TU Delft

PROCEEDINGS OF

EUROSIM 2001

SHAPING FUTURE WITH SIMULATION

The 4th International EUROSIM Congress, in which is incorporated the 2nd Conference on Modelling and Simulation in Biology, Medicine and Biomedical Engineering.

June 26 - 29, 2001
Aula Conference Centre
Delft, The Netherlands

Editors: A.W. Heemink
L. Dekker
H. de Swaan Arons
I. Smit
Th.L. van Stijn

ISBN: 90-806441-1-0

IDENTIFICATION OF COMBINED PATIENT PHARMACOKINETICS AND PHARMACODYNAMICS USING NEURAL NETWORKS

Hannes Kerschner, Martin Kozek

IDENTIFICATION OF COMBINED PATIENT PHARMACOKINETICS AND PHARMACODYNAMICS USING NEURAL NETWORKS

Hannes Kerschner, Martin Kozek

Institute for Machine- and Process-Automation
Vienna University of Technology
Gußhausstr. 27-29, A-1040 Vienna, Austria
kozek@impa.tuwien.ac.at
http://www.impa.tuwien.ac.at

ABSTRACT

For the control of depth of anaesthesia (DOA) several models have been developed. With the bispectral index (BIS) a single parameter is used as input which represents a non-invasive measurement of the DOA. The standard model consists of a linear dynamic pharmacokinetic part and a nonlinear static pharmacodynamic part. On-line identification of the model parameters based on input-ouput measurements is desireable and may be achieved by nonlinear identification schemes. In the present paper the performance of artificial neural networks with a feedforward structure in the identification of both static nonlinearities and nonlinear dynamic physiological systems is investigated. From these realizations it is evident that the neural networks are able to reproduce the system dynamics even in the presence of measurement noise.

KEYWORDS

Identification, Artificial Neural Network, Radial Basis Function, Pharmacokinetic-Pharmacodynamic Model.

1 NONLINEAR IDENTIFICATION

1.1 Pharmacodynamic — Static Model

The pharmacodynamic part is modeled by the Hill equation (Shafer and Gregg 1992)

$$y(k) = E_0 - \frac{E_{max} c_e^{\gamma}(k)}{c_{50}^{\gamma} + c_e^{\gamma}(k)}, \tag{1}$$

where $c_e(k)$ is the drug concentration at the effect site, $y(k)$ is the drug effect, E_0 is the effect without any drug presence, E_{max} is the maximum deviation from E_0, c_{50} is the concentration at 50% of the maximum effect, and the parameter γ determines the steepness of the nonlinearity. Using the BIS as an effect (Rampil 1998) the following model parameters can be used (Table 1):

Since eq.(1) defines a static input-output relation a feedforward network with a single input and a single output neuron is a sufficient structure. If the activation function of the hidden neurons is chosen to match the shape of the nonlinearity a minimum number of hidden neurons becomes necessary. However, the specific parameters are not known prior to the identification so a standard activation function has to be used. Furthermore, in order to identify the isolated pharmacodynamics the effect site concentration has to be measured.

Table 1. Parameters for the Hill equation

E_0	100	
E_{max}	95	
c_{50}	4	$\mu g/ml$
γ	3	

1.2 Training of Radial Basis Function Networks

To identify a static relation is a standard problem in the field of system identification. Artificial neural networks have been applied succesfully to many identification problems (Narendra and Parthasarathy 1990). The radial basis function networks (RBF) have a feedforward structure with a single hidden layer and radial basis functions as activation functions. To find an optimal variance for the basis function small nets with only a few number of neurons and different values of variances are trained using a small input and target vector. Plotting the net performance over the variance an optimal value for the spread of the radial basis function can be found.

The number of neurons in the hidden layer was varied until an optimal validation result was achieved.

The training of the neural network and the selection algorithm which determines the position of the centres of the RBFs is based on orthogonal estimation (Pottmann 1993). The calculations and simulations were executed with Matlab/Simulink.

With this neural network the nonlinear static model was identified, using the effect compartment concentration $c_e(k)$ as input and the drug effect (BIS) as output. Training data sets were generated as uniformly distributed random numbers between 0 and 20. Furthermore, the length of training data sets was reduced in order to minimize the amount of time needed for identification. Before using the data sets for training a standardization algorithm transforms the data to values between -1 and 1.

1.3 Results for static identification

The static nonlinearity was identified effectively by RBF networks. The structure necessary for a satisfactory result is relatively small (1 input, 8 neurons in the hidden layer) and therefore fast learning becomes possible. The optimal spread of the radial basis functions was determined at 10.

In Fig.1 the output of the Hill equation (1) to a ramp function is plotted (solid line). As can be seen in the plot the gradient at $c_e = 0$ is not equal to 0. This curve should be the reference output for the validation of the trained networks. A comparison with different network structures is given, too. The output of a net with 8 neurons and a spread of 10 is plotted with a dashed line. The third line (dashed-dotted) shows the output of a neural net with 11 neurons in the hidden layer and a spread of 5.

The comparison with the two networks shows that the smaller network exhibits a stronger underestimation of the reference signal. At $c_e = 0$ the output of the network with 8 neurons is only 98, the output of the network with 10 neurons is 99,5. At $c_e = 0,5$ overprediction can be observed as an result of both networks (100,1 with 10 neurons, 100,2 with 8 neurons). Looking at the right side of the nonlinear function it is obvious that a small bias persists with the 8 neuron-network. The difference is 1,1 at $c_e \to \infty$, respectively, 2,6 with the other network. In the middle part of the Hill equation (steep branch from $c_e = 2$ up to $c_e = 10$) both networks are well trained. This area is the operating range during general anaesthesia (BIS value ranges from 10 to 90).

The presence of zero-mean white Gaussian measurement noise is well tolerated and displays the robustness of neural network. The performance of the network was satisfactory until the noise amplitude reaches 30% of the highest output signal.

From these realizations it is evident that the neural networks with radial basis functions as activation functions are able to reproduce the system even in the presence of measurement noise.

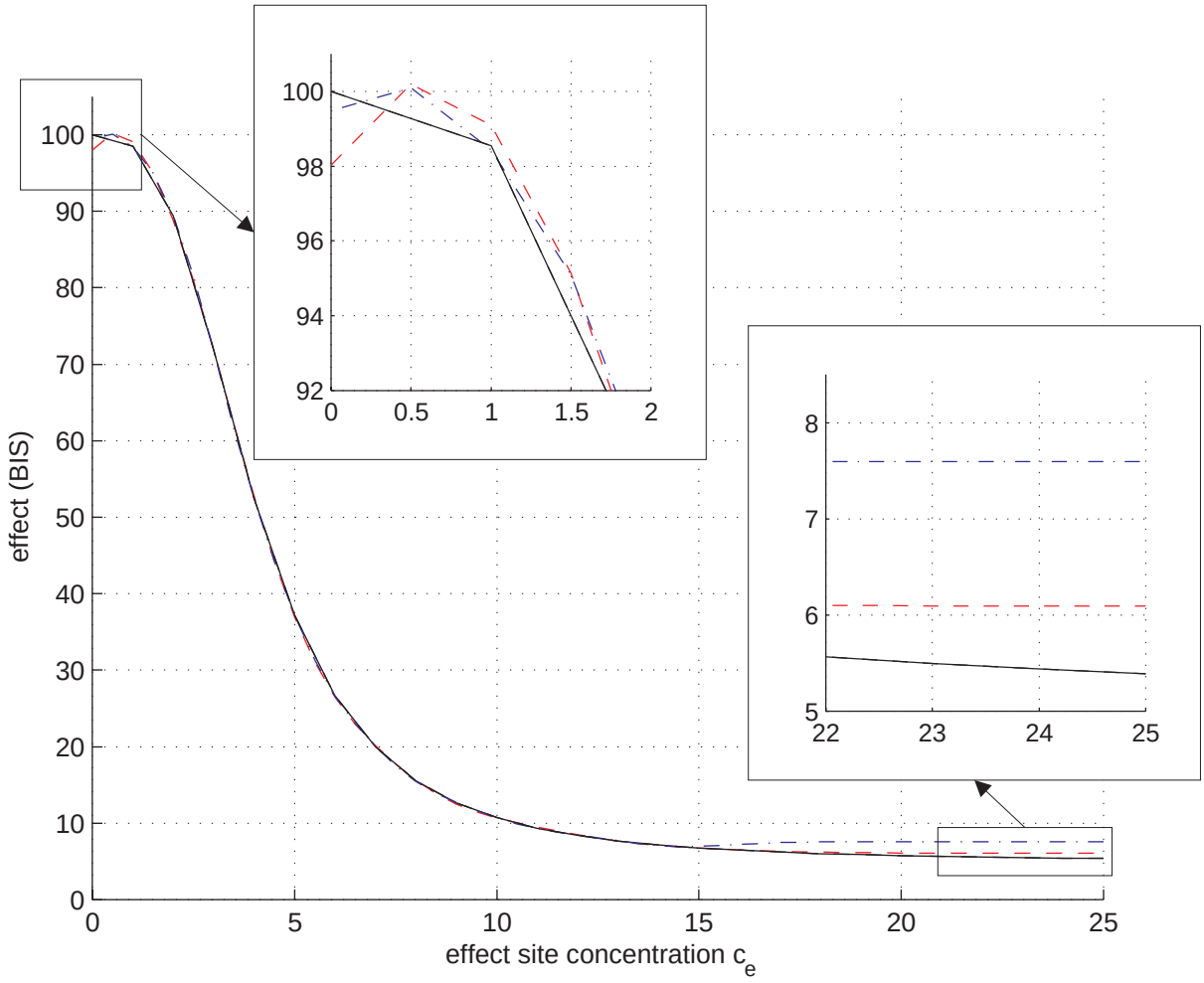

Figure 1. Validation: reference output (solid), 8 neurons (dashed), 10 neurons (dashed-dotted)

2 COMBINED PHARMACOKINETIC/PHARMACODYNAMIC MODEL

2.1 Dynamic Model

The dynamics of the standard model are given by a linear time invariant transfer function

$$c_e(k) = \frac{B(q^{-1})}{A(q^{-1})} u(k), \tag{2}$$

where the input $u(k)$ is the drug infusion rate. Usually, this system consists of 3 compartments plus one effect compartment representing the effect site (Schwilden, Schüttler, and Stoeckel 1985). Various elimination rates between these compartments and the environment can be found in (Marsh, White, Morton, and Kenny 1991) and (Shafer, Shafer, Doze, and White 1988), for example.

Therefore, the overall structure consists of a serial connection of the linear dynamic system (2) with the static nonlinear relationship (1). Since the model parameters may vary considerably and the effect site concentration $c_e(k)$ is not available in clinical routine (requires invasive measurement), the whole nonlinear dynamic system may be considered unknown and a neural network can be employed to learn the dynamics of the system from input-output data.

In the case of a dynamic black box model either recurrent neural networks or additional delayed system inputs and outputs employed as net inputs can be used. In this paper we focus on pure feedforward networks with delayed input signals.

2.2 Identification of the Combined Model

In order to get optimal results the output area is divieded into 3 operating ranges (operating points). The first operating range includes the upper part of the Hill-Equation (1) and represents BIS-values from 100 down to 85. The steep middle part of the nonlinearity represents the second operating point reaching from 85 down to 30. Finally, the right side of the nonlinear graph is the third operating range which includes values from 30 down to 5, respectively, 0. Training data sets were generated in Matlab/Simulink. The input signals were choosen as uniformly distributed random signals with amplitudes between 0 and $+1$. With an additional gain the amplitudes were amplified to the corresponding operating range.

The transfer function was transformed from the Laplace domain to the discrete z-domain using matched pole-zero mapping with a sample time $T_s = 1$s. This method ensures a relative degree of one in the discrete transfer function.

Before training the data undergo a standardization algorithm to values between -1 and $+1$. Because of this the results have to be transformed back to get correct results.

2.3 Results

2.3.1 Identification of the Upper Part (Operating Range 1)

As in section 1.2, the optimal variance of the RBF was determined at 85. With 25 neurons the best performance was reached. Measurement noise is well tolerated until the zero-mean white Gaussian noise reaches a noise power of 0,5. Fig. 2 presents the comparison between the net output and a linear system identified with Matlab using the same input/output data.

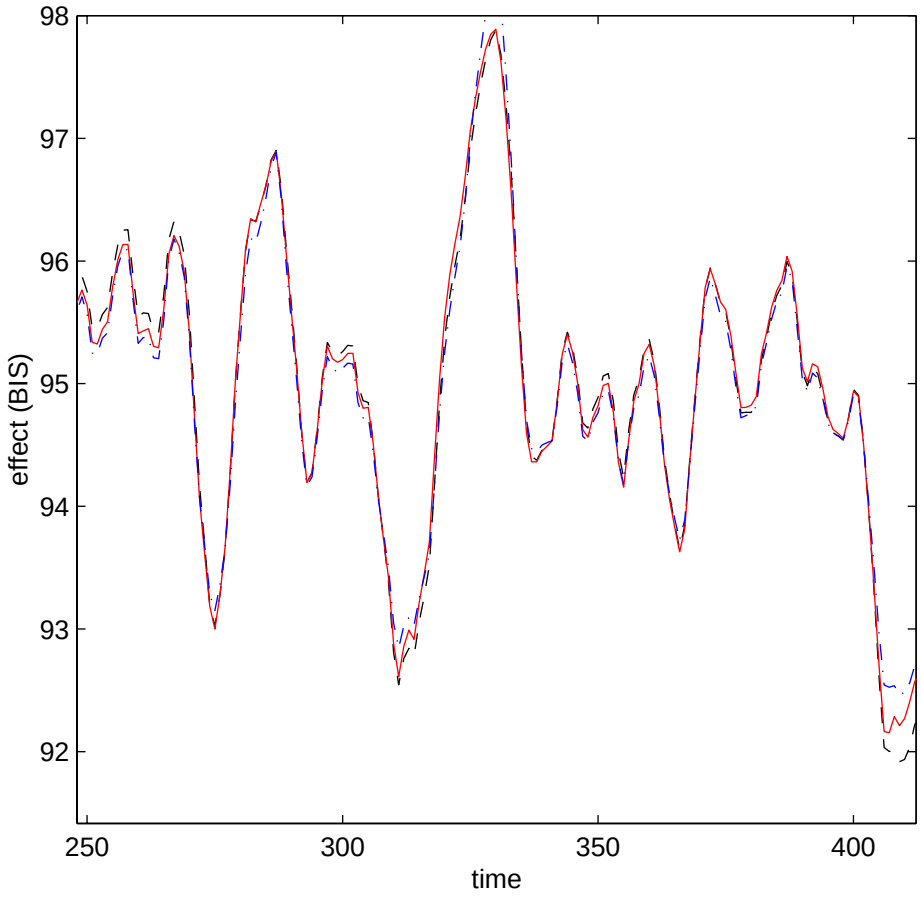

Figure 2. Comparison of Target (dashed), net output (solid), linear model (dashed-dotted)

2.3.2 Identification of the Middle Part (Operating Range 2)

The optimal performance was reached with only 17 neurons and a variance of 140. The reasons for this small structure and large variance is the nearly linear shape of the middle part. If measurement noise is present the performance of the network was satisfactory until the noise power reaches 0,5.

2.3.3 Identification of the Right Part (Operating Range 3)

Defining the variance of the RBF as 85 (like in section 2.3.1) and using 35 neurons a small error is reached. This large number of neurons is necessary because of the flat branch in this operating range. Measurement noise with a noise power of 0,5 is tolerated.

3 CONCLUSIONS

The model parameters vary considerably between patient groups and especially during the stay of critically ill patients at the intensive car unit. Therefore, on-line and adaptive identification of the model parameters is desireable. In this paper the identification of both static nonlinearities and nonlinear dynamic physiological systems with feedforward neural networks with RBF is investigated. Only few input/output data are necessary to train a suitable neural net. Using 150 data points and a sample time of $T_s = 1$s the BIS value has to be stored for a time period of 2,5 min. A Comparison with linear models (e.g. output error model) shows the advantage of neural networks. Although the linear model is also capable of correctly representing small amplitudes the linear output shows an increasing error with growing amplitudes. Since the data shown in Fig.2 only vary within a small range this effect will become more important for large oscillations or transient changes.

From these realizations it is evident that the neural networks can reproduce the system dynamics with short input/output data even in the presence of measurement noise. Especially static models are very robust in the presence of disturbances.

A very important point is the standardization of the input/ouput data before starting the training algorithm.

REFERENCES

Marsh, B., M. White, N. Morton, and G. Kenny (1991). Pharmacokinetic model driven infusion of propofol in children. *British Journal of Anaesthesia* (67), 41–48.

Narendra, K.S. and K. Parthasarathy (1990). Identification and control of dynamical systems using neural networks. *IEEE Transactions on Neural Networks 1*(1), 4–27.

Pottmann, M. (1993). Radial basis function networks for process identification and control. Master's thesis, Institute for Machine- and Prozess-Automation, Vienna University of Technology, Gußhausstr. 27–29, A-1040 Vienna.

Rampil, I.J. (1998). A primer for eeg signal processing in anaesthesia. *Anaesthesiology 89*(4), 980–1002.

Schwilden, H., J. Schüttler, and H. Stoeckel (1985). Quantitation of the eeg and pharmacodynamic modelling of hypnotic drugs: Etomidate as an example. *European Journal of Anaesthesiology* **2**, 121–131.

Shafer, A., S.L. Shafer, A. Doze, and P.F. White (1988). Pharmacokinetics and pharmacodynamics of propofol infusions during general anesthesia. *Anaesthesiology* (69), 348–356.

Shafer, S. and K. Gregg (1992). Algorithms to rapidly achieve and maintain stable drug concentrations at the site of drug effect with a computer controlled infusion pump. *Journal of Pharmacokinetics and Biopharmaceutics 20*(2), 147–169.