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EFFECT OF NOISE ON BLOCK-ORIENTED IDENTIFICATION OF THE PHYSIOLOGICAL PROPOFOL MODEL

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ABSTRACT

The identification of the pharmacokinetic-pharmacodynamic propofol model from noisy measurement data is desirable, since it enables automatic open- and closed-loop drug delivery schemes to adapt to varying patient parameters. In order to investigate the influence of measurement noise on the performance of different nonlinear block-oriented identification algorithms a simulation study with a standard Wiener block structure for the physiological propofol model is performed. The results indicate that suitable nonlinear identification methods outperform linear models even in the presence of strong measurement noise.

KEYWORDS

Identification, Nonlinear Block Model, Noise, Pharmacokinetic-Pharmacodynamic Model.

1 INTRODUCTION

Propofol is a hypnotic drug which is administered during anaesthesia to achieve a desired depth of anaesthesia (DOA). Within the past few years a lot of interest has been taken in the automatic control of DOA using direct and indirect measurements of the hypnotic drug effect (Mortier, Struys, Smet, Versichelen, and Rolly 1998; Linkens, Abbod, and Backory 1997). The main problems in an automatic drug delivery system are reliable measurements of anaesthetic depth and an accurate physiological model of the patient.

Although a widely accepted propofol model consisting of a linear dynamic pharmacokinetic part (Shafer and Gregg 1992) and of a nonlinear static pharmocodynamic part (Schwilden, Schüttler, and Stoeckel 1985) exists, the drug effect (and model parameters) may not only vary within different patients but also based on their clinical condition.

Therefore, on-line identification of the model parameters based on input-ouput measurements is desireable and may be achieved by nonlinear identification schemes. Among artificial neural networks and other more general nonlinear model structures there also exist block-oriented models. The present paper investigates recently published algorithms (Bai 1998; Pelt and Bernstein 2000) to study their performance in the presence of measurement noise. This influence is of great importance since the measurement of DOA is still a problematic task.

2 IDENTIFICATION ALGORITHM

2.1 Block-Oriented Models

Block-oriented models consist of blocks with linear dynamic systems described by discrete-time transfer functions $G(q^{-1})$ interconnected with static nonlinearities $f(u)$. In Figure 1 the Hammerstein model ($f \rightarrow G$), the Wiener model ($G \rightarrow f$), and the nonlinear feedback model ($G \rightarrow f \rightarrow G$) are shown. The propofol model mentioned above has the structure of a Wiener model.

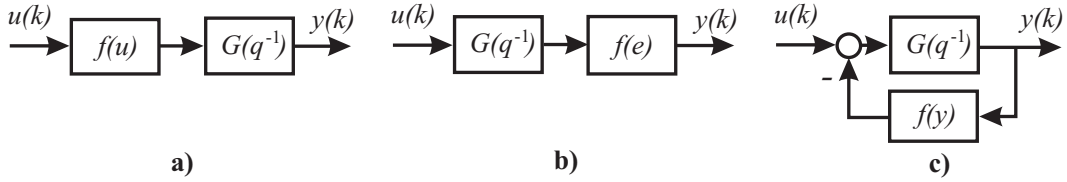

Figure 1. Different Types of Block-Oriented Nonlinear Models: a) Hammerstein Model, b) Wiener Model, c) Nonlinear Feedback Model

2.2 Algorithm

The algorithm for identification presented in (Bai 1998) and extended in (Pelt and Bernstein 2000) consists of two comparatively simple steps. Instead of solving the nonlinear least squares optimization problem, an approximation consisting of a standard least squares optimization and a fixed rank approximation in the Frobenius norm. The procedure provides simultaneous approximations of the linear and nonlinear blocks of the system. Moreover, the least squares optimization may be implemented in recursive formulation enabling the algorithm to be used on-line.

2.2.1 Method by E.W. Bai

In (Bai 1998) a method to identify nonlinear systems of the structure given in Figure 2 is presented. Although this is obviously a combined Hammerstein-Wiener model, the algorithm does not directly

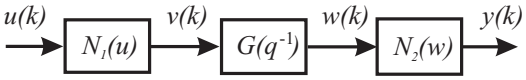

Figure 2. General Model Structure Used by Er-Wei Bai

identify the nonlinearities N_1 and N_2 directly but the more general model description

$$y(k) = \sum_i a_i \left(\sum_m c_m f_m \left(y(k-i) \right) \right) + \sum_j b_j \left(\sum_n d_n g_n \left(u(k-j) \right) \right), \tag{1}$$

where the functions f and g represent a priori known smooth nonlinearities. This is certainly a strong restriction to the applicability of the method since a direct analytical relationship between f and g and the block-nonlinearities N_1 and N_2 does not exist in general. Therefore, even if the generic type of the nonlinearities N_1 and N_2 is known (e.g. the Hill-equation for N_2), it cannot be incorporated into the identification algorithm and the nonlinearities f and g can only be chosen and optimized by guess.

The estimation of the model parameters a_i, b_j, c_m, and d_n is performed in two steps: First, the parameter combinations $a_i c_m$ and $b_j d_n$ which enter the model (1) as linear coefficients are identified by standard least squares estimation. Second, an optimal solution for the model parameters is found by approximating the exact performance criterion with a Frobenius norm. By selecting only appropriate nonlinearities a pure Hammerstein or a pure Wiener model may also be identified.

Although an analytical result for the convergence of the algorithm in the presence of noise is also included, only asymptotic behaviour is guaranteed and no quantitative statements on the performance of the algorithm are possible.

2.2.2 Method by T.H. Van Pelt and D.S. Bernstein

A substantial extension to the above described algorithm is given in (Pelt and Bernstein 2000). The structure is a combined nonlinear feedback-Wiener model (Figure 3) where the nonlinearities f and g are modeled by piecewise linear continuous functions. In this case, no a priori knowledge of the

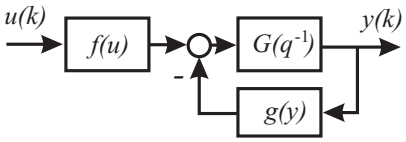

Figure 3. General Model Structure Used by T.H. Van Pelt and D.S. Bernstein

nonlinearities f and g is required and only the number and positions of the knots between the linear functions have to be chosen. This choice is not critical and may be adapted according to a first estimate. Similar to the algorithm described above a pure nonlinear feedback model, a pure Wiener model or a combination may be identified.

The parameter estimation is almost identical to the afforementioned algorithm, some additional mathematical results are incorporated in the nonlinear estimation part. No analytical results on the effect of noise are given.

3 SIMULATION

3.1 Physiological Reference Model

Reference data for the study were generated using a Wiener model for the effect of propofol. The pharmacokinetics are modeled by a linear discrete-time transfer function, and the pharmacodynamic part is modeled by the Hill equation:

$$e(k) = \frac{B(q^{-1})}{A(q^{-1})}u(k)\ , \quad y(k) = E_0 - \frac{E_{max}e^{\gamma}(k)}{e_{50}^{\gamma} + e^{\gamma}(k)}, \tag{2}$$

In the transfer function the input $u(k)$ is the propofol infusion rate and the output $e(k)$ is the drug concentration at the effect site. The transfer function is of order 4, corresponding to a three-compartment model with an additional effect compartment. In the Hill equation E_0 is the effect without any drug presence, E_{max} is the maximum deviation from E_0, e_{50} is the concentration at 50% of the maximum effect, and the parameter γ determines the steepness of the nonlinearity.

Two data sets were generated using uniformly distributed white noise sequences with different positive ranges as input $u(k)$. Data set 1 corresponds to an output $y(k)$ which is equivalent to a drug effect of only 5%, while data set 4 is equivalent to a drug effect of 70%. Measurement noise $n(k)$ was in all cases a zero-mean white noise Gaussian sequence. Noise intensity is given by the signal-to-noise ratio (SNR)

$$SNR = \sqrt{\frac{\sigma_y^2}{\sigma_n^2}}, \tag{3}$$

where σ_y^2 denotes the covariance of the signal and σ_n^2 is the noise covariance.

Table 1. Model Names and Structures

Name	Structure
Bai1	Hammerstein
Bai2	Hammerstein/Wiener
Pelt02	Nonlinear Feedback
Pelt12	Hammerstein/Nonlinear Feedback
Linear	Output Error Model

3.2 Identification

Identification was performed with several model structures including linear, Wiener, Hammerstein, nonlinear feedback, and a combined Hammerstein/nonlinear feedback model. The motivation to include models with obviously different structure is given by the fact that the actual nonlinear dynamic effect of propofol may not be accurately modeled by a Wiener structure. Additionally, the robustness of the identification algorithms with respect to a structural mismatch can be tested. Model names and structures as used in this paper can be found in ...

All models were identified with and without measuring noise of different signal-to-noise ratios. For both data sets SNRs of ∞ (no noise), 1000, 200, 100, 40, 4, 2 were generated by adding appropriate noise signals.

All input-output data sets were normalized between -1 and $+1$. To ensure proper model validation, data sets were split up in two independent parts with similar spectral and time domain properties. The input signal of the validation part was used as input to the identified model and the simulated model output was compared to the reference validation output by computing the mean squared error (MSE). This validation procedure emphasizes the importance of a good model prediction.

3.3 Results

The comparison between the different model identification schemes clearly indicates that measurement noise is well tolerated by most of the nonlinear identification algorithms. If a structural model mismatch exists the identification with measurement noise may still yield an acceptable performance.

The example of Figure 4 shows the validation results for a Hammerstein model (dotted), a combined Hammerstein/nonlinear feedback model (dash-dotted), and a linear output-error model (dashed). In the left plot no measurement noise was added, leading to a very good performance of all nonlinear models. The linear model yields a four times larger MSE than the nonlinear models. In the right plot the signal-to-noise ratio due to measurement noise was $SNR = 3.53$. Although the performance of all models has clearly deteriorated in the presence of strong measurement noise, the linear model is now performing best, indicating a more robust behaviour with respect to noise.

However, the relative performance of the algorithms also depends on the underlying nonlinearity in the data set. Since the Hill equation (2) represents a static nonlinearity with varying slope the operating point is also of great influence. In Figure 5 the results for data set 1 (5% drug effect operating point) and data set 4 (70% drug effect) are depicted (numerical values can be found in Table 2 in the appendix). While the linear model never performs optimal in the absence of noise, it is clearly best for small SNRs in data set 1. The situation is similar for data set 4, but the overall performance of the linear model is now so poor that an advantage can only be expected for unreasonable high levels of noise.

The performance of the nonlinear identification algorithms can be summarized as follows: Model structures with only one nonlinearity (Bai1 and Pelt02) show both good performance in the presence of small measurement noise and with small SNRs. The pure Hammerstein model Bai1 outperforms all other algorithms except for the linear model in the case of SNR=2.

It should be noted that the model order of the best linear model was 5 while for the nonlinear models orders 2 to 3 achieved best results. Higher orders often lead to unstable systems for the nonlinear

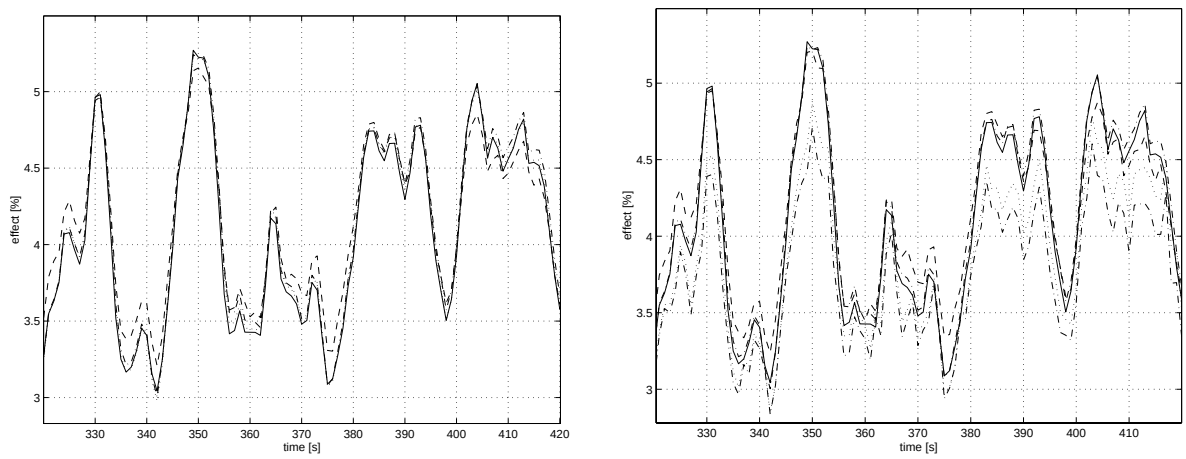

Figure 4. Model Validation (Left-Identification Without Measurement Noise, Right-With Measurement Noise): Actual Output (solid), Hammerstein Model (dotted), Combined Hammerstein/Nonlinear Feedback Model (dash-dotted), Linear Output-Error Model (dashed)

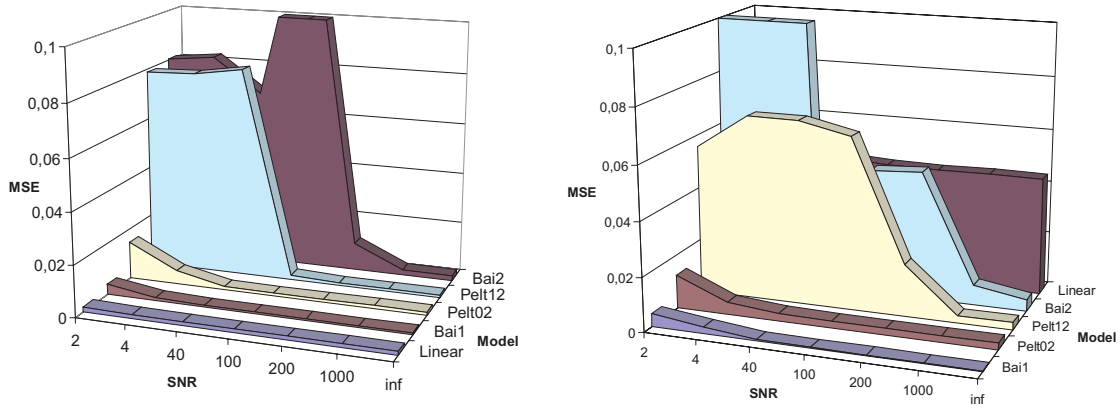

Figure 5. Model Validation: Left – Results for Data Set 1, Right – Results for Data Set 4

algorithms.

4 DISCUSSION

The results of our simulations indicate that nonlinear block oriented model identification may yield better performance than linear models in the presence of noise, depending on the operating point of the original nonlinear system. Nevertheless, classical linear models show a very robust behaviour with respect to noise and may be more accurate for small SNRs.

The model structure mismatch obviously affects the complicated models more strongly than the simple models with only one nonlinearity. This can be seen in Figure 5 for data set 4 where the simple models achieve better results even in the absence of noise. The same is true for the robustness with regard to measurement noise. The Hammerstein model Bai1 and the nonlinear feedback model Pelt12 show the smallest increase in MSE with growing SNR.

The identification of a pure Wiener model is not possible with the algorithms treated here, since a static nonlinearity at the output of the linear dynamic block directly affects both the filtered input and output of the linear system.

An application of the hammerstein model Bai1 in a clinical trial seems justified. The algorithm is quite robust with respect to noise, it achieves best performance in the absence of noise and may be im-

plemented in recursive form. It could be used to monitor the changes in the patients pharmacokinetics as well as the pharmacodynamics. The resulting model may easily be used for a model predictive controller in closed loop or only as an indicator of the patients' clinical state.

5 APPENDIX

Table 2. Model Performance Expressed as Mean Squared Prediction Error From Validation Data

Model	data set	2	4	40	100	200	1000	∞
Bai1	1	$4,1.10^{-3}$	$1,20.10^{-3}$	$6,60.10^{-4}$	$6,26.10^{-4}$	$6,22.10^{-4}$	$6,38.10^{-4}$	$6,40.10^{-4}$
Bai1	4	$4,7.10^{-3}$	$2,40.10^{-3}$	$3,86.10^{-4}$	$3,16.10^{-4}$	$2,70.10^{-4}$	$2,11.10^{-4}$	$2,07.10^{-4}$
Bai2	1	$8,04.10^{-2}$	$8,24.10^{-2}$	$6,91.10^{-2}$	$1,51.10^{-1}$	$1,09.10^{-2}$	$2,10.10^{-3}$	$2,00.10^{-3}$
Bai2	4	$3,39.10^{-1}$	$4,22.10^{-1}$	$1,30.10^{-3}$	$4,71.10^{-2}$	$4,82.10^{-2}$	$7,40.10^{-3}$	$4,20.10^{-3}$
Pelt12	1	$7,87.10^{-2}$	$7,94.10^{-2}$	$8,24.10^{-2}$	$1,60.10^{-3}$	$9,04.10^{-4}$	$9,09.10^{-4}$	$9,24.10^{-4}$
Pelt12	4	$5,57.10^{-2}$	$6,87.10^{-2}$	$6,86.10^{-2}$	$6,44.10^{-2}$	$1,94.10^{-2}$	$2,60.10^{-3}$	$2,70.10^{-3}$
Pelt02	1	$1,48.10^{-2}$	$5,30.10^{-3}$	$1,2.10^{-3}$	$1,1.10^{-3}$	$1,2.10^{-3}$	$1,2.10^{-3}$	$1,2.10^{-3}$
Pelt02	4	$1,25.10^{-2}$	$4,6.10^{-3}$	$2,9.10^{-3}$	$2,6.10^{-3}$	$2,6.10^{-3}$	$2,5.10^{-3}$	$2,5.10^{-3}$
Linear	1	$1,99.10^{-3}$	$1,55.10^{-3}$	$1,43.10^{-3}$	$1,43.10^{-3}$	$1,41.10^{-3}$	$1,42.10^{-3}$	$1,40.10^{-3}$
Linear	4	$4,50.10^{-2}$	$4,48.10^{-2}$	$4,54.10^{-2}$	$4,44.10^{-2}$	$4,41.10^{-2}$	$4,44.10^{-2}$	$4,41.10^{-2}$

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