Artificial Neural Networks As a Novel Approach to Integrated Pharmacokinetic–Pharmacodynamic Analysis

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Received October 11, 1995, from the *Department of Pharmaceutical Sciences, North Dakota State University, Fargo, ND 58105, and ‡Department of Drug Metabolism and Pharmacokinetics, Hoffmann-La Roche, Nutley, NJ 07110. Accepted for publication February 19, 1996⊗.

Abstract □ A novel model-independent approach to analyze pharmacokinetic (PK)–pharmacodynamic (PD) data using artificial neural networks (ANNs) is presented. ANNs are versatile computational tools that possess the attributes of adaptive learning and self-organization. The emulative ability of neural networks is evaluated with simulated PK–PD data, and the power of ANNs to extrapolate the acquired knowledge is investigated. ANNs of one architecture are shown to be flexible enough to accurately predict PD profiles for a wide variety of PK–PD relationships (e.g., effect compartment linked to the central or peripheral compartment and indirect response models). Also, an example is given of the ability of ANNs to accurately predict PD profiles without requiring any information regarding the active metabolite. Because structural details are not required, ANNs exhibit a clear advantage over conventional model-dependent methods. ANNs are proved to be robust toward error in the data and perturbations in the initial estimates. Moreover, ANNs were shown to handle sparse data well. Neural networks are emerging as promising tools in the field of drug discovery and development.

Introduction

The primary motive in studying the pharmacokinetic (PK)−pharmacodynamic (PD) characteristics of a biologically active compound is to deduce meaningful correlations between the conveniently measurable variable(s) (e.g., plasma concentration) and the effect of the compound. This knowledge is useful in drug candidate selection, product development, and formulating optimal dosage regimens. Currently, a battery of parametric and (semi) nonparametric methods to elucidate the relationship between the body drug levels and the corresponding pharmacological change are in practice. Link and indirect response models to define the effect in terms of the PK profile are known.[1−3] Link models proposed by Sheiner et al.[1] and Colburn [2] are widely applied at present. These models differ in the assumptions that the 'effect' compartment is linked to the central compartment or to peripheral compartment, respectively. Four basic indirect-response models dealing with either endogeneous substance inhibition or stimulation have been developed.[3] Also, significant efforts are being devoted toward developing physiological models. A summary of current PK−PD methods can be found in recent literature.[4]

Existing methods face several challenges. Often the active molecules are involved in very complex biological phenomena. Such phenomena range from complicated endogenous ligand interactions with the drug to the PD effect due to more than one form of the drug. Effective application of the traditional modeling procedures requires specific knowledge or assumptions about the underlying mechanism. Lack of adequate information regarding the compound during the preclinical or phase I stage often impedes effective drug design. But, it is during this early phase that the capability of correlating PK and PD characteristics can be potentially valuable in optimizing drug discovery and developement processes. This issue is particularly true considering the vast number of drug candidates screened in the industry and constraints on the resources available for each project. Consequently, a novel approach of handling PK−PD data was explored using artificial neural networks (ANNs; Figure 1).

ANNs are versatile computational tools that are well suited to recognize complex nonlinear relationships. Neural networks could be envisaged as a model-independent approach to PK and PD modeling, in that ANNs do not attempt to capture the intricacies of the in vivo characteristics (i.e., in terms of individual rate processes) but endeavor to generalize the association of the observed concentrations of active substance(s) in biofluid(s) with the detected PD effect as a function of time (and other variables where applicable). Previously, ANNs were successfully applied to a variety of interesting areas.[5−11] In particular, Veng-Pedersen and Modi[6] discussed ANNs with respect to PD modeling in which neural networks were employed for handling the input rate and effect relationship as measured from the EEG signals.

The objectives of this communication are to (1) demonstrate that ANNs are capable of emulating and predicting the PD effect from PK profiles generated from various conventional models (link and indirect-response models); (2) investigate the PK−PD structural sensitivity of ANNs; (3) examine the behavior of neural networks toward error in data, conduct sparse data anaysis, and study the stability toward initial estimates; and (4) to show the ability of ANNs to predict the PK profile given the PD profile.

Experimental Section

Data—Data required for the study were simulated with standard mathematical relations governing the PK and PD of hypothetical drugs by Q-Basic programming. The PK profiles were simulated with both one- and two-compartment models. PD profiles were simulated using link models (effect compartment linked to central or peripheral compartments) and with indirect-response models (inhibition of the production or loss of the response). A sigmoidal function was used to synthesize effect data. Each profile was defined by the time, dose, concentration of the drug (and active metabolite when applicable) in the body, and PD effect. The data were generated at 12 time points, reflecting a number of samples generally collected in typical experiments. Model features were derived from previous studies.[2,12] The structures and values of the various PK and PD parameters used for the simulation are given in the Appendix.

ANNs—The ANN paradigm that is based on the back-propogation algorithm was used in this work.[13] All networks used in this study were fully connected and three layered, with input, hidden, and output layers. The hidden and output neurons received an additional constant input that is called the 'bias'. The sigmoid function was used as the neuron transfer or the so-called 'squashing' function. The set of inputs in this study included time, dose, and PK (or PD) at that time, and the PD effect (or PK) at that time was the target. In the training process, each set of inputs and target(s) that constitute a 'training-pair' was presented to the network. A training set of 36 training pairs (unless otherwise specified) was derived from three different dose levels. Doses were selected carefully to reflect a

⊗ Abstract published in *Advance ACS Abstracts*, April 1, 1996.

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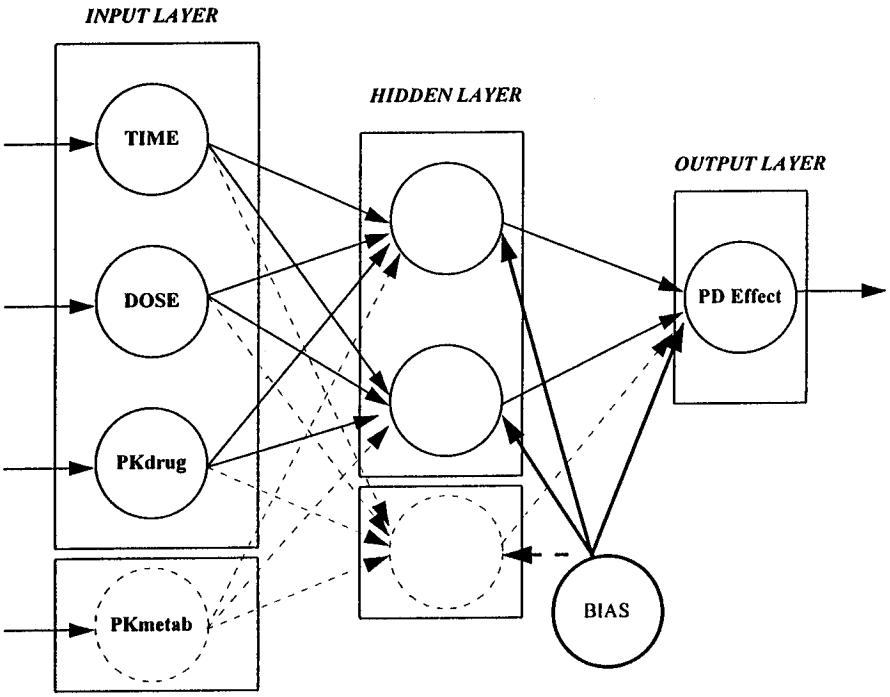

Figure 1—Topology of a typical ANN employed in the present study. The illustrated ANN consists of two hidden neurons and an output neuron. The number of inputs and hidden neurons depends on whether a metabolite contributed to the PD effect (broken lines). PKdrug = concentration of parent drug at sampling site; PKmetab = concentration of active metabolite at the sampling site. The bold circle indicates a 'bias' or an external input to hidden and output neurons, and bold lines represent the corresponding connections.

saturation of effect. The entire data set was scaled to lie in the range 0.1−0.9 (instead of the range 0.0−1.0), so as to allow margin for network predictions at the extremes. The output of the network was calculated each time, and the difference between the output and the actual target or the 'error' was propagated back to adjust the strengths of the connections or weights. Each such iteration or cycle is called an 'epoch'. Theoretical background information on ANNs can be found elsewhere.[14−16] All computations were conducted on a pentium-based microcomputer.

A crucial aspect of applying neural networks to a particular problem is arriving at an optimal network architecture. The criterion for selecting a network was aimed at the emulation capacity while keeping the size of the network at a minimum. The networks were trained until no further significant change in the total sum of squares (tss), which is the square of the difference between the output and the target of the network, was observed. The optimal number of hidden neurons was determined by gradually adding more nodes (hidden), starting from a network with no hidden nodes, until no significant reduction in the tss was observed. Another important aspect of the networks is variable transformation (e.g., transforming an input or output variable to its logarithm). Both transformed as well as untransformed variables were employed to calculate the tss in separate experiments. The change in the tss with respect to the number of epochs elapsed in a simple one-compartment case when the drug was administered as an intravenous (iv) bolus is shown in Figure 2. The effects of the number of hidden neurons as well as logarithmic transformation of the input variable, drug concentration are shown (Figure 2). This analysis resulted in selecting a network consisting of two hidden neurons, with dose, time, and ln(concentration) as input variables and PD effect as the output variable, because the emulation capacity of such a network was better (lower tss). Further increase in the size of the network did not yield any significant improvement in the performance of the network. Similar experiments were performed to determine the ANN architecture that resulted in employing a network with two hidden neurons in all the cases except for the metabolite model in which case a network with three hidden neurons was used. Unless otherwise specified, time, dose, and the logarithm of the drug concentration served as input variables, and the PD effect served as the target.

The trained network was employed to predict the PD effect given similar inputs at a higher dose. The prediction quality of a network was assessed by employing the correlation coefficient between the output and the target variable (CCOT) as the numerical performance index. The CCOT is the measure of the simple linear relation between the output and target. In cases where data included error or noise, CCOT would be the correlation coefficient between the output and the actual error-free target.

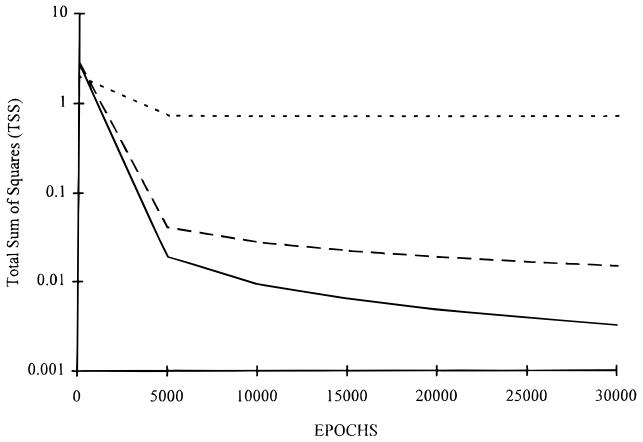

Figure 2—Effect of the size of the network and variable transformation on the emulation capacity through the training cycles or epochs. Key: (- - -) ANN with one hidden neuron and trained with transformed input (logarithm drug concentration); (– – –) ANN with two hidden neurons and trained with untransformed input variable; (—) ANN with two hidden neurons and trained with transformed input variable (logarithm of drug concentration).

Traditional modeling, whenever necessary, was conducted with PCNONLIN, version 4.2, (SCI Software Inc., Lexington, KY).

Results and Discussion

Link Models—The emulated time- versus PK−PD profiles at three different iv bolus dose levels (10, 40, 70) of drug, when the drug behavior could be defined by a linear one-compartment model (CCOT > 0.99 at all doses) are shown in Figure 3 (panel A). The PD model was simulated with a sigmoidicity

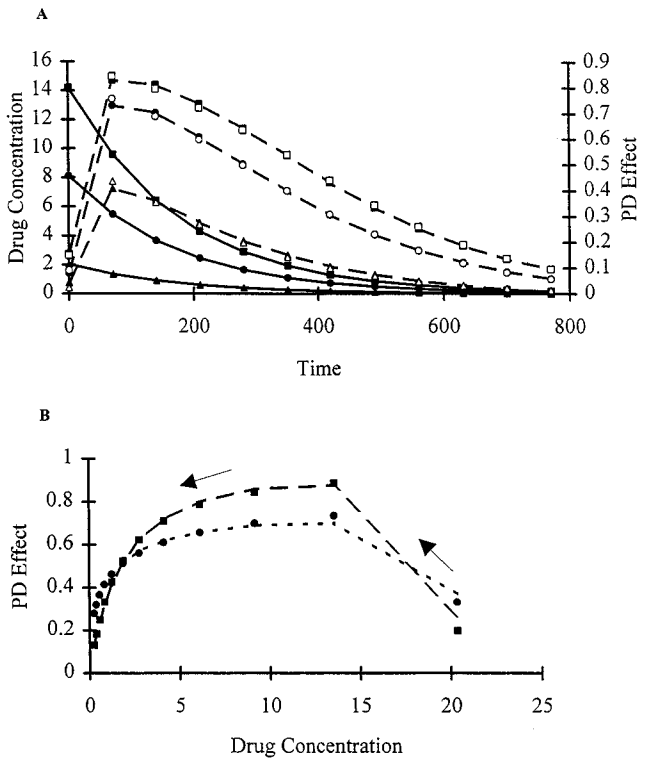

Figure 3—(A) Plot showing the ability of ANN to emulate the PK–PD profiles in a one-compartment model with an iv bolus administration at three different doses (CCOT > 0.99): concentration of drug at dose levels 10 (▲), 40 (●), and 70 (■); corresponding solid symbols with broken lines indicate the ANN output PD effect; corresponding hollow symbols indicate the simulated effect profiles. (B) ANN-predicted effect profile against the simulated profile in a one-compartment model when the drug was given as a iv bolus: (– – –) ANN-predicted profile; (■) simulated values (CCOT > 0.99) at $\gamma = 1.0$; (- - -) ANN-predicted profile; (●) simulated values at $\gamma = 0.5$.

factor (γ) of 1.0. The pharmacological effect was assumed to be free of any contributions from an active metabolite. Subsequently, the same network was used to predict the PD effect at a higher dose (100). A network was also developed when the sigmoidicity factor was 0.5. ANN predictions at the two different sigmoidicity factor values ($\gamma = 0.5$ and 1.0) are presented in Figure 3 (panel B). ANNs were successful in predicting the saturable PD profile quite accurately (CCOT > 0.99).

Similar tests were conducted when the drug was administered extravascularly (first-order input) and in another instance when drug was given as an iv infusion. ANNs were successful in predicting the PD profiles accurately in both cases (CCOT > 0.99). When studying the behavior of the infused drug, either the total dose administered or the logarithm of infusion rate could be utilized as an input variable. Both networks perform equally well, but in the present study the latter was employed.

The proposed network to handle a one-compartment model could be easily extended to a multicompartment case. Slight alterations in the ANN to incorporate the added complexity are required. This aspect is illustrated by considering a hypothetical drug, administered as an iv bolus, whose profile could be defined by a linear two-compartment model. The link model with the effect compartment connected to the central compartment was used. Though the size of the network was identical to that for one-compartment (i.e., three input, two hidden, and one output neurons), the multicompartment case required the logarithm of dose, time, and logarithm of drug concentration as inputs. The trained network at three different doses, similar to one-compartment experiments, was

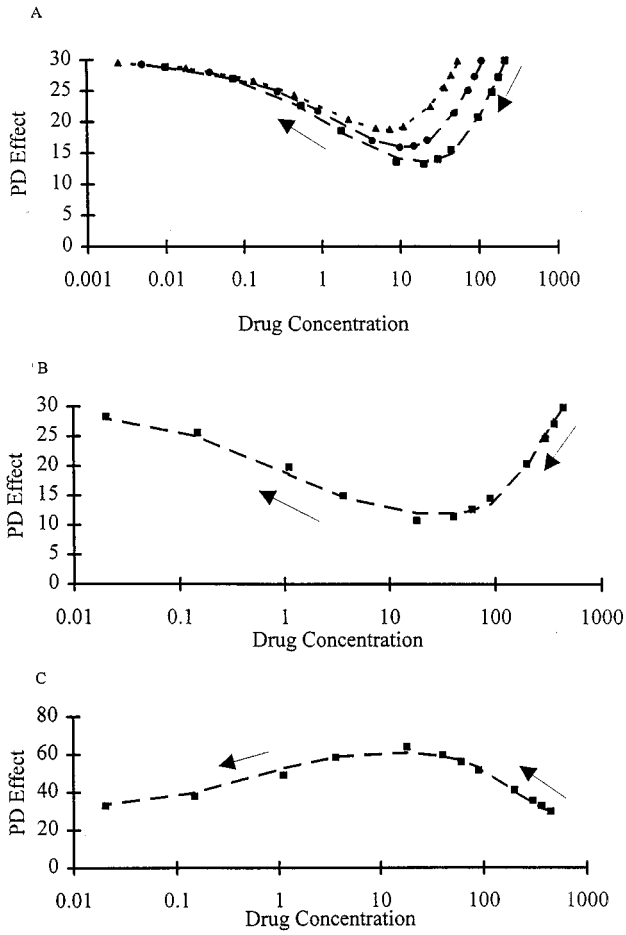

Figure 4—Indirect response models. (A) Plot showing the ability of ANN to emulate the PD profile when the production of the response is inhibited at three dose levels of 5 (▲), 10 (●), and 20 (■). (B) ANN prediction when production of response is inhibited at a dose of 40. (C) ANN prediction when loss of response variable is inhibited at a dose of 40. Key to panels B and C): (– – –) ANN-predicted profile; (■) simulated values.

employed to predict the PD profile at the higher dose. The ANN-predicted profile was in good agreement with the actual simulated (target) values (CCOT > 0.99).

Indirect Response Models—ANNs for predicting the inhibition of the production or loss of response were constructed when the drug, given as an iv bolus, followed linear one-compartment kinetics. Two hidden node networks, as in the case of link models, were used. Training was performed with time, dose (5, 10, 20), and concentration of the drug in the biofluid as inputs and the indirect response as the target. The training outcome is presented in Figure 4 (panel A) at the three doses. An interesting feature in the indirect PD response profiles is that the network was successful in recognizing the shift in the time to elicit the maximum response. Subsequent predictions at the higher dose (40), when the production of the response was inhibited, are shown in Figure 4 (panel B). Network predictions in similar experiments when the drug inhibited the loss of the response variable are also presented (Figure 4, panel C). It is important to note that the networks employed for emulation and prediction are identical in architecture to that of the link models with one-compartment kinetics.

Structural Sensitivity—A major issue in the traditional approach to PK–PD analysis is that of structural specification. For instance, model mis-specification may occur in identifying the number of kinetically distinguishable spaces or when the number of active chemical moieties are not known. An earlier

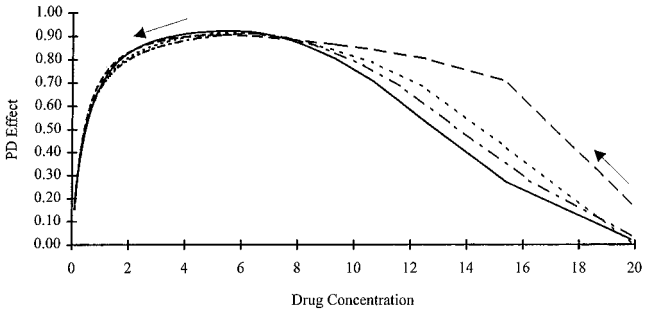

Figure 5—ANN predictions in the two-compartment iv model when the effect compartment was linked to the peripheral compartment instead of the central compartment. Key: (–•–) ANN-predicted profile when trained with five points before peak effect; (—) ANN-predicted profile when trained with one point before peak effect; (– – –) predicted profile using traditional method; (- - -) simulated values (CCOT > 0.99).

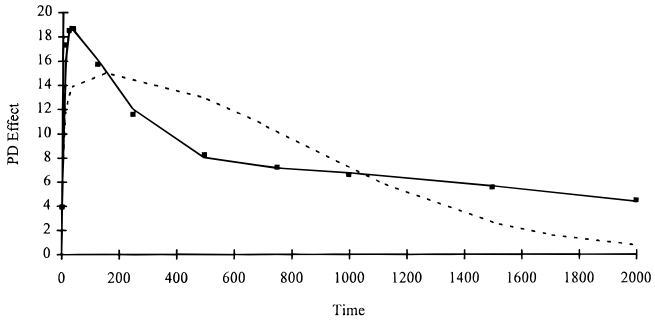

Figure 6—ANN-predicted versus simulated PD profiles when no information regarding the active metabolite was provided to the network. Key: (—) ANN-predicted profile; (- - -) predicted profile using traditional method; (■) simulated values (CCOT > 0.99).

report discussed the drawbacks of not considering appropriate models to construct a sound relation between the body drug levels and the effect.[2] Being a model-independent method, ANNs are not handicapped by the lack of knowledge on the specific structural details. The capability of neural network systems in recognizing the relationship between PK and PD effect when the so-called 'effect' compartment is linked to the peripheral compartment instead of the central compartment is illustrated in the case of a hypothetical drug given as an iv bolus. The ANN architecture was identical to that developed for the one-compartment model. Network was trained with three doses (10, 40, 70). ANN was successful in predicting the effect at higher dose (100) with the trained information at the lower doses, with CCOT > 0.99.

The same data as used to train the network were fitted to a link model using PCNONLIN, with the effect compartment intentionally connected to the central compartment (to test the sensitivity to model mis-specification). The predictions of ANN as well as mis-specified traditional model at the higher dose are shown in Figure 5. Evidently, ANN showed superior accordance with the simulated values. The final estimates of the traditional fit ($EC_{50} = 0.67$, $k_{e0} = 0.016$, $\gamma = 1.09$) were different from the actual values of the parameters ($EC_{50} = 1.9$, $k_{e0} = 0.047$, $\gamma = 1.0$). This test shows that ANN is not prone to model mis-specification. The classical approach could lead to errors in dosage calculations simply because the right model was not used. However, it is important to note that the performance of ANNs, like other modeling tools, is dependent on the quality of the training set. The predictions of ANN when it is trained with (i) only one point before the peak effect is reached and (ii) five points before the peak effect is reached, at the same time keeping the total number of points constant, are shown in Figure 5. The performance of the network trained with the latter set was superior to the former (Figure 5). Nevertheless, both the (network) predictions were in better accordance with the simulated values than were the predictions using the fitted estimates to a wrong model (Figure 5).

Substantial evidence is available in the literature regarding the biotransformation of a drug to metabolite(s) capable of contributing to the dynamics. Attempts to develop integrated models to account for the effect elicited by both parent as well as the metabolite(s) molecules also were made.[12,17] Nonetheless, the presence of an active metabolite, its site of action, and mechanism of interaction with the parent drug may not be known, particularly if the drug is still in preclinical or phase I stage. The situation is even more complicated when studying the kinetics and dynamics of protein drugs. Whether endogenous substances compete with the active molecule(s) or not is unknown.[18–20] Applying conventional techniques in such cases would require major assumptions that may not be accurate. Ethical and regulatory issues prevent the investigation of the in vivo characteristics of the biotransformation product separately. Since neural networks generalize the relationship between the inputs and the target without requiring specific structural details, the power of ANNs to predict PD effect without knowledge of active metabolite or any competing molecule thereof was investigated.

On the basis of some of the data presented in a previous study,[12] simulations were conducted in a hypothetical case where the parent drug and the metabolite were assumed to bind competitively at a common receptor. The parent compound was defined by a two-compartment model, whereas the metabolite was defined by a one-compartment model. ANN with three hidden neurons (Figure 1) was trained with dose (0.5, 1.0, 1.5), time, and the logarithm of concentration of the parent drug only (no metabolite information provided) and tested for prediction at a higher dose (2.0). Network predictions were well correlated with the actual simulated effect based on the parent and metabolite concentrations in the effect compartment (CCOT > 0.99), as shown in Figure 6. ANN predictions when the metabolite neuron was switched-on were also in good agreement with theoretical values (data not shown). To compare the performance of conventional method to that of ANN, the same data as presented to the network were fitted to a purposefully mis-specified E_{max} model (assuming the parent compound is the only active moiety) as given in the Appendix. The final parameter estimates were employed to predict the response at the higher dose. It is evident, from the results in Figure 6, that the predictions of the mis-specified traditional approach are indequate. Model mis-specification would ultimately result in an incorrect dosage regimen.

Behavior of ANN toward Error—In any real situation both the concentration–time data and the effect data contain significant error and, consequently, it would be required for any new data manipulation technique to prove unaffected by such circumstances. To investigate the robustness of the developed ANN, the training data was adulterated with 30% random noise in both the concentration of the drug and the observed PD effect for a hypothetical drug, given as an iv infusion, whose profile is explained by linear one-compartment kinetics at three doses (10, 40, 70). The link model with the effect compartment connected to the central compartment was used. This adulteration formulates quite a severe test in that both the predictor and the response variables contain significant error. The trained network was employed to predict the PD profile when presented with noisy PK data at a higher dose (100). The network prediction and CCOT were calculated to be >0.99, with respect to the error-free data (Figure 7). Whereas CCOT gives information on the precision, the bias (mean difference between the predicted and target values) is calculated to be −0.014 effect units.

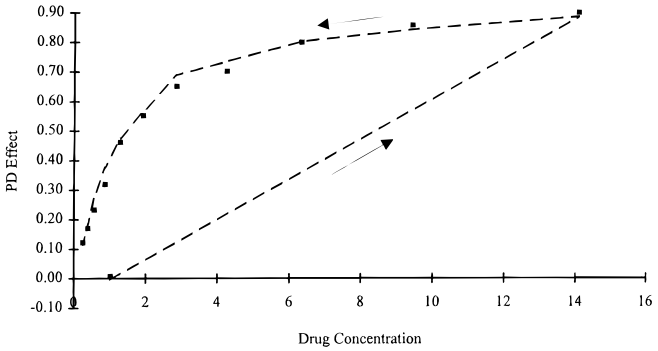

Figure 7—Plot showing the predictions of ANN in the case of a one-compartment model, with the drug given as an iv infusion and when the training and test data consisted of 30% noise in both the PK and PD variables. Key: (– – –) ANN-predicted profile; (■) simulated values (CCOT > 0.99).

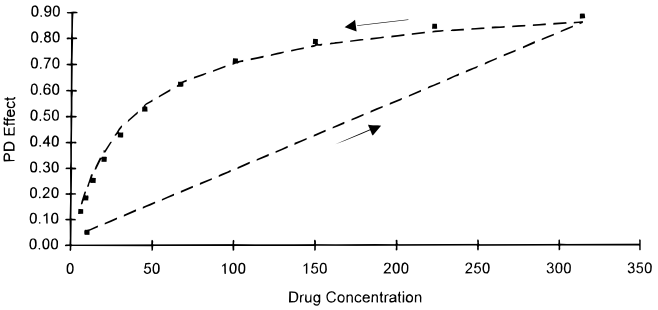

Figure 8—Outcome of the sparse data analysis when the network was trained with EV (one-compartment) data at three doses and used to predict at the higher dose. Key: (– – –) ANN-predicted profile; (■) simulated values. The mean error was –0.7%, and the absolute prediction error was 6% (CCOT > 0.99).

Sparse Data Analysis—Another practical problem concerning any real PK–PD experimentation is the number of samples that could be collected from each subject over a period of time. Efficient model building is frequently impeded by lack of adequate data points. Previously, ANNs were shown to deal with sparse data well in nonlinear PK situations.[21] The one-compartment case was used to evaluate the ability of the neural network to conduct sparse data analysis at three doses (10, 40, 70) in the training set. The link model with the effect compartment connected to the central compartment was used. Instead of data simulated at 12 time points, ANNs were trained with only four points from each dose. In the ensuing period, the trained network was utilized to predict the complete PD profile at the higher dose (100). Not surprisingly, random selection of the time points led to a poor fit (data not shown). Therefore initial, peak, and two more time points thereafter were considered, which defined the curvature fairly well and at the same time minimized the length of the study (i.e., collection of samples). Predicted profiles were in good accordance with the target profiles, as depicted in Figure 8 (CCOT > 0.99).

Stability toward Initial Estimates—A very critical aspect in any modeling tool involving nonlinear parameter estimation procedure includes the choice of appropriate initial values for the parameters. The sensitivity of ANN with respect to random perturbations in the initial estimates (of the various weights of the connections) was examined. Four sets of random initial estimates were generated, and each time the network was trained at three doses (10, 40, 70) and used for prediction at higher dose (100). The training data, generated from a one-compartment model, consisted of 30% error in both PK and PD variables. The results were compared by visual inspection of the plots (and values). The link model with the effect compartment connected to the central compartment was used. The network prediction at the higher dose when trained

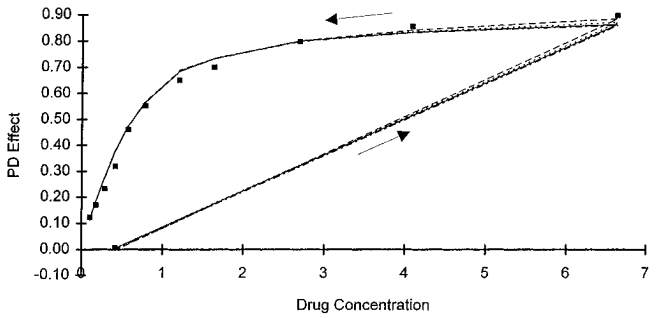

Figure 9—Plot exemplifying that ANNs are insensitive to the initial estimates and yield similar predictions each time the network is trained with dose, time, and drug concentration. Key: (—), (- - -), (– – –, —•—) ANN-predicted profiles with different initial estimates; (■) simulated values.

with time, dose, and logarithm of the concentration of the drug as inputs and the PD effect as the target along is shown in Figure 9 with the simulated profile with different intitial estimates overlapped.

Predicting PK from PD—In the previous cases, ANN was used to predict the PD effect given the concentration of drug at the sampling site. In some circumstances, it is beneficial to have a system that could predict the concentration of drug in the body given the effect profile along with the other inputs. To demonstrate this aspect, the PK and PD neurons were swapped in the one-compartment case, while leaving everything else in the network unchanged. The link model with the effect compartment connected to the central compartment was used. The network was trained at the three aforementioned dose levels and used for prediction at the higher dose. ANN-predicted drug concentrations showed good correlations with the actual target values (CCOT > 0.99). This experimental setup could be quite useful in designing amounts of drug to be given in a subject if the desired magnitude and time course of the PD effect is known. For instance, ANN can be effectively used in optimal drug delivery devices aided by continuously monitoring the PD effect by noninvasive techniques.

So far, networks were trained with three doses and subsequently utilized for prediction. However, it is not mandatory to use three doses, as demonstrated in the one-compartment link model with a first-order input. ANN was trained with two doses (50, 75), and the trained network was used for prediction at the higher dose (100). The network predictions were in good agreement with the actual simulated values (CCOT > 0.99). However, it is important to note that the dose(s) cannot be selected arbitrarily or randomly for the training set. Appropriate data for the network learning should be carefully determined to contain information to indicate a saturation of effect. In other words, profiles resulting only from the linear range of the pharmacological effect would not give adequate information to extrapolate to higher doses.

Conclusions

ANNs are shown to be powerful data manipulation techniques to emulate the kinetic–dynamic relationship and predict future events. Particularly, the experiments involving the mis-specification of the effect compartment as connected to the central compartment when actually the data were simulated using effect compartment linked to a peripheral compartment shows that ANNs could be utilized as a model-independent approach to PK–PD studies. The importance of ANNs, especially when the pharmacological effect is due to more than one bioactive substance and delineation of individual effects is impossible, is discussed and compared with

conventional methods. Moreover, neural networks are shown to be robust toward error in the data and to perturbations in the initial estimates. Sparse data analysis proves that pattern recognition could be performed with minimum information. The effect of noise and sparse data on the performance of ANN requires a more thorough examination and is an area of interest for future studies. Some of the areas in which ANNs are yet to be explored are also pointed out. Overall, neural networks offer a practical solution to the generally encountered problems in PK–PD analysis. Continuing research in applying the state-of-the-art technology to other areas in pharmacodynamics such as nonlinear PK systems, enterohepatic recycling, reversible metabolism, irreversible PD effects, etc., would certainly enhance the utilitarian outlook of ANNs. However, one of the limitations of ANNs is that network features do not hold any physiological relevance. ANNs are not surrogates to the phenomena-based approaches, but worthwhile alternatives.

Appendix

The individual compartmental models are abstracted from literature, and references are mentioned in the text. Following are the values of the pharmacokinetic parameters used to simulate the PK and PD data.

Symbol	Description	Value
α	hybrid rate constant (intermediate)	0.09
β	hybrid rate constant (slow)	0.0057
γ	sigmoidicity factor	1.0 or 0.5
EC(50)	effect compartment concentration to attain 50% of the maximal effect	1.9
k_a	apparent absorption rate constant	1.0
k_{eo}	elimination rate constant from the effect compartment	0.047
k_{1e}	transfer rate constant from central to effect compartment	0.035
k_{12}	transfer rate constant from central to peripheral compartment	0.15
k_{2e}	transfer rate constant from peripheral to effect compartment	0.035
k_{21}	transfer rate constant from peripheral to central compartment	0.04
V_1	volume of distribution of central compartment	4.9
V_2	volume of distribution of peripheral compartment	6.0
k_{in}	rate constant for the production of response	6.0
k_{out}	rate constant for the loss of response	0.2
IC_{50}	concentration producing half-maximal inhibition	12.0

The pharmacodynamic models used for various experiments described in the text are as follows.

Link Model

$$\text{effect} = (X)^{\gamma}/((X)^{\gamma} + (\text{EC}_{50})^{\gamma}) \quad \text{(A1)}$$

$$X = k_{eo}A_e/(k_{NE}V_N) \quad \text{(A2)}$$

In eq A2, A_e is the amount of drug in the effect compartment, k_{NE} is the transfer rate constant into the effect compartment, and V_N is the volume of the driving pharmacokinetic model compartment.

Indirect Model

Inhibition of the production of response:

$$R'(t) = k_{in}(1 - C_p/(\text{IC}_{50} + C_p)) - k_{out}R \quad \text{(A3)}$$

Inhibition of the loss of response:

$$R'(t) = k_{in} - k_{out}(1 - C_p/(\text{IC}_{50} + C_p))R \quad \text{(A4)}$$

In eqs A3 and A4, $R'(t)$ is the rate of change in R (response) with respect to time, k_{in} is the rate of production, k_{out} is the rate of output, C_p is the concentration of drug in plasma, and, IC_{50} is the drug concentration that produces 50% of maximum inhibition.

Parent + Active Metabolite Model

Correct—competitive binding of parent and active metabolite at the receptor:

$$E_{D+M} = \frac{E_{\text{max}D}C_D}{\text{EC}_{50D}\left(1 + \frac{C_m}{\text{EC}_{50M}}\right) + C_D} + \frac{E_{\text{max}M}C_M}{\text{EC}_{50M}\left(1 + \frac{C_p}{\text{EC}_{50D}}\right) + C_M} \quad \text{(A5)}$$

Mis-specified—only parent drug contributing to the effect:

$$E_D = \frac{E_{\text{max}D}C_D^{\gamma}}{\text{EC}_{50D}^{\gamma} + C_D^{\gamma}} \quad \text{(A6)}$$

In eq A5, $EC_{50D} = 5.0$, $EC_{50M} = 0.5$, $E_{maxD} = 25$, and $E_{maxM} = 10$.

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JS950433D