

Prediction of Cyclosporine Dosage in Patients after Kidney Transplantation Using Neural Networks

Gustavo Camps-Valls, Begoña Porta-Oltra, Emilio Soria-Olivas, José D. Martín-Guerrero, Antonio J. Serrano-López, Juan J. Pérez-Ruixo and N. Víctor Jiménez-Torres

Abstract—This communication proposes the use of neural networks for individualizing the dosage of cyclosporine A (CyA) in patients who have undergone kidney transplantation. Since the dosing of CyA usually requires intensive therapeutic drug monitoring, the accurate prediction of CyA blood concentrations would decrease the monitoring frequency and thus improve clinical outcomes. Thirty-two patients and different factors were studied to obtain the models.

Three kinds of networks (multilayer perceptron, FIR network, Elman recurrent network) and the formation of neural-network ensembles are used in a scheme of two chained models where the blood concentration predicted by the first model constitutes an input to the dosage prediction model. This approach is designed to aid in the process of clinical decision making. The FIR network, yielding root-mean-square errors (RMSE) of 52.80 ng/mL and mean errors (ME) of 0.18 ng/mL in validation (10 patients) showed the best blood concentration predictions and a committee of trained networks improved the results (RMSE = 46.97 ng/mL, ME=0.091 ng/mL). The Elman network was the selected model for dosage prediction (RMSE=0.27 mg/Kg/d, ME=0.07 mg/Kg/d). However, in both cases, no statistical differences on the accuracy of neural methods were found. The models' robustness is also analyzed by evaluating their performance when noise is introduced at input nodes, and it results in a helpful test for models' selection.

We conclude that neural networks can be used to predict both dose and blood concentrations of cyclosporine in steady state. This novel approach has produced accurate and validated models to be used as decision-aid tools.

Index Terms— Clinical pharmacokinetics, drug monitoring, kidney transplantation, blood concentration, cyclosporine, time series prediction, neural networks.

I. INTRODUCTION

At present, despite progress with newer agents, cyclosporine A (CyA) is still the cornerstone of immunosuppression in renal transplant recipients and its use continues to expand globally. Although CyA has been used as a primary immunosuppressive agent for nearly 20 years, significant advances in dose formulation, therapeutic drug monitoring

G. Camps-Valls, E. Soria-Olivas, J. D. Martín-Guerrero, and A. J. Serrano-López are with the Digital Signal Processing Group, Universitat de València, Spain. E-mail: {gcamps,soriae,jdmg,ajserran}@uv.es.

B. Porta-Oltra is with the Pharmacy Service at the Dr. Peset University Hospital, València (Spain)

J. J. Pérez-Ruixo was with the Pharmacy Service at the Dr. Peset University Hospital, València (Spain), when this paper was initially submitted. Currently, he is with the Advanced PK/PD Modeling & Simulation, Global Clinical Pharmacokinetics and Clinical Pharmacodynamics Division, Johnson & Johnson Pharmaceutical Research & Development, a Division of Janssen Pharmaceutica N.V. Beerse (Belgium). E-mail: jperezru@prdbe.jnj.com

Prof. N. V. Jiménez-Torres is with the Pharmacy and Pharmaceutical Technology Department, Universitat de València (Spain) and with the Pharmacy Service at the Dr. Peset University Hospital, València (Spain). E-mail: victor.jimenez@uv.es.

(TDM) and guidelines, and the emerging role of CyA-based combined therapies have resulted in a substantial improvement in clinical outcomes in renal transplant recipients [1].

CyA is generally considered a critical dose drug. Its narrow therapeutical range is an important issue in the clinical management of transplant patients, whereas underdosing may result in graft loss and overdosing causes kidney damage, increases opportunistic infections, systolic and diastolic pressure, and cholesterol. The relationship between pharmacokinetics and safety has been studied and provides the basis for the generally accepted therapeutic drug monitoring. Moreover, the pharmacokinetic behavior of CyA presents a substantial inter- and intra-individual variability [2]. Several factors such as clinical drug interactions and patient compliance can also significantly alter blood concentrations of CyA [2], [3]. The pharmacokinetic variability of cyclosporine appears to be particularly evident in the earlier post-transplantation period (less than three months), when the risk and clinical consequences of acute rejection are higher than in stable renal patients (six months or more). For this reason, a more intensive strategy of TDM is necessary during the early post-transplantation period [4].

Since the trough blood concentration has traditionally been used to monitor CyA therapy, improved mathematical models which are capable of predicting the next trough concentration of CyA and then determining the optimal dosage become necessary. Several studies have been done on the CyA blood concentration prediction but only one, to our knowledge, uses state-of-the-art neural networks [5]. Limitations such as non-uniform sampling during routine clinical data collection, the presence of non-stationary pharmacokinetic processes and the high variability in the CyA blood concentration time series, led us to use artificial neural networks (ANN). In a neural approach it is not strictly necessary to assume a specific relationship between variables and they have proven to be effective techniques in a wide range of applications. Few attempts have been made to predict drug behavior using ANN and, additionally, they have been limited to the use of the classical multilayer perceptron [6], [7]. In this paper, we propose the use of dynamic neural networks to predict CyA blood levels and establish the correct dosage in patients with kidney transplants.

The paper is organized as follows. Data collection is introduced in Section II. We then go on to establish the experimental setup and to review the predictive techniques used. The results are presented in Section IV and a discussion is provided in Section V. Finally, Section VI contains concluding remarks and a proposal for further work.

II. MATERIAL

A. Patients and data collection

Thirty-two renal allograft recipients treated in the Dr. Pe-set University Hospital in the city of València (Spain) were included in this study. The patients received a standard immunosuppressive regimen with a microemulsion lipidic formulation of CyA (Sandimmun Neoral[®]), mycophenolate mofetil (2 g/d) and prednisone (0.5-1 mg/kg/d). Patients who received metabolic inducers or inhibitors were excluded because they modify the pharmacokinetic profile of CyA. The initial oral dose of CyA (5 mg/kg b.i.d) was reduced according to the measured CyA blood concentration and the desired target range (150-300 ng/mL) [8].

The patients were randomly assigned to two groups: twenty-two patients were used for training (364 samples) the models and the other 10 patients constituted the validation set (217 samples). CyA blood concentration was monitored in every patient on different occasions. The data collected on each occasion were the following: CyA blood concentration (C [ng/mL]), daily dosage of CyA (DD [mg/Kg/d]), creatinine levels (CR [mg/dL]), anthropometric factors (age, AG [yr], gender, GE , and total body weight, WE [Kg]) and the post-transplantation days, PTD [d]. Some basic population statistics for the training and the validation sets are shown in Table 1.

Both blood concentration and dosage distribution within the population are shown in Fig. 1, where the high inter-subject variability observed in the early post-transplantation days makes it necessary to raise or lower dosage while closely monitoring the patient's blood concentration.

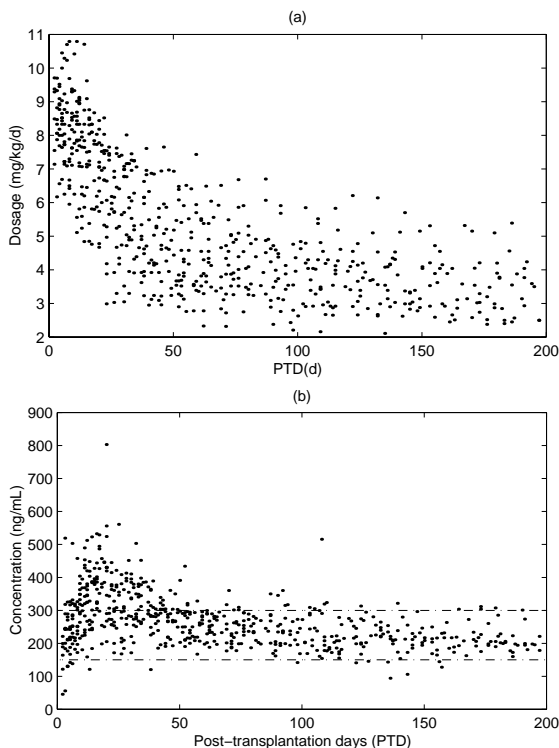


Fig. 1. Distribution of the (a) dosage (mg/kg/d) and (b) blood concentration (ng/mL) of CyA. Dashed lines indicate the desired target range.

B. Blood sampling and CyA assay

Steady state blood samples were taken just before drug administration (predose situation). CyA trough levels were measured by a specific monoclonal fluorescence polarization immunoassay (Abbott, TDx), with inter- and intra-assay variation coefficients of less than 7.5% [9].

III. METHODS

A. Experimental setup

The predictions are carried out using two models in a chained scheme; the predicted blood level of cyclosporine at day $t + 1$, $\hat{C}(t + 1)$ constitutes an input to the dosage prediction model, as illustrated in Fig. 2. This graph represents an approach for establishing a protocol of CyA administration and is designed merely to provide a methodology to aid in clinical decisions [10]. The models does not provide a diagnosis but rather an estimation of the next blood concentration, leaving the final decision to the clinicians.

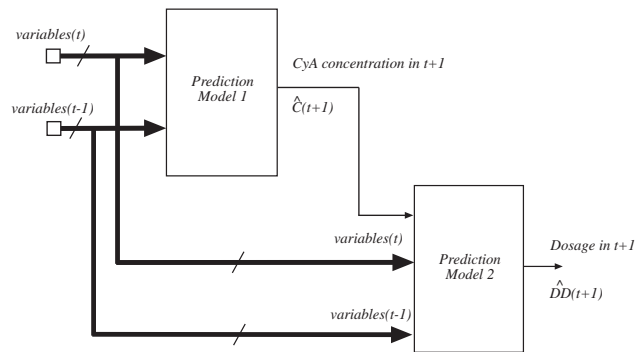


Fig. 2. Chained prediction structure. The first model predicts the future value of concentration and can be referred to as the “patient body modeling”. The second one tries to model the clinical criterion of administration and takes one more input: the future concentration prediction $\hat{C}(t + 1)$.

Two basic steps must be followed in order to complete the scheme:

- *Individual predictors.* To build individual models for both dosage and blood concentration prediction.
- *Robustness analysis.* Firstly, to test the models' robustness by evaluating their performance when noise is introduced at input nodes and secondly, to validate the cascaded architecture proposed.

B. Prediction models

The task of time series prediction has been undertaken by many researchers, and a great number of methods and approaches have been used. One of the most widely used methods is the AutoRegressive Moving Average (ARMA) model due to its ease of implementation and understanding. The ARMA model, nevertheless, does not yield good results in a lot of applications because most systems to be modeled possess nonlinear characteristics.

More modern techniques employ non-linear prediction schemes. In this paper, ANN are used to extend the linear model and overcome identification problems when dealing with

TABLE I

CHARACTERISTICS OF PATIENTS IN THE STUDY FOR THE TRAINING AND THE VALIDATION SETS. RESULTS ARE PRESENTED AS MEAN \pm STANDARD DEVIATION (SD) AND THE RANGE, EXCEPT FOR THE GENDER WHICH IS GIVEN AS THE NUMBER OF SUBJECTS.

Predictor	Training		Validation	
	Mean \pm SD	Range	Mean \pm SD	Range
Samples/patient	18 \pm 3	14-23	19 \pm 3	14-24
PTD [d]	184 \pm 8.2	170-197	183 \pm 8.2	170-197
C [ng/mL]	260.6 \pm 80.6	45.8-803.3	289.20 \pm 87.10	106.08-560.9
WE [kg]	66.57 \pm 15.36	37.5-106.0	76.32 \pm 10.65	52.0-93.0
CR [mg/dL]	1.7 \pm 0.9	0.7-10.2	1.8 \pm 1.1	0.8-8.0
AG [yr]	47.9 \pm 9.6	28.8-68.2	51.4 \pm 10.3	36.2-68.9
GE				
Male		13		8
Female		9		2
DD [mg/kg]	5.5 \pm 2.0	2.1-10.8	5.2 \pm 2.1	2.4-10.5

a large number of explanatory variables, non-uniform sampling and non-stationarities. Three kinds of networks and the formation of neural-network ensembles are used.

1) *The multilayer perceptron:* The multilayer perceptron (MLP) is composed of a layered arrangement of artificial neurons in which each neuron of a given layer feeds all the neurons of the next layer. This model forms a complex mapping from the input to the output, but it is, nevertheless, a static mapping; there is no internal dynamics [11], [12]. This problem can be easily addressed by including an array of unit-delay elements, called a tapped-delay line model, to make use of spatially-converted temporal patterns. There are two more approaches for introducing dynamic capabilities into a static neural network:

- 1) To substitute the static synaptic weights for dynamic connections which are usually linear filters.
- 2) To construct loops in the connections between neurons or layers of the network.

2) *The FIR neural network:* The FIR neural network falls into the first category by modeling each synapsis as a Finite Impulse Response (FIR) filter [13]. There are striking similarities between this model and the MLP. Notationally, scalars are replaced by vectors and multiplications by vector products. These simple analogies carry through when comparing standard back-propagation for static networks with *temporal backpropagation* for FIR networks [11].

3) *Recurrent networks:* The Elman recurrent network is a simple recurrent model with feedback connections around the hidden layer. In this architecture, in addition to the input, hidden and output units, there are also context units (CU), which are only used to memorize the previous activations of the hidden units [14].

4) *Combining predictors:* Previous work has shown that combining the output of many models can generate more accurate predictions than any of the individual ones [15]. An effective combination should consist of networks that are not only correct, but that also make their errors in different parts of the input space. Therefore, uncorrelated predictions are desirable and it is assumed that, in principle, using different kinds of

prediction techniques can be more appropriate for this purpose. We will focus on simple linear combinations such as the equal weights (EW) method, the minimum-variance (MV) method and the Optimal Linear Combination (OLC). All of them are extensively described in [16].

C. Model development

ARMA models are not suitable when non-uniformly sampled time series must be modeled, and therefore their application to our problem must be taken merely as an approximation [17]. The graphical analysis of simple and partial autocorrelation functions showed an optimum autoregressive term of one for the dosage model, AR(1), and a value of three for the concentration model, AR(3). No moving-average terms were identified. Similar results were obtained when Information Criteria (IC) were used¹.

Regarding the MLP model, we varied the number of hidden neurons (<20 to avoid overfitting), the weight initialization range and the learning rate (between 0.001 and 0.3) to determine the best topology. Patterns were built using the actual and the past samples of all time-dependent variables.

The training process for the FIR network was difficult because of its complexity since the number of free parameters increases geometrically with the number of inputs, as shown in [13]. In order to obtain accurate models, a great many sweeps were performed, varying the number of hidden neurons (from 2 to 25), the number of taps per synaptic connection in a layer (from 1 to 4) and the learning rate (typically between 0.0001 and 0.01). Initialization of the weights depending on the structure of the net was also used, as proposed by many authors [13], [12]. Models with few taps (<4) are preferred in order to be able to predict early blood concentrations even though more than a single hidden layer was strictly necessary to obtain significant results. Moreover, in some cases, it was necessary to sharply increase the number of epochs (>10000).

¹The IC used were the following: Final Prediction Error (FPE), Akaike Information Criterion (AIC), Bayesian Akaike Information Criterion (BIC), Schwartz' Bayesian Criterion (SBC), Minimal Description Length Criterion (MDL) and Parzen's CAT Criterion (CAT).

The training of the Elman network depends to a large extent on the learning rate and the number of context neurons. In fact, the network must be trained using high values of the momentum term ($\alpha > 0.8$) because this prevents weight oscillations in the training process.

All models were developed in MATLAB[®] environment. Since the computational burden was very high, *m-files* were translated to *MEX-files* and programs were run on fast workstations.

The criterion used to select a candidate model for the final system was based on the model predictive performance in the validation data set. Bias was measured using the mean prediction error (ME), and the model accuracy was tested by the one-way analysis of variance (ANOVA) method. The root-mean-square error (RMSE) was used as a measure of precision. We used the mean of the absolute prediction error to compare the precision of the models using the one-way ANOVA method. Their results were also assessed by inspecting the correlation coefficient (r) as a measure of goodness-of-fit. During the development of the models, the data were preprocessed to give zero mean and unit variance.

IV. RESULTS

A. Concentration prediction

ARMA modeling shows poor results due to the high variability in the time series, the presence of non-stationary pharmacokinetic processes in the early post-transplantation days and the direct influence of the non-uniform sampling. Results did not improve when we considered more autoregressive terms.

The Elman network was slightly more accurate (-0.019 ng/mL) than the MLP (-0.279 ng/mL) and the FIR net (0.176 ng/mL). Precision for the FIR network was slightly better as can be observed from the RMSE measurements in Table 2, whereas a comparison of the predictive performance of the models developed is shown for the validation set.

The construction of network ensembles from these models is completely justified since correlation coefficients between errors of the models were not very high ($r < 0.81$). Outcomes clearly improve when simple combined forecasts are considered. The best mixture was formed by the OLC, which reduced the RMSE by 11.03%. More complex combinations using different numbers of experts were also attempted but results were similar.

The 95% confidence intervals (95%CI) of the mean errors include the null value in the models developed. Therefore the models' predictive accuracy shows no systematic bias. Moreover, since one-way ANOVA test did not show any statistical differences when we compared the mean of prediction errors ($F=1.900$, $df1=5$, $df2=1296$, $p=0.091$) and neither did the mean of absolute prediction errors ($F=0.0019$, $df1=5$, $df2=1296$, $p=0.999$), we concluded that the models' predictive performance of CyA blood concentration is similar.

An easy way to show results graphically is to make predicted versus observed representations. A plot of the FIR network is shown in Fig. 3a. The solid line represents the line of identity, and the dotted one is the regression line

TABLE II

MODELS COMPARISON FOR BLOOD CONCENTRATION PREDICTION IN THE VALIDATION SET. ARCHITECTURES OF THE NETWORKS ARE INDICATED IN THE FORM **Input** \times **Hidden** \times **Output** NODES. THE ROOT-MEAN-SQUARE ERROR (RMSE), THE MEAN ERROR (ME) AND THE CORRELATION COEFFICIENT (r) ARE GIVEN. 95% CI ARE GIVEN IN BRACKETS.

Performance	r	ME (ng/mL) ($\pm 95\%$ CI)	RMSE (ng/mL) ($\pm 95\%$ CI) [†]
AR(3)	0.325	9.878 (-8.907,10.849)	90.96 (79.65,102.27)
MLP (14\times7\times1)	0.728	-0.279 (-8.106, 7.547)	58.69 (52.43,64.91)
ELMAN (14\times3\times1, CU=3)	0.762	-0.019 (-7.379,7.342)	55.19 (49.43,61.62)
FIR (7\times4\times4\times1, Taps per layer: 1:1:1)	0.785	0.176 (-6.865,7.217)	52.80 (47.79,58.27)
EW	0.801	-0.041 (-6.862,6.781)	51.15 (44.75,57.22)
MV[‡] [0.3,0.4,0.3]	0.807	0.042 (-6.694,6.778)	50.51 (44.95,56.09)
OLC[‡] [4.5,12.85,7.31]	0.838	0.091 (-6.173,6.354)	46.97 (41.44,52.62)

[†] 95% confidence intervals of the RMSE were calculated using bootstrap methods. [‡] Weights of neural network ensembles are indicated in the form [MLP, FIR, ELMAN].

(RL). In the same figure, we also show the predicted values against the residuals for this model (Fig. 3b). These goodness-of-fit graphics confirm the good predictive performance of the FIR model. Acceptable coefficient of determination ($r^2=0.62$) and no biased estimations (Slope $\pm 95\%$ CI: 0.99 ± 0.11 , intercept $\pm 95\%$ CI: 2.06 ± 31.55) or errors are observed.

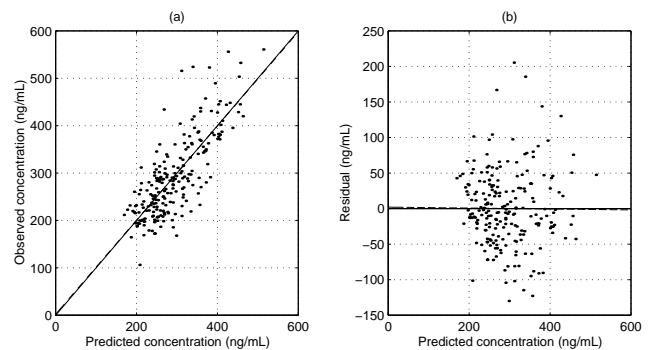


Fig. 3. FIR network performance in the validation set for the concentration prediction. (a) Predicted versus observed concentrations and (b) predicted versus residuals.

B. Dosage prediction

ARMA model performance is good even when a very simple model is considered. The reasons for this can be stated as follows:

- 1) Dosage follows a clinical criterion of administration and predicting it is an easy task because a high correlation between subsequent samples is identified.
- 2) The earlier post-transplantation days are the most difficult samples to predict, but the number of samples is larger at that time. This could be referred to as a “slightly non-uniform sampling”.

Neural networks show better results than ARMA modeling but their performance is similar numerically, as observed in Table 3. Moreover, Elman network showed slightly more accurate estimations than the MLP and FIR models. Due to the excellent outcomes achieved by all the models, it was not necessary to implement neural network ensembles.

TABLE III

MODEL COMPARISON FOR DOSAGE PREDICTION IN THE VALIDATION SET. ARCHITECTURES OF THE NETWORKS ARE INDICATED IN THE FORM Input \times Hidden \times Output NODES. THE ROOT-MEAN-SQUARE ERROR (RMSE), THE MEAN ERROR (ME) AND THE CORRELATION COEFFICIENT (R) ARE GIVEN. 95% CI ARE GIVEN IN BRACKETS.

Performance	r	ME (mg/Kg/d) ($\pm 95\%$ CI)	RMSE (mg/Kg/d) ($\pm 95\%$ CI) [†]
AR(1)	0.938	0.197 (0.101,0.294)	0.748 (0.640,0.842)
MLP (14\times2\times1)	0.991	0.074 (0.038,0.111)	0.282 (0.242,0.318)
ELMAN (14\times3\times1, CU=3)	0.992	0.070 (0.036,0.105)	0.267 (0.228,0.300)
FIR (7\times2\times10\times1, Taps per layer: 1:2:1)	0.989	0.083 (0.042,0.123)	0.314 (0.269,0.353)

[†] 95% confidence intervals of the RMSE were calculated using bootstrap methods.

However, none of the models included the null value in their 95%CI of the mean errors and their predictions were slightly positively biased. One-way ANOVA test showed statistical differences when we compared the mean of prediction errors ($F=4.263$, $df1=3$, $df2=864$, $p=0.0053$) and the mean of absolute prediction errors ($F=36.58$, $df1=3$, $df2=864$, $p=0.001$). However, if the ARMA model is not included in the comparison, no statistical differences in bias ($F=0.1116$, $df1=2$, $df2=648$, $p=0.8944$) or precision ($F=1.49$, $df1=2$, $df2=648$, $p=0.2262$) are found.

In Fig. 4, the performance of the Elman network for dosage prediction is represented using predicted-versus-observed and predicted-versus-residuals plots in the validation set. Excellent coefficient of determination ($r^2=0.984$) but slightly positively biased estimations (Slope $\pm 95\%$ CI: 1.01 ± 0.02 , intercept $\pm 95\%$ CI: 0.03 ± 0.09) are found.

C. Prediction robustness

Since no numerical or statistical differences were observed between the neural models, we decided to test their robustness.

1) *Noise introduction:* We can test models introducing Gaussian noise with zero mean and standard deviation σ , $\mathcal{N}(0,\sigma)$, together with the inputs. This can simulate real cases

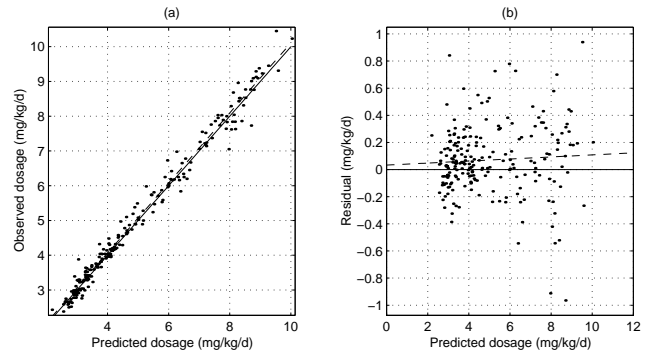


Fig. 4. Elman network performance in the validation set for the dosage prediction. (a) Predicted versus observed dosages and (b) predicted versus residuals.

such as blood sampling errors, patient compliance and the sensitivity of the dosage model to exact input values. In Fig. 5, we show the performance in both models when different levels of noise are introduced.

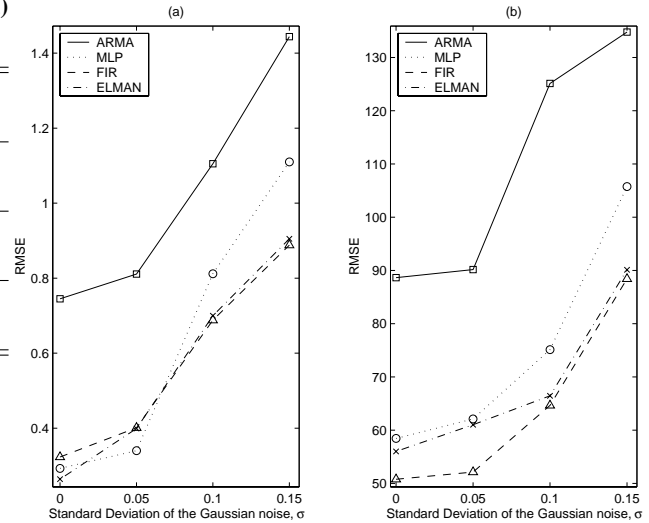


Fig. 5. Evaluation of the RMSE measurement when additive Gaussian noise with zero mean and standard deviation σ is introduced in the individual (a) dosage and (b) concentration models. Mean values within the validation set are indicated.

The FIR and Elman networks show good performance throughout the whole process both in the dosage and the blood concentration models. As the noise level is increased ($\sigma > 0.05$), the performance of the ARMA and MLP models rapidly deteriorates. All neural models offer excellent robustness capabilities in concentration prediction when low noise levels are introduced ($\sigma < 0.05$), which indicates less sensitivity to exact input values in normal situations.

2) *Chained prediction scheme:* An optimum chained prediction would be the one formed by the most robust model for predicting the dosage and the model with the best error and success ratio for blood concentration prediction. A combination of models produces worse, but more realistic, results than individual dosage prediction because now the (unknown) value of $C(t+1)$ is substituted by its estimation, $\hat{C}(t+1)$.

After evaluating all possible combinations², we conclude that the best global modeling of the cyclosporine problem is achieved by linking an FIR network for predicting the concentration to an Elman network for modeling the dosage administration. This combination yields an ME = 0.010 (± 0.002) mg/Kg, RMSE=0.299 (± 0.04) mg/Kg and $r=0.977$ in the validation set.

V. DISCUSSION

The prediction of immunosuppressive blood concentrations is a challenging issue and leads to difficulties in selecting the optimum dose of drug to avoid graft rejection and minimize adverse effects. Intensive drug monitoring is necessary in order to keep blood concentrations within a proper range. In this context, we have presented the formulation of neural models that could help to individualize the CyA posology. Dosage and blood concentration models have been built to achieve accuracy and robustness, and they have been included in a chained scheme. This approach attempts to assist the health care team in dosage individualization since physicians could take the blood concentration estimation as a helpful guide for dose administration.

The models captured abrupt changes in the time series of blood concentration in the patients, and all of the models performed similarly in the early post-transplantation period. Nevertheless, 21% of the patients had very poor predictions (RMSE>65 ng/mL) which can be due to errors in drug dosage administration, to the inter- and intraindividual variability in the drug absorption process, in the recording of blood sampling times or abrupt changes in each patient's clinical condition. As an example of these situations, we show three patients with good (Fig. 6a), acceptable (Fig. 6b) and poor (Fig. 6c) predictive performances. FIR network predictions are better (RMSE values ranging between 37 and 47 ng/mL) in patients under 50 years old, with total body weight superior to 50 Kg and with non-subtherapeutic CyA blood levels. Creatinine or gender had no significant effect on CyA prediction accuracy.

Whenever the initial daily dose for a patient is superior to 9 mg/Kg, CyA blood concentration is very difficult to predict (see Fig. 6c) due to its higher variability in the absorption and disposition process of CyA during the first four weeks of post-transplantation. In fact, under-prediction in this period is a common characteristic of the models for almost all the patients, and the prediction of CyA blood concentration or dosage present serious difficulties. This is one of the main problems in TDM of trough blood concentrations. Actually some authors suggest sampling times of two hours after administration (C_{2h}) to solve this situation [4]. More clinical studies are needed before changing TDM from trough levels to C_{2h} levels. In any case, this problem is lessened as long as blood levels become more stable, which is when slight over-predictions are obtained (see patients in Fig. 6a and 6b).

Although the results obtained for the blood concentration prediction are acceptable, they are lower than the dosage prediction because dosing follows a therapeutic guideline

²The ARMA models and combined forecasts were discarded because of their poor results and their complexity, respectively.

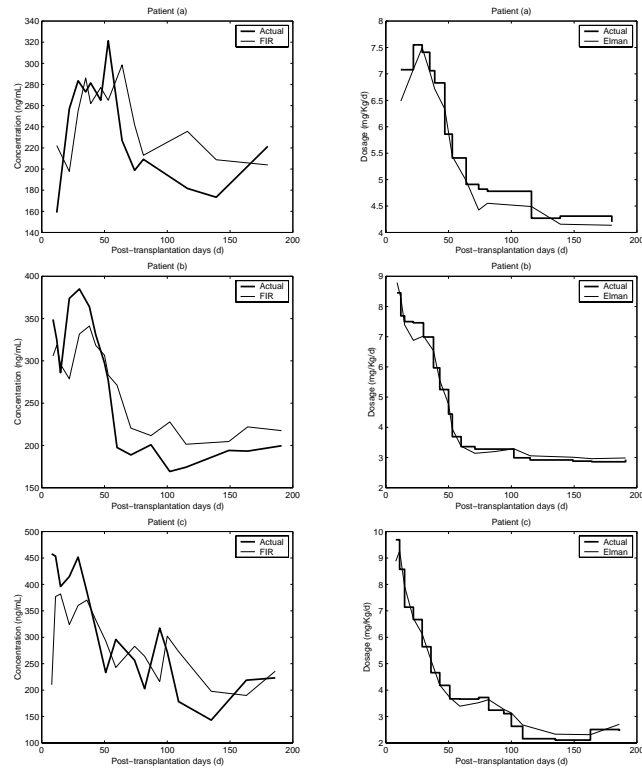


Fig. 6. Plots of observed and predicted CyA concentration (ng/mL) and oral dose (mg/Kg/d) versus postoperative day in individual patients showing (a) good, (b) acceptable and (c) unsatisfactory predictive performance. Only the Elman network for dosage prediction and the FIR network for concentration prediction are shown.

and presents lower inter-subject variability in the early post-transplantation days ($CV=24\%$). The best results for the CyA blood concentration prediction are obtained using the FIR network, where an ME of 0.18 ng/mL and a RMSE of 52.80 ng/mL were observed in the validation set. We have also shown how combined forecasts can be used to easily improve the accuracy and bias of predictions (ME=0.09 ng/mL, RMSE=46.97 ng/mL). Our results clearly improve a previous work following the time series methodology [5]. In [5], a multilayer perceptron with lagged inputs was used to predict CyA levels in renal allograft recipients but the results were not optimal (bias: 25 ng/mL, precision: 74 ng/mL in the test set).

From a statistical point of view, there are no significant differences between the neural models developed, possibly because the sample size is too small to detect these differences. Therefore, additional work is needed to compare the predictive performance of these models in a larger data set. However, from our analysis of the models' robustness, we can conclude that dynamic neural models give good results and that, more specifically, the FIR network constitutes a powerful tool for solving this problem. The best combination of models is formed by an FIR network for predicting the CyA blood concentration and an Elman network for modeling the dosage administration.

VI. CONCLUSIONS AND FURTHER WORK

In this paper, we have presented several approaches to a complex pharmacokinetic prediction problem: ARMA models,

MLP with lagged inputs, the FIR network and the Elman recurrent network. Neural models have proven to be well suited to this problem not only because of the accuracy of their estimations but also because of their precision and robustness. Based on these results, the application of neural networks in the context of TDM is a clinically useful tool.

Our future work is tied to the use of more sophisticated neural networks and committees of trained models since some patients' dynamics have not been captured. Additional studies are necessary in order to explore statistical differences between methods, the influence of clinical covariates and the expansion of the predictive performance up to long-term follow-up.

ACKNOWLEDGEMENTS

This paper has been partially supported by the European FEDER Project IFD1997-0935 entitled "Desarrollo de Sistemas Neuronales Aplicados en Atención Farmacéutica".

We want to express our thanks to Prof. Jacek M. Zurada for the references provided and his interest.

REFERENCES

- [1] P. Belitsky, "Neoral used in the renal transplant recipient," *Transplantation Proceedings*, vol. 32, pp. S10–S19, May 2000.
- [2] A. Lindholm, "Factors influencing the pharmacokinetics of cyclosporine in man," *Therapeutic Drug Monitoring*, vol. 13, pp. 465–477, Nov 1991.
- [3] C. Campana, M. B. Regazzi, and B. I., "Clinically significant drug interactions with ciclosporin," *Clinical Pharmacokinetics*, vol. 30, pp. 141–179, Feb 1996.
- [4] G. Levy, P. Burra, A. Cavallari, C. Duvoux, J. Lake, and A. D. Mayer, "Improved clinical outcomes for liver transplant recipients using cyclosporine monitoring based on 2-hr post-dose levels (c2)," *Transplantation*, vol. 73, p. 953, Mar. 2002.
- [5] M. E. Brier, "Empirical pharmacokinetic predictions for cyclosporine using a time series neural network," *Pharmaceutical Research*, vol. 12, no. S363, 1995.
- [6] A. S. Hussain, R. D. Johnson, N. N. Vachharajani, and R. W. A., "Feasibility of developing a neural network for prediction of human pharmacokinetic parameters from animal data," *Pharmaceutical Research*, vol. 10, pp. 466–469, Mar 1993.
- [7] P. Veng-Pedersen and N. Modi, "Application of neural networks to pharmacodynamics," *Journal of Pharmaceutical Sciences*, vol. 82, pp. 918–926, 1993.
- [8] M. Oellerich, V. W. Armstrong, B. Kahan, L. Shaw, D. W. Holt, R. Yatscoff, A. Lindholm, P. Halloran, K. Gallicano, and K. Wonigeit, "Lake Louise consensus conference on cyclosporin monitoring in organ transplantation: report of the consensus panel," *Therapeutic Drug Monitoring*, vol. 17, pp. 642–654, Dec 1995.
- [9] T. A. S. Assays, "Manual analytique." RundiX Cedex, France: Laboratories ABBOTT, Division Diagnostic, XII-CYCLO-MONO-13.
- [10] G. Camps, E. Soria, B. Porta, J. J. Ruixo, J. D. Martín, A. J. Serrano, and N. V. Jiménez, "A neural approach to cyclosporine dose prediction," in *World Congress on Medical Physics and Biomedical Engineering, July 23-28, 2000*, (Chicago, IL), World Congress on Medical Physics and Biomedical Engineering, July 2000.
- [11] A. S. Weigend and N. A. Gershenfeld, *Time Series Prediction. Forecasting the Future and Understanding the Past. Proceedings of the NATO Advanced Research Workshop on Comparative Time Series Analysis held in Santa Fe, New Mexico, May 14–17, 1992. Proceedings Volume XV*, vol. XV. Addison-Wesley, 1994.
- [12] S. Haykin, *Neural Networks: A Comprehensive Foundation*. Prentice Hall, 1999.
- [13] E. A. Wan, *Finite Impulse Response Neural Networks with Applications in Time Series Prediction*. PhD thesis, Department of Electrical Engineering, Stanford University, November 1993.
- [14] J. L. Elman, "Finding structure in time," *Cognitive Science*, vol. 14, pp. 179–211, 1988.
- [15] R. Clemen, "Combining forecasts: A review and annotated bibliography," *International Journal of Forecasting*, vol. 5, pp. 559–583, 1989.
- [16] S. Hashem, "Optimal linear combinations of neural networks," *Neural Networks*, vol. 10, no. 4, pp. 599–614, 1997.
- [17] L. Ljung, *System Identification. Theory for the user*. Prentice-Hall, 1987.

Gustavo Camps-Valls He was born in València, Spain in 1972. He received a B.Sc. degree in Physics (1996), a B.Sc. degree in Electronics Engineering (1998), an M.Sc. degree in Physics (2000), and a PhD degree in Physics (2002) from the Universitat de València. He is currently an associate professor in the Electronics Engineering Dept. at the Universitat de València. His research interests are neural networks and kernel methods for time series prediction and biomedical signal processing.

Emilio Soria-Olivas is an assistant professor at the University of València. He obtained his PhD degree in Electronics Engineering in 1997. His research is centered mainly in the analysis and applications of adaptive and neural systems in health sciences.

José David Martín-Guerrero received the BS degree in Physics in 1997 and the BS degree in Electronics Engineering in 1999, both from the University of València (Spain). He obtained the MS Degree in Electronics Engineering in 2001 from the same university. He is currently working towards his PhD degree in Artificial Intelligence Methods. Furthermore, he teaches Electronics and Artificial Intelligence in the University of València. His research interests include neural networks, fuzzy logic and statistical methods. He is a Member of the European Neural

Network Society.

Antonio José Serrano-López received a BS degree in Physics in 1996, a MS degree in Physics in 1998, and a PhD degree in Electronics Engineering (2002) from the University of València. He is currently an associate professor in the Electronics Engineering Department at this same university. His PhD thesis is related to the development of a clinical decision support system based on neural networks.

Begoña Porta-Oltra is with the Pharmacy Service of the Dr. Peset University Hospital of València. She obtained the PhD Degree in Pharmacy from the University of Valencia (Spain) in 2002. Her main research interest is the characterisation of the drugs pharmacokinetic behaviour, NONMEM modeling and Bayesian prediction models for pharmacokinetic and pharmacodynamic processes.

Juan José Pérez-Ruixo received a PhD degree from the University of València, and a Master Degree in Biostatistic from the University of Barcelona, both in 2000. During the work of this paper, he was a staff Clinical Pharmacist in the Pharmacy Department of Dr. Peset University Hospital. Currently, he joins to the Advanced Pharmacokinetic and Pharmacodynamic Modeling and Simulation Group of Johnson and Johnson Pharmaceutical Research and Development, a Division of Janssen Pharmaceutica N.V.

Nicolás Víctor Jiménez-Torres is a professor at the University of València and the Pharmacy Service Chief of the Dr. Peset University Hospital of València. He obtained his PhD Degree from the University of Santiago de Compostela (Spain) in 1970 in Pharmacy. His main research interest is the characterisation of the drugs pharmacokinetic behaviour.