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Prediction of Hemodialysis Treatment Results with Neural Networks and Two-Compartment Model***

1. Introduction

In the Chronical Kidney Disease (CKD), when for some reason transplantation is not possible, the peritoneal dialysis and hemodialysis are the most commonly applied treatments to help the patient survive [4]. Out of these two methods, hemodialysis (HD) is doubtlessly the most commonly used technique [14]. Precise planning and arrangement of the treatment series is crucial for the whole therapy. While planning the treatment it becomes obvious that some optimum HD time exists. Especially when we realize that the demand for the treatments often exceeds the capabilities of the units. Moreover, the life quality of patients, which is important feature affecting the survival ratio, also calls for reducing of treatment time. On the other hand, the shortened sessions may result in underdialysed patients and entirely spoil the therapy [5, 4, 19]. Therefore, already for several decades [4, 5], the computer based modelling of the patient-dialyser system has been proposed, developed and utilized. Such approach, known as Kinetic Modelling (KM), is typically based on urea, being both a toxin and marker, simultaneously. In spite of the fact, that other markers have been successfully tested, urea is still commonly used in practice. KM is typically used at two levels of depth. Either in the form of complete computations [4, 5, 13], which is rather uncommon, or with use of the simplified formulas [11, 12], obtained in the way of intensive research and available in the literature of the subject. Such formulas are typically simple enough to be used with pocket calculator or commonly used spreadsheet packages. While the simplified recipes have rather limited accuracy, the profound KM computations require dedicated software and a person prepared to handle it efficiently.

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The reasonable compromise between model usability and its adequacy proved to be the two-compartment model, being an extension of the most basic single-compartment structure. The analytical solution for the single-compartment model has been known for decades, and also for the two-compartment model [5, 19], however, for the latter only for the constant volume assumption. Such limitation makes the model somewhat irrelevant, as the volume changes are typically introduced during treatment, which is performed not only to remove the toxins but also the excess of water accumulated between HD sessions. Therefore, computations of the two-compartment model with variable volume have to be performed numerically. Such feature makes it inconvenient to use in the typical dialysis unit, and is a kind of obstacle in the scientific research, when intensive, multi-option comparative computations are necessary to find useful solutions. There were several trials to overcome this problem. In [12] the authors suggested some simplifying changes during analytical reasoning, which lead to analytical solution, but in fact not of the original problem. Alternatively, other authors changed the assumption about the location of volume changes. While originally the volume reduction during HD is said to be done exclusively in the external compartment, keeping the internal volume intact, they proposed to distribute the volume changes uniformly over both compartments. The analytical solution for such a modified model have been found in several ways, either for the second order differential equation [22], or for the set of two first order equations [15, 21]. The analytical solution creates possibility to quickly compute the values of the toxin concentrations at the end of the treatment, and thus making it possible to straightforwardly assess the efficiency of the modelled HD session. In such context, the idea of using the neural networks to perform nonlinear regression to find approximate solution for any reasonably selected set of input values came to existence. The network of relatively small structure should be possible to implement even in the spreadsheet of any common package, therefore, if obtained, should create a tempting solution for both researchers and practitioners. The described work is continuation of the introductory study reported in [17], where the neural networks were successfully tried to find the model parameters from the measurement data. Here, the assumed model parameters are used to compute the result of the treatment. The artificial neural networks have already been used in the area comprising hemodialysis and kinetic modelling. In [9], the study based on 80 patients and 480 sets of data was described. The sigmoidal transfer function in the hidden layer of multilayer perceptron (MLP) network was used to approximate the Kt/V, PCR and hypotension episodes. The Kt/V was predicted from 15 variables: nutritional, anthropometric, biological and describing the treatment. The reference Kt/V was computed with Daugirdas single pool second generation formula. The obtained network accuracy was 0.17, while the typical Kt/V values are in the order of 1. In [23] the MLP with sigmoidal transfer functions was used to predict equilibrated Kt/V from the similar set of data as in [9], when the reference was computed from additional measurement performed 30 minutes after the end of the treatment. The data collected for 180 patients resulted in the average eqKt/V error of 3.8%. In [10] a similar study based on 194 patients and 598 sets of data was described. A feedforward network predicted the single pool Kt/V (spKt/V) with the resulting

correlation coefficient $r = 0.634$, which indicates rather wide range of error. In [1] the radial basis function neural model was used to predict the treatment time necessary to provide the assumed level of dose. Within the input variables, there was a set of 9 blood samples and 9 weight measurements at 30 minutes intervals during the treatment. For the group of 15 patients, the resulting average error after taking into account the last sample was 10.8%. In [7] the data was obtained from 52 patients (73 treatments). The on-line measurement of the urea concentration in the dialysate with use of the relevant device provided data to model the shape of the concentration line, and such shape was used to predict final Kt/V – a) based on the whole treatment, and b) based on the first half of the treatment. The average prediction error was 6.59% and 5.58%, respectively. In the study the MLP network, with sigmoidal transfer function in the hidden layer, was used. The reference eqKt/V values were computed by the same device that sampled the dialysate. Almost identical experiment was described in [3], and the statistical results were different only at the third digit. In [8] the authors describe continuation of the work from [7], however this time the reference eqKt/V came from the direct blood measurement 60 minutes after the end of the treatment and the concentration values for the input of the network were measured from three blood samples per treatment. The data from 113 patients enabled prediction of Kt/V with average error 11.1%. It should be noted, that in all cited references the neural network was used to omit the kinetic modelling, to predict the Kt/V directly from some measurement data, and thus to avoid the necessity to find the parameters of the kinetic model. In our study the aim was entirely different. The neural network was used to approximate the analytical solution of the differential equations of the kinetic model. The reported ranges of relative error seemed to be rather discouraging when considering the use of neural networks in more theoretical studies, as in [4, 18], when the use of neural networks might be possible between the modelling phase and dialysis efficiency assessment. Therefore, in the described work the pseudo-randomly generated model parameters were considered as reference values, and neural networks were tested as a tool to approximate solution of the set of differential equations. The described experiment was designed to verify the hypothesis that in such arrangement the available relative error could be considerably smaller than 2%.

The consecutive sections contain: 2 – summary of the two-compartment model and neural network, 3 – description of the technique used to obtain the data, 4 – report on the obtained results, 5 – concluding remarks.

2. Modelling and computation techniques

2.1. Two-compartment model

The two-compartment model consists of two volume sections [5, 14, 19], *Ve* and *Vi*, with time-dependent concentrations, *Ce* and *Ci*, of a marker substance in each. The input is provided by generation rate, *G*, and the exchange of the marker between compartments and the removal rate are governed by the clearance parameters, *Kd* and *Kc* – for units see Table 1.

Table 1
Two-compartment model parameters

	Symbol	Description	Units
1	*Ve*	extracellular volume	L
2	*Vi*	intracellular volume	L
3	*Ce*	concentration of marker substance in *Ve*	mg/L or mmole/L
4	*Ci*	concentration of marker substance in *Vi*	mg/L or mmole/L
5	*Kc*	clearance, controlling the substance exchange rate between compartments	L/min
6	*Kd*	Clearance, controlling the substance removal rate during HD treatment	L/min
7	*Qu*	ultrafiltration flow, describing the rate of volume removal during HD	L/min
8	*G*	marker generation rate (in case of urea results from the metabolic activity of liver)	mg/min

The following set of equations provides detailed description of the model, based on the mass balance.

$$\begin{aligned} \frac{d\left(Ce(t)\cdot Ve(t)\right)}{dt} &= -Kc\cdot\left(Ce(t)-Ci(t)\right)-Kd\cdot Ce(t)+G \\ \frac{d\left(Ci(t)\cdot Vi\right)}{d} &= -Kc\cdot\left(Ci(t)-Ce(t)\right) \end{aligned} \tag{1}$$

If necessary, the volume removal is described by the ultrafiltration flow, *Qu*.

$$\begin{aligned} &Ve(t) = Ve(0) - Qu\cdot t \quad : \quad Qu = \frac{Vu}{td} \\ &Vi(t) = Vi = \text{const} \end{aligned} \tag{2}$$

To simplify computations formula (1) was rewritten to extract the derivative of the desired functions – i.e. concentrations of marker – so in fact the following equations have to be solved.

$$\begin{aligned} \frac{dCe(t)}{dt} &= -\frac{Kc}{Ve_0 - Qu\cdot t}\cdot\left(Ce(t)-Ci(t)\right)-\frac{Kd}{Ve_0 - Qu\cdot t}\cdot Ce(t)+ \\ &+\frac{Qu}{Ve_0 - Qu\cdot t}\cdot Ce(t)+\frac{G}{Ve_0 - Qu\cdot t} \\ \frac{dCi(t)}{d} &= -\frac{Kc}{Vi}\cdot\left(Ci(t)-Ce(t)\right) \end{aligned} \tag{3}$$

Quite surprisingly, the analytical solution of such a simple set hasn't been found yet. However, according to the neural network theory [6, 24, 25, 26, 27] the unknown hypothetical functions: $Ce(t)$ and $Ci(t)$, should be correctly approximated with the relevantly selected nets, and this paper reports the experiment designed and performed to learn about such networks structures.

2.2. Neural networks

The approximating neural networks were assumed to be multilayer perceptron [6, 24, 27], trained with use of the BFGS [20] algorithm, with sum of squares as the error function. During the experiment, the activation functions of the hidden and output layers and number of neurons in the hidden layer were selected to provide the best match for the assumption that the relative error for the most of the data from the training set stays within the range ±2%. Such limitation came from the modelling experience in the KM area, when such level of error is typically acceptable, and does not importantly affect the diagnostics and related reasoning. However, if necessary, the described experiment can be repeated with some stronger limitations. The networks were optimized with use of the Statistica package, version 9.0 [29], licensed to the AGH UST.

The approximating function resulting from the considered neural network can be described by the following general formula

$$y = f_{out}\left(\sum_{m=1}^{M} w_m \cdot f_h\left(\sum_{n=1}^{N} v_{nm} \cdot x_n\right)\right) \tag{4}$$

where v and w are weights from input to hidden layer and from hidden to output layer, respectively; f_h and f_{out} are the activation functions of the hidden and output neurons. N denotes the number of input signals, including bias value, and M is the number of hidden neurons plus bias value at the input of sole output neuron. The input layer is not represented in the formula as a result of its activation function being identity and all weights set to 1. Prior to all computations the values from the training set are used to define linear mapping, so that the inputs from such set cover range from 0 to 1.

3. Pseudo-random data set generation and experiment organization

Similarly as in [17], the data was generated with use of the pseudo-random number generator implemented in Matlab [28] package, assuming uniform distribution of all considered parameters within ranges specified in Table 2. This phase of experiment was enriched, as compared to [17], with additional variable parameter, i.e. treatment time, td. The total volume, $V = Ve + Vi$, was set to $30L$.

Table 2
Parameters of the assumed uniform distributions for considered model parameters.

Parameter	$C(0)$	G	Kd	Kc	$Ve/(Ve+Vi)$	$Vuf/(Ve+Vi)$	Td
Minimum value	1000	5	0.1	0.3	2/9	0	120
Maximum value	2000	15	0.2	0.9	4/9	1/10	360
Units	mg/L	mg/min	L/min	L/min	L/L	L/L	Min

To provide realistic sets of data, after having generated given set the numerical procedure was used to verify the dose, defined with the commonly used *KtV* value [4, 5, 14, 19]

$$KtV = \log\left(\frac{Ce(td)}{C(0)}\right) \tag{5}$$

The sets resulting in *KtV* not within the range from 0.5 through 2.5 were rejected. The generation was repeated until assumed number of sets, $N = 1000$, was reached.

In the dialysis unit the measureable concentration value is *Ce*, making formula (5) easy to use. However, the two-compartment model was introduced to represent the fact that sole concentration did not described properly the process, so to exploit the model features instead of *Ce* rather the equilibrated concentration between both compartment has to be used [5, 14, 19]

$$Ceq(t) = \frac{Ce(t)\cdot Ve(t) + Ci(t)\cdot Vi(t)}{Ve(t) + Vi(t)} \tag{6}$$

Therefore, more adequate *KtV*-based dose should be expressed with use of the *Ceq* value

$$KtVeq = \log\left(\frac{Ceq(td)}{C(0)}\right) \tag{7}$$

The practical problem is that *Ceq* is not available for direct measurement, and can be obtained only from modelling.

To verify the efficiency of neural network in approximating unknown functions, the following experiments were conducted. The input data consisted of the following eight values: $C(0)$, G, Kc, Kd, td, Qu, $Ve(0)$, Vi. The output was selected consecutively as: a) $Ci(td)$, b) $Ce(td)$, c) $Ceq(td)$, d) $KtVeq$. The criterion to select the network was that the number of relative error values, expressed in %, within the range from –2% to 2% for given output parameter should be roughly around 90%.

4. Results

For the compartmental concentrations, $Ci(td)$ and $Ce(td)$, the results are presented in Figure 1, Tables 2 and 3. The number of input data sets, out of $N = 1000$, for which the absolute value of relative error did not exceed 2% was 91% and 90%, respectively for *Ci* and *Ce*.

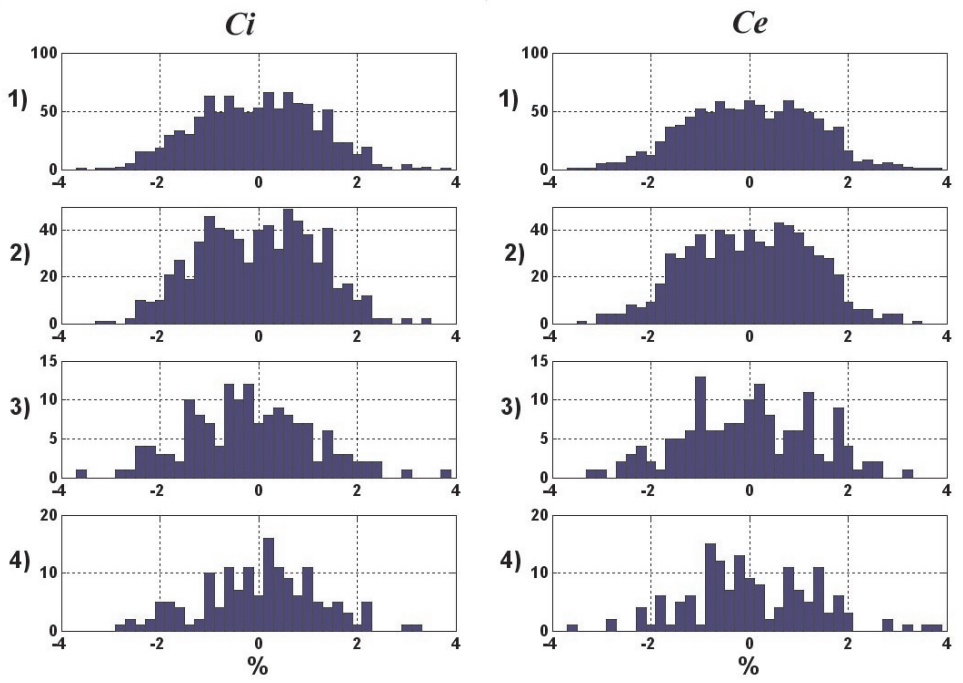

Fig. 1. Histograms depicting results, expressed as relative error in %, after training the neural network to approximate *Ci*(*td*) and *Ce*(*td*), respectively: 1) for all data ($N = 1000$), 2) for training data set ($N = 700$), 3) for testing set ($N = 150$), 4) for validating set ($N = 150$) – see also Tables 2 and 3

Table 2

Results for approximating *Ci*(*td*). *NN* structure: 8-12-1; activation functions: logistic (hidden) and hyperbolic tangent (output). The values are in the format: *mean* (*standard deviation*)

	All data	Training	Test	Validation
Error in mg/L	–0.4098 (7.6391)	–0.1958 (7.4755)	–1.3985 (8.6439)	–0.4195 (7.2926)
Rel. err. in %	–0.0318 (1.2058)	–0.0138 (1.1927)	–0.1723 (1.2682)	0.0249 (1.2006)

Table 3

Results for approximating *Ce*(*td*). *NN* structure: 8-8-1; activation functions: logistic (hidden) and exponential (output). The values are in the format: *mean* (*standard deviation*)

	All data	Training	Test	Validation
Error in mg/L	0.0452 (6.9962)	0.1202 (6.6762)	–0.2251 (8.0696)	–0.0347 (7.3384)
Rel. err. in %	0.0868 (1.5634)	0.0836 (1.5535)	0.0831 (1.7728)	0.1054 (1.3868)

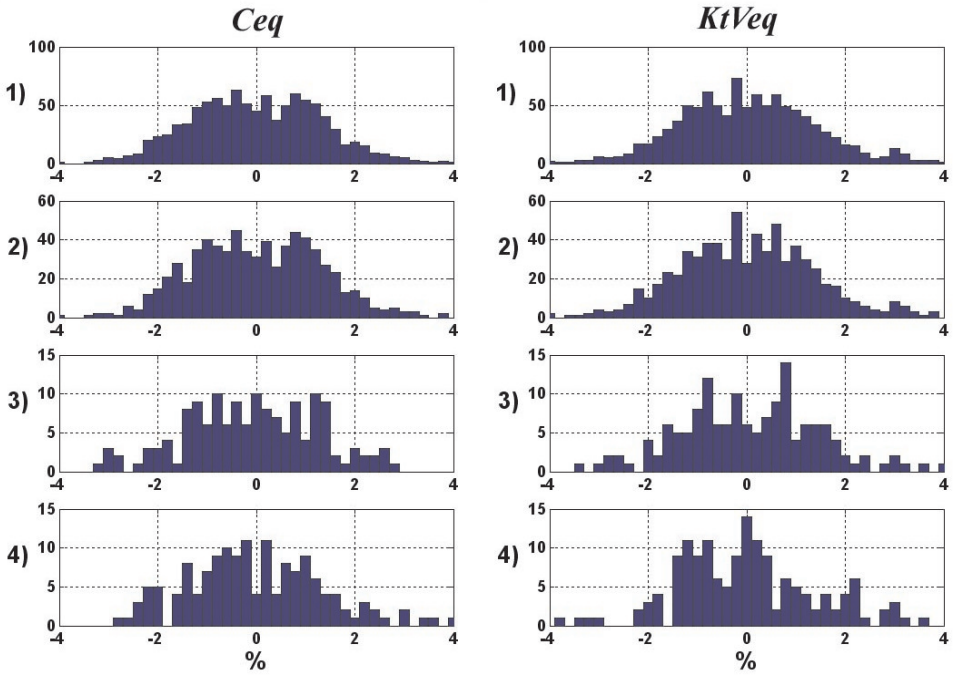

Fig. 2. Histograms depicting results expressed as relative error in %, after training the neural network to approximate *Ceq* and *KtVeq*, respectively: 1) for all data (N = 1000), 2) for training data set (N = 700), 3) for testing set (N = 150), 4) for validating set (N = 150) – see also Tables 4 and 5

Table 4
Results for approximating *Ceq*. *NN* structure: 8-8-1; activation functions: exponential (hidden) and hyperbolic tangent (output). The values are in the format: *mean* (*standard deviation*)

	All data	Training	Test	Validation
Error in mg/L	–0.1804 (7.9935)	–0.0724 (7.8516)	–0.7434 (8.9346)	–0.1214 (7.6805)
Rel. err. in %	0.0129 (1.3409)	0.0144 (1.2979)	–0.0242 (1.4276)	0.0430 (1.4537)

Table 5
Results for approximating *KtVeq*. *NN* structure: 8-12-1; activation functions: hyperbolic tangent (hidden) and exponential (output). The values are in the format: *mean* (*standard deviation*)

	All data	Training	Test	Validation
Error (no unit)	–0.0002 (0.0115)	–0.0000 (0.0113)	–0.0001 (0.0115)	–0.0012 (0.0122)
Rel. err. in %	0.0220 (1.4090)	0.0321 (1.4094)	0.0115 (1.4367)	–0.0145 (1.3876)

For the equilibrated concentration, *Ceq*(*td*), and for the treatment dose defined as *KtVeq*, the obtained results are summarized in Figure 2, Tables 4 and 5. The number of input data sets, out of $N = 1000$, for which the absolute value of relative error did not exceed 2% was 87% and 86%, respectively for *Ceq* and *KtVeq*. Note, that the presented results were obtained for the networks trained directly with the desired parameter values. However, *KtVeq* can be also computed from *Ceq*(*td*) – see (7). When we took the *Ceq*(*td*) values computed with relevant neural network and substituted to (7), the resulting error for *KtVeq* was: 0.0000 (0.0134) and 0.0341% (1.5524%). Comparing with values in Table 5 indicates that the accuracy of both methods is practically similar.

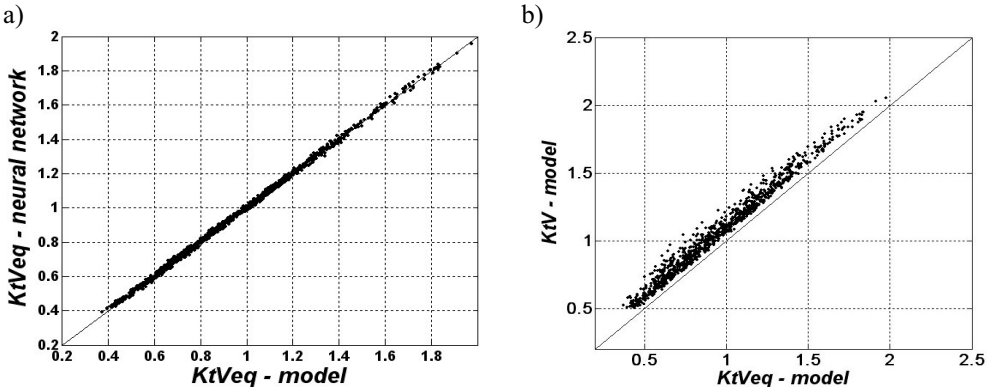

Fig. 3. Accuracy of assessing the treatment dose in *KtVeq*: a) with neural network; b) with *KtV* ($N = 1000$). The points are compared with the identity line. The reference values taken from the model solved numerically

The results obtained with neural networks may be compared with results of direct computations with *KtV* defined by (5). Figure 3 indicates that the results from neural network, with relative error values as shown in Figure 2 and Table 5, should be considered very satisfactory, while assessment with *KtV* contains noticeable offset, which could have been anticipated [5, 19], but also with considerably larger deviation. The average offset is 0.1107 (average error value), or 12.9963% (average relative error), quite nicely confirming results described in [16]. The corresponding standard deviation values are: 0.0462 (for error) and 7.2714% (for relative error), which is five times larger than obtained with neural network and thus indicates the efficiency of the latter.

5. Concluding remarks

The obtained results positively verified the hypothesis that the neural network could be efficiently used to approximate the unknown functions resulting from two-compartment variable volume model, especially to assess the equilibrated concentration and the treatment

dose expressed as *KtVeq*. The presented results combined with those described in [17] suggest a compound neural network system to supervise the process of model tuning and exploitation. Moreover, the relative simplicity of the model defined by the set of two ordinary differential equations [2], however without know analytical solution, creates an interesting educative example, when neural networks help while classical analysis fails.

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