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Predicting the anti-hypertensive effect of nitrendipine from plasma concentration profiles using artificial neural networks

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Abstract

Nitrendipine is an effective and safe calcium-channel blocker for the treatment of mild to moderate hypertension. The aim of this study is to show that an artificial neural network (ANN) model of the relationship between nitrendipine plasma levels and pharmacodynamic effects can be built and used for pressure-drop prediction after oral administration of the drug in spite of the poor correlation between plasma concentrations and the effect. To achieve the goal, the following steps were taken: evaluation of the quality of the database for training the ANN, definition of the optimal input set for the ANN, and prediction of the diastolic pressure drop using the ANN. The possible consequences of successful ANN modelling are an optimisation of the drug administration regimen, to achieve the best possible effect, as well as optimal drug formulation for drugs with complicated pharmacokinetic/pharmacodynamic relationships.

Keywords: Pharmacokinetics; Pharmacodynamics; Artificial neural networks; Statistics; Modelling

1. Introduction

Nitrendipine [1–4] is a long-acting calcium channel blocker that possesses both peripheral and coronary vasodiletary properties. It inhibits the movement of calcium through the channels of cardiac and vascular

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muscle that results in peripheral vasodiletation and leads to elevated blood pressure. Nitrendipine 20 mg, administered as a single oral dose to mild-to-moderate hypertensive patients at rest, produced a 15–20% reduction in the mean arterial pressure, the systolic pressure, and the diastolic pressure within 2 h of being administered. However, the blood pressure response to oral nitrendipine administration does not correlate well with detectable serum concentrations. Presumably, the anti-hypertensive effect of the drug is better correlated with its activity at the calcium channel [5,6] than its concentration in the plasma. After peroral application, nitrendipine is rapidly and completely absorbed in portal blood, while in the liver it is subjected to extensive presystemic metabolism, the consequence of which is an approximately 25% absorption into the systemic blood circulation. The absolute bioavailability does not depend on the size of the administered dose and on its release rate, which is manifested in linear kinetics. It has been demonstrated that no saturation of the liver enzymes occurs with doses of 5–40 mg. The biological half-life of nitrendipine is about 12 h (range 2–24 hours). Although nitrendipine is a well-established drug that has been used for more than 15 years, studies to evaluate its therapeutic effects are still taking place [7].

It is well known that blood pressure is influenced by the physicochemical and psychological states of an organism as well as by its surroundings. Therefore, it is difficult to investigate the effects of a single influence on a change in blood pressure, because all the other influences cannot be controlled or measured. The aim of this study is to show that a model of the relationship between nitrendipine plasma levels and pharmacodynamic effects can be composed and used for predicting the drop in blood pressure after oral administration. Raised systolic and diastolic blood pressure have destructive effects on the cardio-vascular system; however, diastolic pressure is more dangerous to health. The most desired effect of hypertensia treatment is, therefore, to lower the diastolic pressure. The correlation between nitrendipine plasma levels and diastolic pressure dynamics also seems better than the correlation with systolic blood pressure. Therefore, only the diastolic blood pressure was predicted using an artificial neural network (ANN). Although, ANNs were traditionally used for pattern recognition problems, some references can be found that report of function approximations using ANN [8].

To achieve the goal, the following steps are needed:

- An evaluation of the database quality for training the ANN,
- a definition of the optimal input set for the ANN,
- a prediction of the diastolic pressure drop with the ANN.

Statistical methods were used to evaluate the database quality for the ANN training and to define the optimal input set for the ANN. The ANN training curve of the different input sets also served as an optimal input-set selector. The relationship between the nitrendipine plasma levels and the pharmacodynamic effect was modelled using the ANN.

2. Modelling of the relationship between the nitrendipine plasma profiles and its effect

In order to investigate the relationship between the nitrendipine plasma profiles and its effect, the so-called pharmacokinetic-pharmacodynamic (PK-PD) relation, a compartment model was built [9]. The study described in [9] showed that there are substantial similarities in time courses of levels of nitrendipine in hidden-deep compartment and the effect. The structure of the compartment model indicated that a hidden-deep compartment could simulate the dynamics of the drug in calcium channels. Therefore, the

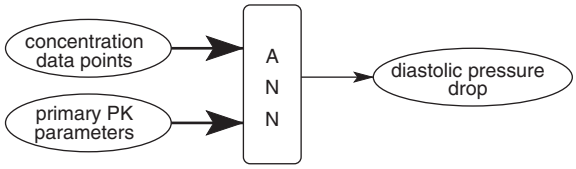

Fig. 1. Input–output structure of the ANN model.

link between the deep compartment and the effect is understandable, and the consequence is that the plasma levels and the effect must be closely correlated too. However, it is possible that this cannot established using linear correlation and regression, since the relationship is unlikely to be linear. Therefore, ANNs were used to model the relationship between the nitrendipine plasma concentrations and their effect (see Fig. 1), since the exact mechanisms that cause nitrendipine effects are not fully understood.

2.1. Database

Large databases of 1000–10 000 samples are usually required for successful ANN training. Such large studies are usually not available in human medicine. However, studies with an ANN have been reported where an outcome was successfully predicted from a relatively small bio-medical database [10]. Smaller databases, however, decrease a reliability of an ANN model prediction.

In our example of ANN training, a data set from a bioequivalence study of 20-mg nitrendipine immediate-release tablets was applied to examine the PK-PD correlation. A bioequivalence study was designed to compare the pharmacokinetic properties of two tablets, usually from different pharmaceutical companies, that have the same substance but a different formulation. Bioequivalent drugs can thus be treated as equally effective. In our bioequivalence study, tablets from pharmaceutical companies B and K were tested. The study was a single-dose, blind, randomised, four-way crossover with two treatments given in a replicate design (AABB) to 40 healthy volunteers. Blood samples were taken 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, and 8 h after administration. Besides nitrendipine blood-level monitoring, systolic and diastolic blood pressure before, and 3 hours after, administration were determined in addition to the following of adverse events in terms of event sign, onset, duration and intensity. In total, data on 160 drug applications were included in the study.

2.2. Database evaluation

To ensure the credibility of the ANN prediction, the quality of the database must be evaluated first. The elimination of duplicate information carried by database items is a helpful step. These items can be compressed into a single parameter, thus simplifying the ANNs structure and improving the quality of the prediction. The large number of parameters of artificial intelligence (AI) models means that AI models can be successful interpolators of data; however, they are usually poor extrapolators. Therefore, when applying AI methods for modelling, the databases should be as evenly spread throughout the problem space as possible, to ensure that as many as possible situations were encountered during the study. The number of subjects having statistically unusual values of the measured parameters can be a good estimate of the database's homogeneity [11]. Therefore, the database was statistically tested for outlying subjects, considering blood pressure and nitrendipine concentration profiles for each group of four applications. The analysis was performed in MATLAB [12] using two different methods. First, standard statistics was

applied by estimating the median values of the measured quantities and intervals containing a half of all the subjects, a quarter above and a quarter below the median. The outliers were all subjects that were outside 3/2 of the interval [11]. At the same time the database was analysed using linear principal component analysis (PCA) [13]. The basic idea of PCA is to transform the base of the space in which the subjects are defined, to a more natural space base for the problem, and then to reduce the dimensionality by eliminating, wherever possible, nonessential dimensions. The transformations include translation and rotation of the original Cartesian coordinate system, which is defined by measured quantities of the subjects. The new space base is defined by eigenvectors of the covariance matrix of the measured properties. The eigenvectors whose variances are arbitrarily small compared to the sum of the remaining variances can be omitted. The outliers were determined in new coordinates by calculating the Hotteling distance [11] of the subjects from the centre of the new coordinate system. All the subjects whose distance from the centre was extreme were determined as outliers.

2.3. Artificial neural networks (ANN)

To model the relationship between the pharmacokinetic data and the effect of the drug, a perceptron neural network was used [14] with error back-propagation as the learning algorithm. In our case a four-layer ANN was configured as follows:

- 1st layer: 4–10 neurons (depending on the number of inputs),
- 2nd layer: 15–20 neurons (depending on the number of inputs),
- 3rd layer: 10–20 neurons (depending on the number of inputs),
- 4th layer: 1 neuron (output—the difference in diastolic pressure).

Three types of inputs were used: the primary pharmacokinetic parameters (*AUC*, the integral of the concentration vs. time curve over the time interval [0 h,8 h]; C_{max}, the maximal concentration; t_{max}, the time at maximal concentration; β, the terminal slope of the concentration vs. time curve calculated from the last three measured points); the measured concentrations; and the measured concentrations mixed with primary pharmacokinetic parameters. The process of learning was monitored via the root mean squared (RMS) error between the measured and the ANN prediction of the diastolic pressure change. A monotonically decreasing RMS error curve between the learning cycles indicates a satisfactory learning process. If the learning process does not proceed satisfactorily, either the learning method or the ANN structure is not correct for the proposed problem, or there is only a weak connection between the input and the output of the system. Cheshire Neuralyst ver.1.41 [15], add-on software for Microsoft Excel, was used for the ANN building and training. The database was divided into training and evaluation sets: 75% of the database was used as the training set, and the remainder was used as the evaluation set.

Two goals can be achieved with the ANN. To establish if there is a relationship between the plasma concentrations and the diastolic pressure change, and, if that is true, to establish which are the most significant inputs for predicting the diastolic pressure drop. Both of these can be assessed from observing the RMS error curve. If there is no relationship between the input and the output, the value of the RMS error curve will not decrease during the ANN training. If there is a relationship but the inputs are poorly selected, the RMS error curve experiences oscillations; however, the general tendency of decreasing is significant. Finally, by successfully achieving the first two goals, diastolic pressure drops can be predicted reasonably well.

2.4. Statistical estimation of input significance

Input significance was estimated using the ANN as well as with three methods of selection based on statistical evaluations of the input and output data (linear regression and correlation coefficients) [16].

The first method was based on a linear-regression model between the output and the inputs. The database was divided into learning and validation sets. A linear regression model was estimated on the learning set for all inputs and then the input that most decreased or least increased the prediction error of the model was omitted. The whole procedure was repeated until only one input remained [16]. The remaining input is the most significant and the first omitted input is the least important.

The second method involved a calculation of the correlation coefficients between each input and output. All inputs and outputs were first scaled to variance 1. Then in a stepwise procedure the input with the highest absolute value of correlation coefficient was omitted and its effect subtracted from the output. The first omitted input has the highest relevance to the output [16].

In the third method, correlation coefficients were calculated and inputs sorted according to absolute values of the correlation coefficients. The highest coefficient value signifies the highest relevance of input [16].

3. Results and discussion

3.1. Database quality

Blood-pressure data was tested for outliers using the two mentioned methods. The first one showed that the database was very compact and that only a few subjects could be omitted. However, there are differences between the tablets supplied by the two companies. The effects of the B tablets were statistically more consistent (see Fig. 2) and two subjects could be uniquely identified as outliers. On the other hand, for the K tablets, four different outliers could be identified (see Fig. 2), and only one of these was the same as for the B tablets. After the B applications, subjects 22 and 25 were distinct outliers. After the K applications there were no distinct outliers; however, 12, 13, 18 and 22 lay outside the interval. All the outliers were identified for systolic pressure, and so, this had little effect on database quality regarding the diastolic pressure.

The pressure data were also examined using PCA. Since there were differences between the B and K tablets, the database was divided in two parts. Each subject was described by eight dimensions (diastolic and systolic pressure before and after application and each tablet applied twice). After the transformation of the coordinates using PCA, six of the eight dimensions remained significant for both tablets. By calculating the Hotteling distance from the centre of the new coordinate system for all the subjects (see Fig. 3), the results provided the same conclusion as in the first test.

The outlier in the B application is still 22, this time accompanied by 18 and 26, and after the K application there are no distinct outliers (see Fig. 3). Thus, for the case of blood pressure the database is suitable for ANN training.

The concentration data were also tested for outliers. The database was again divided into two groups depending on the application (B or K). Each subject was defined in 18-dimensional space (each measurement of concentration represented one dimension and each tablet applied twice). The concentrations at

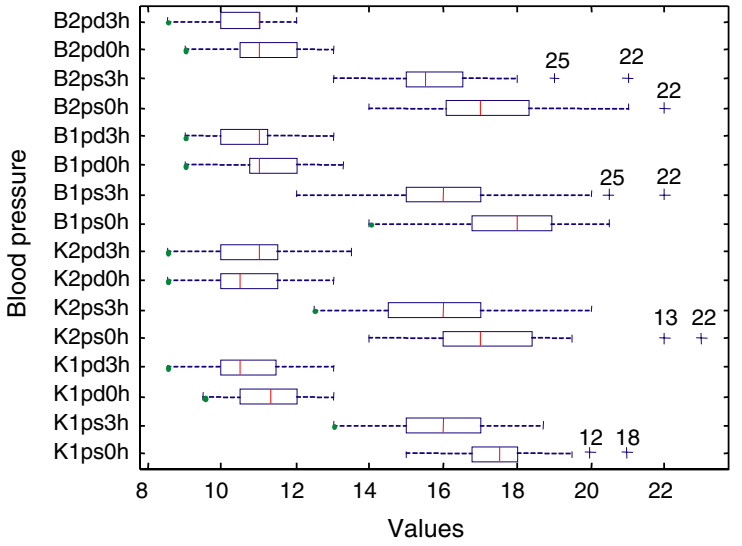

Fig. 2. Estimation of outliers in the blood-pressure set for all subjects differed by different company tablet applications (B and K).

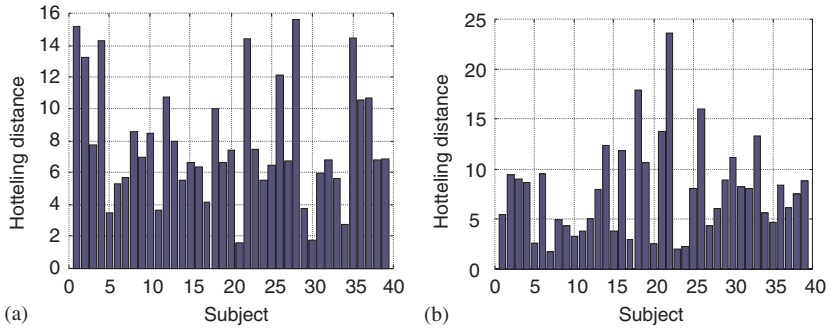

Fig. 3. Estimation of outliers in the blood-pressure set for all subjects for applications of K (a) and B (b) after principal component analysis.

10 and 12 h were omitted because these measurements were not available for all the subjects. The first method showed a number of outliers for both tablets (see Fig. 4); however, no subject dominated.

PCA showed that after transformation, 90% of the data variance could be described with only four components. Thus, the 18-dimensional space could be reduced to 4-dimensional space without any significant loss of information (see Fig. 5).

After calculating the Hotteling distance no significant outlier could be found for either tablet (see Fig. 6). Therefore, it could be stated that the concentration data are equally spread throughout the problem space. It could be concluded that the database was homogeneous enough and all the subjects could be used for ANN building and training. Furthermore, the two tablets were statistically not significantly different and, therefore, the database could be used as a whole.

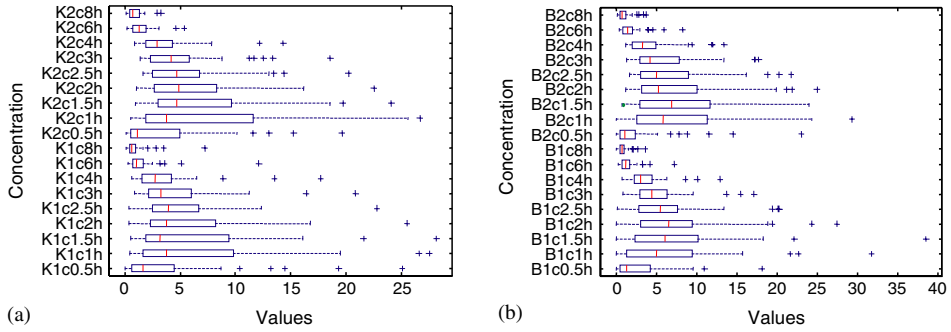

Fig. 4. Estimation of outliers in the concentration set for all subjects for applications of K (a) and B (b).

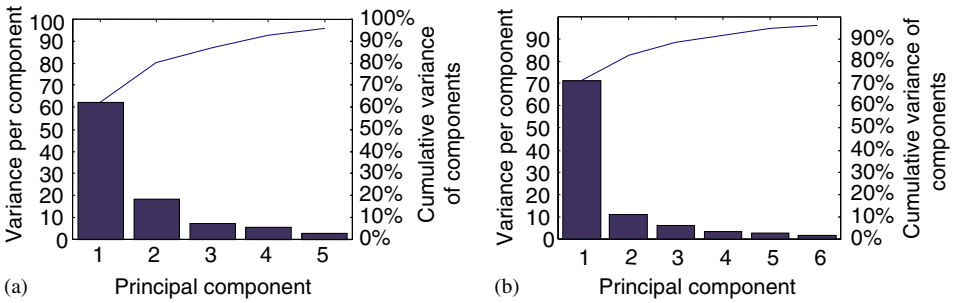

Fig. 5. Variance of components for the applications of K (a) and B (b) after PCA application.

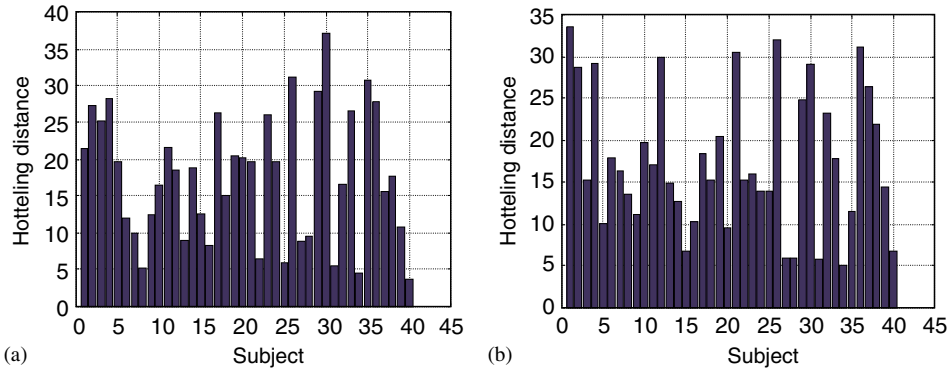

Fig. 6. Estimation of outliers in the concentration set of all subjects for applications of K (a) and B (b) using PCA.

3.2. Optimal ANN input set

As suggested by the preliminary test with the ANN, some relationship between the plasma concentrations exists, and a further evaluation of the ANN structure should be made. By testing the quality of the database it became clear that the dimension of the problem could be reduced, especially in the

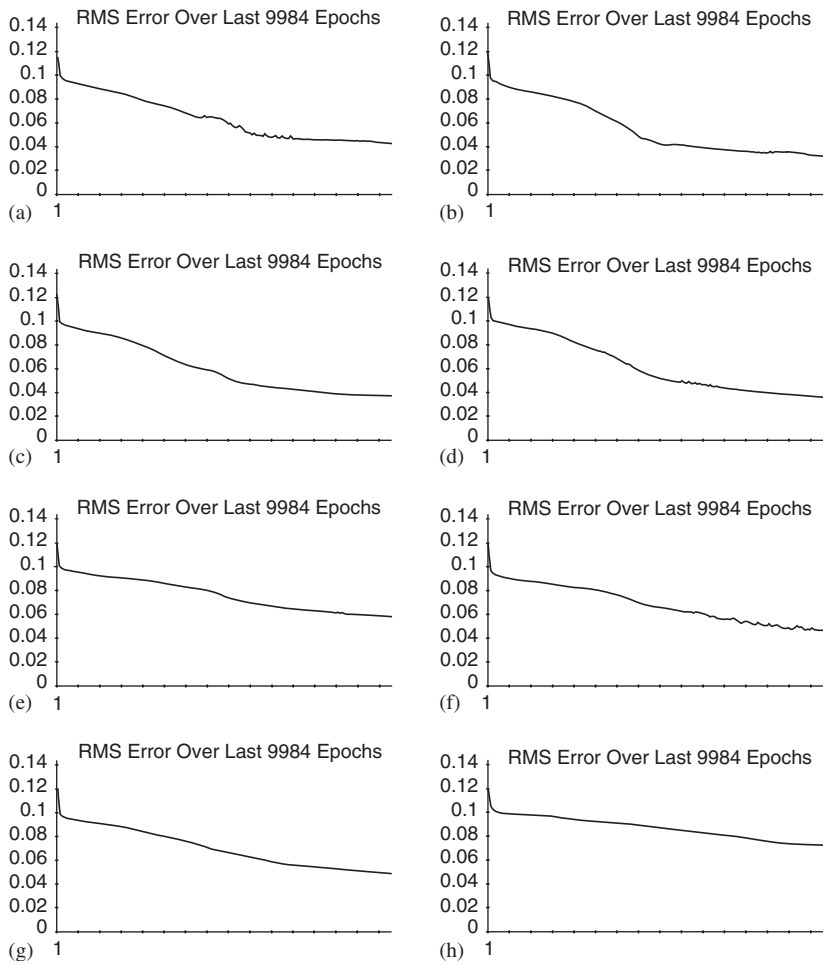

Fig. 7. Estimating optimal input set for an ANN from concentration raw data: (a) concentration samples up to 8 h, (b) concentration samples up to 6 h, (c) concentration samples up to 4 h, (d) concentration samples up to 3 h, (e) concentration samples up to 2.5 h, (f) concentration samples up to 2 h, (g) concentration samples up to 1.5 h (in all cases diastolic pressure before drug administration was added as input).

case of concentrations. Thus, an optimal input set could be found to achieve faster ANN training and a less complicated structure. Two methods were applied: first, the process of training was observed; and second, the statistical analysis was carried out. Measured concentration values were used as the inputs and diastolic pressure changes as the output of the ANN. However, no significant relationship between the plasma concentrations and the diastolic pressure changes could be found unless the diastolic pressure before the drug application was included as one of the inputs. Training of the ANN provided the results shown in Figs. 7 and 8. The training procedure was set to 3000 epochs and was repeated 50 times with similar results.

As can be seen from Fig. 7, the best training is achieved with structures c and d. If more concentration points are used, there are problems with the training (oscillations). If fewer concentration points are taken

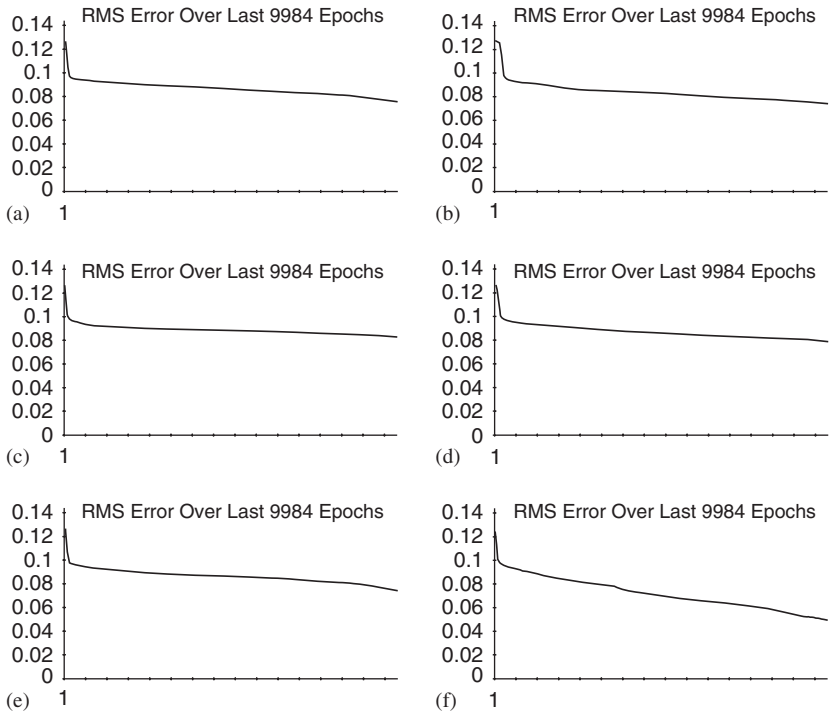

Fig. 8. Estimating the optimal input set for an ANN from mixed data sets (raw concentrations and primary pharmacokinetic parameters): (a) concentrations at 2, 3, 4, and 6 h plus C_{max}, (b) concentrations at 2, 3, 4, and 6 h plus C_{max}, *AUC*, (c) concentrations at 2 and 3 plus C_{max}, *AUC*, (d) concentrations at 0.5, 1, and 1.5 h plus *AUC*, β, (e) concentrations at 0.5, 1, and 1.5 h plus *AUC*, (f) concentrations up to 3 h (in all cases diastolic pressure before drug administration was added as an input).

as inputs, training stops at a higher RMS error, and some training problems are observed (f). In case d there are also some minor oscillations in the RMS error curve; however, at the end of the training the curve monotonically decreases, which makes the oscillations less important. Oscillations in the error curve can also be a consequence of the over-learning phenomenon. Therefore, an optimal input set is chosen to be as follows: concentrations up to 3 h and diastolic pressure before drug administration. The choice seemed logical, since the second pressure measurement was performed 3 h after the administration, and later concentrations could not have had any effect.

However, in bioequivalence studies, concentration profiles are compressed into *AUC*, C_{max}, t_{max}, and β to be compared. Thus, these parameters were also used as the inputs into the ANN. The results of the training were much worse than with the raw concentrations as inputs. Therefore, a combination of raw concentrations and primary pharmacokinetic parameters was used as an input. As can be seen in Fig. 8 the training was less successful than with the raw concentrations.

Statistical methods were also applied in the case of the optimal input-set search. The three referenced methods provide more or less the same results as the ANN training (see Table 1). Raw concentrations are better correlated with the diastolic pressure drop than the primary pharmacokinetic parameters.

The proposed three input sets were also tested using the ANN; however, the input set estimated by the ANN resulted in better ANN training.

Table 1
Most correlated parameters of plasma concentration measurements with diastolic pressure drop

	Inputs						
Method1	dp0h	dp3h	C2h	C2.5h	C1h	C8h	C_{max}
Method2	dp0h	C2h	C1h	C4h	β	C3h	C0.5h
Method3	dp0h	dp3h	C2h	C4h	C3h	C6h	C_{max}

Since the problem is highly nonlinear it is surprising that linear statistical methods and the ANN provide such similar optimal input sets.

3.3. Prediction of diastolic pressure using the ANN

The relationship between the plasma concentrations and the diastolic pressure changes was predicted using the ANN. The ANN was trained many times with the selected optimal input structure. The results varied between different trainings, and the successful prediction of the diastolic pressure was 88–94%. That means that in 88–94% of subjects in the evaluation set the prediction of the ANN was within 10% of the actual pressure change. To enhance the reliability, the output of the neural network was modified to perform a "class" response. The terms "no change", "minor change", "significant change", "big change" and "very big change" were introduced. The clustering into proposed categories proved to be a very good and natural solution for the problem, since the prediction accuracy on the evaluation set varied from 95% to 98%. The results obtained with the ANN prediction compared with measured data for the evaluation set are presented in Table 2.

4. Summary

The use of a nonlinear statistical description of a dynamical system, such as an ANN, requires certain procedures to ensure the credibility of the predicted outcome:

- Database evaluation is the most important procedure prior to ANN training. The basis for the ANN model consists solely of data collected in the database; therefore, any anomaly in the database will have a direct influence on the ANN structure and parameters. The database must be spread as equally as possible through the problem space, whose dimensions are defined by the number of items in the database. Furthermore, successful model prediction is expected in the region of the problem space where the models can interpolate measured data; prediction with extrapolation is not reliable.
- The choice of an optimal input set is important for ANN structure optimisation. In general, the number of inputs to the ANN can be as large as the number of items in the database; however, some items can carry similar information. Therefore, only one of them or their combination used as an input provides the same amount of information as all of them. The reduction of the input set results in a simplified ANN structure as well as more reliable prediction.
- The prediction of the outcome, in this case the drop in the diastolic pressure, is reliable only when both prior steps were carefully taken.

Table 2
Estimation of diastolic pressure difference

Sample	Measured difference in diastolic pressure	Estimated diastolic pressure difference	Sample	Measured difference in diastolic pressure	Estimated diastolic pressure difference
1	3,588908	3,6012	18	3,027784	3,1025
2	3,955375	4,0718	19	−0,09858	−0,1292
3	21,17384	21,4529	20	4,515117	4,5348
4	16,20321	16,2892	21	2,195294	2,2358
5	6,571617	6,5943	22	−1,50872	−1,5960
6	5,136759	5,1781	23	2,62364	2,7074
7	1,615231	1,6022	24	−0,3926	−0,4756
8	12,00834	12,0365	25	7,19115	7,2343
9	4,019229	4,0685	26	7,731962	7,7816
10	0,46792	0,4213	27	4,620182	4,6438
11	1,155107	1,3248	28	9,168842	9,1826
12	8,846901	8,8771	29	7,302544	7,4275
13	0,45182	0,5303	30	13,54449	13,6080
14	11,22608	11,2777	31	5,685198	5,7631
15	8,680601	8,6947	32	4,247672	4,2617
16	0,277871	0,2001	33	2,346256	2,3415
17	13,9208	13,9869			

The study shows that it is possible to predict a diastolic pressure drop with an ANN from a relatively small database if the procedures above are correspondingly applied. To solve this highly nonlinear problem, an ANN as well as linear statistical methods are necessary. Linear statistics are useful for characterising the general properties of the system, whereas the ANN explores the details. Therefore, the two methods can be characterised as complementary. No optimisation of the ANN structure, other than optimal input selection, was performed. Therefore, it should be possible to optimise the ANNs training and prediction quality.

The possible consequences of a successful ANN model are an optimisation of the drug administration regimen, to achieve the best possible effect, as well as optimal drug formulation design. However, when the plasma profiles are not well correlated with the effect, such optimisation cannot always achieve the goal of best possible effect with the least possible number of adverse effects. Mechanistic PD models would be preferred, since they provide better extrapolation possibilities; however, there is still a big gap between the sites of a drug's action and its activity in producing an effect.

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