y}(\hat{\theta}_n, \hat{y}_0(t, \hat{\theta})) \) captures the main trends of the real signal \( y(t) \), discarding the noise and the outliers present in the measurements. The predicted signal is obtained by simulating the system with the parameter estimates obtained in the last iteration of the PEM: \( \hat{\theta}^{(K)} = [0.0594 \ 0.4488 \ 0.1626 \ 0.6131]^T \). The parameter estimates update until convergence is shown in Fig. 4.

For the BIS records, \( K = 200000 \), \( \beta \) has 0.01, 0.01, 0.5 and 0.3 as the diagonal elements and \( \hat{\theta}^{(0)} = [0.4 \ 0.8 \ 1.5 \ 1.0]^T \).

Fig. 3. Identification results for record number 25 in the NMB database. Upper plot: the real measured NMB \( y \) (dashed line) and the predicted output model response \( \hat{y} \) (solid line); lower plot: administered atracurium dose (note that the scale in the yy-axis is split).

Fig. 4. Parameter estimates generated by the PEM algorithm for record number 25 in the NMB database (note that the parameter estimates converge before 2000 iterations and the remaining iterations are not shown).

The identification results obtained after applying the PEM described in 2.2 to record number 9 in the BIS database are present in Figs. 5-7. Fig. 6 shows the input signals (administered propofol and remifentanil doses) of this real record and Fig. 7 shows the parameter estimates generated by the PEM algorithm. As it is clear in Fig. 5, the parameter estimates \( \hat{\theta}^{(K)} = [0.0594 \ 0.4488 \ 0.1626 \ 0.6131]^T \) obtained at the end of the simulations give rise to a predicted BIS that follows the global behavior of the real BIS. Here the presence of noise corrupting the real measurements is highly visible. This supports the need of using a good model of the system able to describe the main characteristics of the real input-output relationship in a system identification perspective. These results show that the proposed minimally parameterized MISO model for the BIS and the developed PEM identification algorithm characterize well the nonlinear dynamics of the real system.

4. CONCLUSIONS

This paper presents Prediction Error Method (PEM) algorithms for the identification of minimally parameterized Wiener models in anesthesia, namely for the Neuromuscular Blockade (NMB) and the Bispectral Index (BIS). Records collected from patients undergoing general surgery are used to exemplify the performance of the proposed algorithms. The results show that the predicted signals, using the parameter estimates given by the PEM, capture the main behavior of the real signals, discarding...
the noise present in the real measurements, as desired. This indicates that the minimally parameterized Wiener models successfully describe the input-output relationship of the real systems. Moreover, the good results indicate that the developed PEM algorithms may be considered useful tools to identify the parameters present in these Wiener models.

The minimally parameterized models are hence expected to provide even better predictions of the system when used in recursive identification algorithms. The knowledge of the models structures and parameters taken from these offline experiments will be very useful to the development of those recursive algorithms, suitable to be incorporated in real-time control platforms for automatic drug dosing in patients undergoing anaesthesia.

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