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Neural Networks 16 (2003) 841–845

Neural Networks

www.elsevier.com/locate/neunet

2003 Special issue

Pharmacodynamic population analysis in chronic renal failure using artificial neural networks—a comparative study

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Abstract

This work presents a pharmacodynamic population analysis in chronic renal failure patients using Artificial Neural Networks (ANNs). In pursuit of an effective and cost-efficient strategy for drug delivery in patients with renal failure, two different types of ANN are applied to perform drug dose-effect modeling and their performance compared. Applied in a clinical environment, such models will allow for prediction of patient response to the drug at the effect site and, subsequently, for adjusting the dosing regimen.

Keywords: Pharmacodynamic modeling; Multilayer perceptron network; Radial basis; Autoregressive model

1. Introduction

Anemia is a nearly universal sequel in an End-Stage Renal Disease (ESRD) patient. Until the advent of Erythropoietin (EPO), ESRD patients faced severe anemia and cardiovascular complications, or the requirement for multiple transfusions and the risk of a variety of blood borne pathogens. The addition of this expensive drug to the already burdensome cost of the Medicare ESRD program has created a fiscal crisis. The Dialysis Outcomes Quality Initiative of the National Kidney Foundation recommends hematocrit maintained within the narrow range of 33–36%. To this end, several strategies (protocols) exist for the dosing of EPO. These protocols adjust the dose amount or the dosing frequency based on the current hematocrit, its 3 month rolling average, as well as previous EPO doses. This process is labor intensive and requires trained personnel to assess monthly hematocrit and iron levels and to make adjustments or assessments every 2 or 4 weeks. Furthermore, such process is not optimal with respect to the cost of the EPO. It is therefore of great significance that the available computational tools be utilized to support the medical personnel in this difficult task and to optimize the treatment cost.

Several attempts at the automation of the EPO delivery have already been reported (Bellazzi, 1992; Bellazzi, Siviero, & Bellazzi, 1994). A multicompartmental model of erythropoiesis and a set of integro-differential state-space equations served as a basis to formulate a parametric description of the process. Parametric identification, performed using Bayesian framework, was then performed on the population data (Bellazzi, 1992). This approach was subsequently enhanced by a fuzzy rule-based control strategy (Bellazzi et al., 1994) to improve the cost-efficiency of the drug delivery process. Unfortunately, as of today, neither one of these methodologies have achieved acceptance in the clinical environment.

The advances in the area of Computational Intelligence, especially the resurgence of Artificial Neural Networks (ANN), have influenced the area of pharmacokinetic and pharmacodynamic (PK/PD) modeling. A number of publications presenting applications of ANN models to PK/PD analysis can be found in the literature (Brier, Zurada, & Aronoff, 1995; Veng-Pedersen & Modi, 1992, 1995). One particular application area which benefits from the data-driven learning capabilities of ANNs is the drug-effect modeling (Veng-Pedersen & Modi, 1992, 1995). It is well known from control theory that an effective control strategy can be achieved only of an adequate system model is available. Hence, an efficient and cost-effective dosing protocol for EPO must be based on an accurate model of patient response to EPO. Only very recently, a few efforts have been undertaken to utilize ANN models in individualized EPO dosing (Jacobs, Lada, Zurada, Brier,

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doi:10.1016/S0893-6080(03)00084-4

& Aronoff, 2002; Guerrero et al., 2002). Such individualized models are applicable when a large data record associated with the specific patient is available. In the clinical environment it is sometimes important to have access to a population model, i.e. a model built upon data from a large population of patients. Such model not only provides useful information about the population of patients, but can also be applied to a patient without a sufficient treatment history, in which case it would be very difficult to provide an individualized model.

This work presents an approach to PK/PD population analysis and modeling of hematocrit response in ESRD patients. Two types of ANN models are studied here, Multi-Layer Perceptron (MLP) network and Radial Basis Function (RBF) network. Their performance is mutually compared based on a modification of a popular validation method. It is also compared to the performance obtained by a linear autoregressive model (ARX). Finally, a statistical significance testing is performed, in order to establish the validity of the obtained results.

2. Method

2.1. Data

Two hundred and nine patients undergoing hemodialysis at the University of Louisville Chronic Dialysis Unit during the period 1/1/96 to 10/31/2001 were studied. Data abstraction was approved by the Human Studies Committee of both, the Department of Veteran Affairs and University of Louisville. Patients were excluded from study only for sickle cell disease, and HIV infection. Demographic, clinical, and laboratory data were abstracted from clinical and laboratory databases. Each data entry contains the following fields: patient number, week, hematocrit, EPO dose for a given week, Ferritin level, Iron saturation, Albumin level, Parathyroid hormone level, Kt/V (hemodialysis quality index), and IV iron dose for a given week. It has been suggested (Bellazzi, 1992) and demonstrated empirically (Jacobs et al., 2002) that the current level of hematocrit and the weekly EPO dose are the most significant factors in influencing the future hematocrit level. Following this finding, the presented analysis focuses on these two variables. Table 1 shows patient demographics as well as mean and standard deviation values of the most relevant variables.

Table 1
Patient characteristics

Race (B/W)	130/35
Gender (M/F)	95/71
Age, years (mean ± SD)	55 ± 15
Study period, weeks (mean ± SD)	157 ± 71
Hematocrit (mean ± SD)	35.2 ± 5.2
Erythropoietin dose (U/week) (mean ± SD)	11,800 ± 12,000

In the clinical environment, hematocrit levels are determined every 2–6 weeks. To address the resulting problem of non-uniform sampling, a linear interpolation between the available samples was first performed. The time series obtained this way was subsequently resampled on a weekly basis. The purpose of using the linear method was to replicate the smooth dynamics of red blood cell production and to prevent the occurrence of peaks, often seen with higher order interpolation methods. Finally, the monthly average hematocrit levels and their standard deviations were derived from the resampled weekly data.

The process of red blood cell production resulting from EPO infusion consists of several stages in which mature red blood cells are derived from a stem cell (Fisher, 2003). The length of this process is estimated as 12 weeks and is subject to intra- and inter-individual variation. To account for this phenomenon, average monthly hematocrit levels over past 2 months, together with their standard deviations, as well as average doses of erythropoietin over past 2 months are used as input variables for the proposed model.

2.2. Multilayer perceptron network model

The first ANN model applied in this study was a MLP network. It contains a single hidden layer with hyperbolic tangent activation functions and a linear output layer. The choice of a single hidden layer is based on the hypothesis that such configuration is sufficient for universal approximation. In the functional form, the MLP model can be represented as:

$$\mathrm{hct}_{\mathrm{avg}}(k+1)=\mathrm{MLP}[\mathrm{hct}_{\mathrm{avg}}(k),\mathrm{hct}_{\mathrm{SD}}(k),\mathrm{hct}_{\mathrm{avg}}(k-1),\ \mathrm{hct}_{\mathrm{SD}}(k-1),\mathrm{EPO}_{\mathrm{avg}}(k),\mathrm{EPO}_{\mathrm{avg}}(k-1)] \quad (1)$$

In this expression $\mathrm{hct}_{\mathrm{avg}}$ is the average monthly hematocrit level, $\mathrm{hct}_{\mathrm{SD}}$ is a monthly standard deviation of hematocrit level, and $\mathrm{EPO}_{\mathrm{avg}}$ is the monthly average erythropoietin dose. The number of the hidden layer neurons was selected using heuristics combined with a trial and error approach. It was established that 10 hidden neurons proved sufficient for accurate prediction. Any increase of this number did not significantly improve the prediction accuracy. Hence, the MLP network has a 6:10:1 structure.

The population analysis was performed using a patient-specific variant of the leave-one-out validation. This means that for each single patient, their data were left out and the MLP model was trained upon the remaining data. The trained model was then evaluated against the previously unseen data records of the left-out patient.

The simulations were performed in MATLAB using Neural Network Toolbox. Due to its robustness and fast convergence, the Levenberg–Marquardt method was used

for training. This method adjusts the network weights using the following formula.

$$\mathbf{w}_{l+1} = \mathbf{w}_l - [\mathbf{J}^T\mathbf{J} + \mu\mathbf{I}]^{-1}\mathbf{J}^T\mathbf{e} \quad (2)$$

where $\mathbf{w}$ are the network weights, $\mathbf{J}$ is the Jacobian matrix that contains first derivatives of the network output with respect to the weights, $\mathbf{e}$ is the vector of network errors, and $\mathbf{I}$ is the identity matrix. The coefficient μ controls the step size of the weight update and is varied based on the error convergence. When μ is large, the method becomes gradient descent with a small step size, whereas for μ close to zero, it acts as Newton's method with an approximate Hessian. In the described simulations, the training was concluded after exceeding the maximum number of epochs (100), or after no error decrease was detected (small μ). To improve the optimization, the input data were uniformly rescaled to the interval $[-1;1]$.

2.3. Radial basis function network model

The second ANN model applied in this study was a RBF network. It contains a single layer of Gaussian basis functions and a linear output layer. In the functional form, the RBF model can be represented as

$$\begin{aligned}\mathrm{hct}_{\mathrm{avg}}(k+1) = \mathrm{RBF}[&\mathrm{hct}_{\mathrm{avg}}(k), \mathrm{hct}_{\mathrm{SD}}(k), \mathrm{hct}_{\mathrm{avg}}(k-1),\\ &\mathrm{hct}_{\mathrm{SD}}(k-1), \mathrm{EPO}_{\mathrm{avg}}(k), \mathrm{EPO}_{\mathrm{avg}}(k-1)] \quad (3)\end{aligned}$$

The RBF network applied in this study contains a maximum of 10 function neurons. The process of selecting the centers of the basis functions relies on the functional equivalence between RBF networks and Fuzzy Rule-based Inference Systems (Jang & Sun, 1993). It has been established that optimal fuzzy rules cover extrema of the approximated function (Kosko, 1995) and that these extrema can be found by identifying the maxima of the absolute approximation error. Based on these foundations, the following iterative procedure for center selection has been employed in this work:

Given: data set $Z = [X\, y]$ of size N, where X is the input and y the output portion of the data, basis function spread s, and the maximum number of basis functions $h_{\max}$

1. Create a mean predictor $\tilde{y} = \bar{y}$
2. Evaluate the mean predictor on data Z, i.e. compute errors $e_i = |y_i - \tilde{y}|,\ i = 1,\ldots,N$
3. Find maximum error $e_{\max} = \max(e_i)$
4. Establish first basis function with center at X_k, s.t. $e_k = e_{\max}$, set $h = 1$.
5. Estimate output weights of the RBF network using lest squares.
6. Evaluate the RBF network on data Z, i.e. compute errors $e_i = |y_i - y_{\mathrm{RBF}}(X_i)|$.
7. Find maximum error $e_{\max} = \max(e_i)$
8. Add new basis function with center at, X_k, s.t. $e_k = e_{\max}$, set $h = h + 1$.
9. Estimate output weights of the RBF network using least squares.
10. Stop if $h = h_{\max}$, otherwise go to 6.

Out of $h_{\max}$ RBF networks the one with the best performance is selected. To select the optimal value of the basis function spread, s, the procedure was repeated for several different spreads, ranging from 0.5 to 2.0. It must be emphasized, though, that the input data was uniformly rescaled to the interval $[-1;1]$.

The so obtained RBF network model was further optimized using the very same Levenberg–Marquardt method, as in the case of the MLP model.

2.4. Linear model

An autoregressive model with exogenous inputs (ARX) was developed as a point of reference to evaluate the performance of the previously developed ANN models. The ARX model has the following form

$$\begin{aligned}\mathrm{hct}_{\mathrm{avg}}(k+1) = {} & a_0 + a_1\mathrm{hct}_{\mathrm{avg}}(k) + a_2\mathrm{hct}_{\mathrm{SD}}(k)\\ & + a_3\mathrm{hct}_{\mathrm{avg}}(k-1) + a_4\mathrm{hct}_{\mathrm{SD}}(k-1)\\ & + a_5\mathrm{EPO}_{\mathrm{avg}}(k) + a_6\mathrm{EPO}_{\mathrm{avg}}(k-1) \quad (4)\end{aligned}$$

The coefficients a_i, $(i = 0,\ldots,6)$ for this model were obtained using least squares estimation.

2.5. Performance measures

For each model, Root Mean Square Error (RMSE) and Normalized Root Mean Square Error (NRMSE) was computed to evaluate its performance

$$\mathrm{RMSE} = \sqrt{\frac{\sum_{i=1}^{N}(y_i - \tilde{y}_i)^2}{N}} \quad (5)$$

$$\mathrm{NRMSE} = \sqrt{\frac{\sum_{i=1}^{N}(y_i - \tilde{y}_i)^2}{\sum_{i=1}^{N}(y_i - y_m)^2}} \quad (6)$$

where y_i is the actual output, $\tilde{y}_i$ is the model output, and y_m is the mean value of y_i, $(i = 1,\ldots,N)$. While the RMSE assesses the quality of approximation, the NRMSE evaluates the relative improvement with respect to mean prediction.

3. Results

Using the aforementioned patient-specific variant of leave-one-out validation, 209 MLP network models and 209 RBF network models were constructed. The average validation RMSE obtained in this way was 1.93% for

Table 2
Comparison between neural network models and the linear model

	MLP	RBF	ARX
RMSE (mean ± SD)	1.93 ± 0.60	2.02 ± 0.65	2.11 ± 0.70
NRMSE (mean ± SD)	0.60 ± 0.25	0.65 ± 0.28	0.68 ± 0.35

the MLP and 2.02% for the RBF model. Using the width of the target hematocrit range (33–36%), one can conclude that this is an acceptable performance. This is particularly true when we consider the fact that no patient specific attributes (age, weight, gender, race) were utilized in the analysis.

A comparison of the errors produced by all the models is presented in Table 2. Mean values and Standard Deviations of RMSE and NRMSE over whole patient population are shown. Both ANN models improve upon the linear model (lower mean error values) and are more consistent (smaller Standard Deviations).

Finally, a statistical significance analysis was performed on the results to establish the significance of difference between the obtained performances. Analysis of variance with repeated measures was performed using SPSS version 11 on both the RMSE and NRMSE for each subject. A post test is shown comparing the errors between ARX, MLP, and RBF. Table 3 shows the results of the significance analysis performed for the RMSE, whereas Table 4 shows the results for the NRMSE. These results imply that the MLP is significantly better than the other two models. The difference in performance between the RBF model and the ARX can also be adjugded as significant.

Fig. 1 presents the performance of the obtained models for a selected patient. The continuous lines represent the model predicted output, whereas the dotted ones represent the actual values. It should be pointed out that the predicted and the actual curve significantly overlap for the MLP model which illustrates its better performance as compared to the RBF and the ARX models. In the case of the latter one, one can almost observe a time shift of one prediction step between the actual and the predicted hematocrit. The RMSE values for this particular patient are as follows

Table 3
Pairwise comparison for RMS error

Model 1	Model 2	Mean difference ($P < 0.5$)	Significance
MLP	RBF	−0.093	0.000
	ARX	−0.181	0.000
RBF	ARX	−0.087	0.001
	MLP	0.093	0.000
ARX	MLP	0.181	0.000
	RBF	0.087	0.001

Table 4
Pairwise comparison for NRMS error

Model 1	Model 2	Mean difference ($P < 0.5$)	Significance
MLP	RBF	−0.050	0.000
	ARX	−0.081	0.000
RBF	ARX	−0.030	0.002
	MLP	0.050	0.000
ARX	MLP	0.081	0.000
	RBF	0.050	0.002

- MLP:RMSE = 1.55; NRMSE = 0.37 (2.7-fold improvement over mean prediction)
- RBF:RMSE = 1.71; NRMSE = 0.41 (2.4-fold improvement over mean prediction)

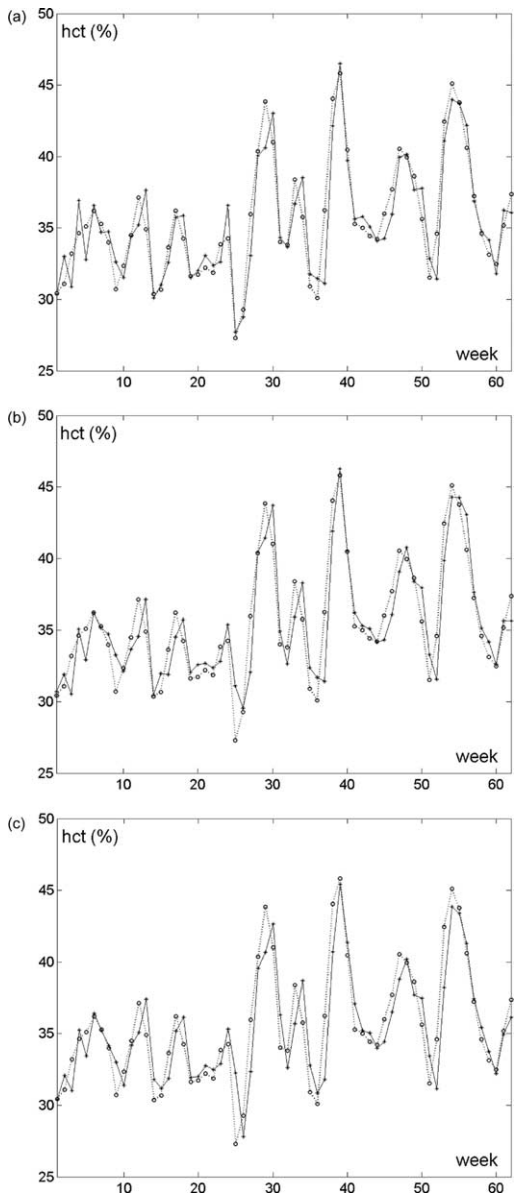

Fig. 1. Illustration of hematocrit prediction for an individual patient: (a) MLP, (b) RBF, (c) ARX.

- ARX:RMSE = 1.80; NRMSE = 0.44 (2.2-fold improvement over mean prediction)

4. Conclusions

An ANN-based approach to pharmacodynamic population analysis of patients with renal failure has been presented. Two different ANN architectures, MLP and RBF network, have been studied and their performance compared and statistically evaluated for significance. The analysis revealed superiority of the MLP model, as well as supremacy of both ANN models over the linear, autoregressive model. In further stages, the developed ANN models of patient response to EPO treatment will form a component of a hybrid intelligent control system for EPO delivery. Given a large population of patients, it has been shown that ANN models are capable of satisfactorily predict the response of an unseen patient. The obtained result is of paramount importance in the clinical environment, because it suggests that the employment of an intelligent drug delivery system to a large number of dialysis patients is feasible.

Acknowledgements

This material is based upon work supported by the Office of Research and Development, Medical Research Service, Department of Veteran Affairs.

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