Empirical Versus Mechanistic Modelling: Comparison of an Artificial Neural Network to a Mechanistically Based Model for Quantitative Structure Pharmacokinetic Relationships of a Homologous Series of Barbiturates

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ABSTRACT The aim of the current study was to compare the predictive performance of a mechanistically based model and an empirical artificial neural network (ANN) model to describe the relationship between the tissue-to-unbound plasma concentration ratios (K_{pu} 's) of 14 rat tissues and the lipophilicity (LogP) of a series of nine 5-n-alkyl-5-ethyl barbituric acids. The mechanistic model comprised the water content, binding capacity, number of the binding sites, and binding association constant of each tissue. A backpropagation ANN with 2 hidden layers (33 neurons in the first layer, 9 neurons in the second) was used for the comparison. The network was trained by an algorithm with adaptive momentum and learning rate, programmed using the ANN Toolbox of MATLAB. The predictive performance of both models was evaluated using a leave-one-out procedure and computation of both the mean prediction error (ME, showing the prediction bias) and the mean squared prediction error (MSE, showing the prediction accuracy). The ME of the mechanistic model was 18% (range, 20 to 57%), indicating a tendency for overprediction; the MSE is 32% (range, 6 to 104%). The ANN had almost no bias: the ME was 2% (range, 36 to 64%) and had greater precision than the mechanistic model, MSE 18% (range, 4 to 70%). Generally, neither model appeared to be a significantly better predictor of the K_{pu} 's in the rat.

INTRODUCTION

The question "Which model?" has been asked ever since modelling started, but it still brings about a lot of confusion and disagreement. Numerous models have been and are constantly being proposed, almost each one of which claiming to add something to the knowledge of a phenomenon or process, but each inherently inadequate to encompass the full complexity of the real world. The latter, however,

should not be and has never been seen as an obstacle by the modellers, who continue to develop new models at varying levels of complexity, generality, and validity. The increasing rate of success of modelling technology in solving various problems in all areas of contemporary life is sufficient justification for its continued development.

The varying extent to which different models describe the underlying functional mechanisms of the processes of interest determines the varying level of the model empiricism. There is constant competition and sometimes disagreement between the two respective schools of thought (1-5): the empiricists say that more empirical, data-based models have a better practical value because of the infinite complexity of the underlying phenomena; the rationalists stress the (theoretically) better cognitive and predictive potential of mechanistically based models, which are able to generate new knowledge. In fact, there are no purely empirical or mechanistic models. Philosophically, all mechanistic models involve an element of empiricism (even if it were in the modelling assumptions). Otherwise, one should be able to describe "fully and completely" the studied phenomenon, which is definitely impossible in the continuous and infinite world. The reverse (all empirical models contain a mechanistic element in them) is also true, even if this element is the list of factors (inputs), influencing the modelled output. Therefore, no strict formal definition of an empirical or mechanistic model can be given. The distinction can only be relative, reflecting the predominance of the empirical or mechanistic elements in a particular model. Consequently, one should not underestimate the extrapolation capabilities of empirical models or, alternatively, overestimate the ability of the

mechanistic models to extrapolate. In reality, both empirical and mechanistic models have found various and successful implementations and developments in different scientific areas.

As pharmacokinetics is a mechanism-oriented science, most of the pharmacokinetic models used so far have included a significant mechanistic element. Even the most common one- and two-exponent models are based on assumptions regarding the functional mechanisms involved, e.g., that the drug is transported by the blood circulation (central compartment), eliminated from there, and so forth. Predominantly empirical models are rarely implemented in pharmacokinetic and pharmacodynamic studies: among the few examples are the partial area under the curve (AUC) calculated from raw concentration-time data using a quadrature formula (note that the subsequent clearance model using this AUC is not an empirical one), and some models used in quantitative structure-pharmacokinetic relationship studies (6). This fact, however, does not mean that empirical models have no potential and are irrelevant to pharmacokinetic and pharmacodynamic problems; it only means that not enough comparative research has been done regarding the benefit of both empirical and mechanistic models in various model implementation situations.

When comparing the potential of the empirical and mechanistic approaches, it is obviously better to select models on both extremes of the empirical/mechanistic scale, (i.e., empirical models with as little mechanistic assumptions as possible and mechanistic models with as few empirical features as possible). Unfortunately, this is seldom the case in the published comparative studies.

The purpose of this article is to compare the predictive performance of a mechanistically based model with an empirically based model, developed by us, for the relationship between the tissue distribution and the lipophilicity of a homologous series of 5-*n*-alkyl-5-ethyl barbituric acids in the rat. The empirical model is in the form of an artificial neural network (ANN). The only mechanistic assumption in this model is the list of factors (inputs), assumed to influence the output signal. The mechanistic model takes into account the tissue water and lipid dissolution and tissue binding mechanisms. Both models have been identified using

the same experimental data set, and their predictive power was tested using the same method to ensure the highest reliability of the comparative conclusions.

Artificial Neural Networks In Pharmacokinetics And Pharmacodynamics

With the recent revival of interest in ANN, there are numerous excellent monographs (e.g., 7-9) and review articles (e.g., 10-12) available in this area. For the purposes of this article, however, only the most essential terms and features of ANN (7-12) are introduced.

ANN technology is a group of computer methods for modelling and pattern recognition, functioning similarly to the neurones of the brain (7-12). Basically, ANNs consist of interconnected layers of processing units, called neurons or nodes. Figure 1 shows an example of the most frequently used network type, the backpropagation ANN (BPANN). The layer that receives the inputs from the environment (i.e., the independent variables for the system) is the input layer. The output layer nodes generate the dependent variables (i.e., the outputs of the system). The layers interconnecting the input and output layer are called hidden layers.

Figure 1. A typical three-layer BPANN. The symbols w_1 to w_{15} are the weights of the individual connections.

Figure 2 illustrates the basic functional principle of the BPANN on a single hidden layer neuron. The net input to the neuron is the weighed sum of the output signals from all neurons in the previous layer:

$$\text{Net Input} = \sum o_i w_i \quad (1)$$

where o_i is the i -th input signal and w_i is its weight.

Figure 2. Functional diagram of a hidden layer node. The output of the node is calculated from the net input using the transfer function (TF), according to Equation (2).

The output of the neuron is calculated using the transfer function of the ANN, which most frequently is a sigmoid function:

$$\text{Neuron Output} = 1/[1 + \exp\{-\text{Net Input}\}] \quad (2)$$

Once the architecture and the transfer function have been determined, the ANN is subjected to training, during which it “learns” the existing relationship between the input and output variables. The training process adjusts the weights of each neuron connection, using the existing <input -; output> data set, until the difference between the observed and the ANN-predicted outputs (the prediction error) becomes sufficiently small. The most common training algorithm is based on the Delta rule, according to which each training iteration (frequently referred to as “epoch”) is described by the following general equation:

$$\text{New weight change} = \text{Learning Rate} * \text{Error} + \text{Momentum} * \text{Last weight change} \quad (3)$$

The two parameters of the Delta rule -; the Learning Rate and the Momentum -; determine the speed of the training process.

To conclude this very superficial review, it should be noted that, when one develops an ANN model, given a particular <input -; output> data set, one has to determine: (1) the type and architecture of the ANN, including the number of hidden layers and neurones in them; and (2) the learning rate and momentum values, so that the ANN training is sufficiently rapid and the error of the ANN is minimal.

Despite the recent rapid growth in the implementation of ANNs, their potential in

pharmacokinetics has gone largely unnoticed (12,13), but prospects are nonetheless good for successful implementation of ANNs in this area. The essential features of ANNs (12) -; nonlinearity, adaptivity, independence of statistical and other modelling assumptions, fault tolerance, universality, and real time operation -; make them quite suitable for pharmacokinetic applications, especially where extremely complex and unfamiliar phenomena are studied for the purposes of decision making.

The scope of published articles on pharmacokinetic applications of ANN in the last 10 years, although quite limited, mainly covers the following areas: (1) prediction of the pharmacokinetic profiles of various drugs (14-;22); (2) pharmacodynamic and pharmacokinetic/pharmacodynamic modelling (14,22,24); (3) population modelling (23,25,26); (4) in vitro/in vivo correlations (27-;29); (5) animal-to-human scale up of pharmacokinetics (30,31); and (6) quantitative structure-;pharmacokinetic relationship studies (32).

As a result of the insufficient number of well-designed comparative studies, the accumulated knowledge and experience regarding the potential benefits and shortcomings of ANN in pharmacokinetic implementations have not been comprehensively explored, sometimes leading to undeserved conservatism, disbelief, and even outright negativism (3-;5).

What is of primary importance to the present study, however, is that ANN are a perfect representative of data-based empirical models. Therefore, an ANN model is quite suitable as an antipode and competitor to a well-defined mechanistic one, and is used as such in the following.

MATERIALS AND METHODS

Experimental Data

In order to relate structural attributes of compounds to their pharmacokinetic behavior, a research program was initiated involving the study of a homologous series of nine 5-n-alkyl-5-ethyl barbituric acids Table 1, administered by i.v. bolus to rats. Based on experimental concentration-time profiles in 14 tissues and arterial blood, a whole-body, physiologically based pharmacokinetic (PBPK) model for the series was developed Figure 3 (33). This model was used to estimate the drug-dependent parameters characterizing the tissue-to-

unbound plasma distribution ratios (Kpu's) for all tissues. The results of the optimization are shown in Table 2 (33), where the missing data in the last two columns (corresponding to C8 and C9) have been supplemented by the Kpu results from an in vitro steady-state tissue experiment (34). These Kpu values serve as a basis for comparative evaluation of the ANN and mechanistic models.

ANN Model

A backpropagation ANN (multilayer perceptron MLP) was selected as an empirical model. The inputs to the ANN were selected from all possible combinations of 2, 3, or all 4 of the following parameters (Table 1): the fraction unbound in plasma of the compound, f_u ; the molecular weight of the congener, MW , its n-octanol-to-water partition coefficient, $LogP$, and its kPa . The output layer had one neuron. All input and output signals were scaled in the interval (0,1) using the following formula:

$$\text{Transformed Parameter} = 0.25 * \log(10 * \text{Original Parameter}) \quad (4)$$

During the initial testing of the empirical model, different network structures with one and two hidden layers and varying numbers of neurones in them were used. ANN with 3, 4, 5, 6, 7, and 12 neurons in the single layer (for one hidden layer structure), and with 5-;3, 9-;4, 12-;5, and 33-;9 neurons in the first and second hidden layer (for two hidden layers structure), respectively, were tested. Different variants for the initial values of the weights used -; generated uniformly in the intervals (-;1, +1); (0,1); (-;3,+3); (-;7,+7) -; were also implemented. Four different training rules were tested: gradient descent method with adaptive learning rate and momentum (GDX), Levenberg-Marquardt (LM), scaled conjugated gradient descent (SCG), and Quasi-Newton (QN) method (39).

As a result of the extensive numerical experiment, the optimal structure and training rule have been chosen. The ANN structures that give the best results are a 1 hidden layer structure, with 5 neurons in the hidden layer, and a 2 hidden layers structure, with 33 and 9 neurons in the first and second hidden layers, respectively. As the latter structure has a large number of adjustable weights, and the training set is relatively small, the former structure should be preferred. The small training set size does not allow the use of a testing set to check for overtraining and loss of generalization. Alternatively, it is suggested

Figure 3. Structure of the whole-body physiologically based model for the barbiturate series [33].

Table 1. Physicochemical properties of the barbiturate homologues

Homologue	Symbol	MW ¹	log P ²	pKa ³	f _u ⁴	R ⁴
5-methyl-*	C1	170.2	0.02	8.11	1.000	1.00
5-ethyl-*	C2	180.2	0.68	7.75	0.964	1.00
5-n-propyl-*	C3	198.2	0.87	7.77	0.860	1.00
5-n-butyl-*	C4	212.2	1.70	7.81	0.600	1.42
5-n-pentyl-*	C5	226.2	2.23 ^d	8.00	0.486	1.52
5-n-hexyl-*	C6	240.2	3.08	7.74	0.180	1.00
5-n-heptyl-*	C7	254.2	3.64	7.78	0.070	1.00
5-n-octyl-*	C8	268.2	3.85	7.78	0.030	1.00
5-n-nonyl-*	C9	282.2	4.13	7.82	0.010	1.00

*-5-ethyl barbituric acid

¹ n-octanol - to - water partition coefficient

² weak acids

³ fraction unbound in plasma

⁴ blood - to - plasma concentration ratio

Table 2. Kpu values for barbiturate homologues in various tissues. *

Tissue	Kpu values for barbiturate homologues in various tissues								
	C1	C2	C3	C4	C5	C6	C7	C8	C9
LUNG	0.61	1.04	1.69	2.55	3.42	6.70	18.9	125	387
LIVER	2.75	3.87	3.41	4.94	6.60	15.3	20.3	92.7	260
KIDNEY	1.25	1.86	4.55	7.33	5.97	11.6	29.4	101	218
STOMACH	0.26	0.30	0.72	2.17	3.22	16.3	45.0	68.2	266
PANCREAS	0.32	0.38	0.69	1.46	2.54	9.06	21.5	96.4	317
SPLEEN	0.58	0.88	1.33	2.17	2.89	6.5	13.7	72.2	322
GUT	0.60	0.72	1.20	3.09	3.95	12.2	20.1	47.6	203
MUSCLE	0.60	0.85	1.61	2.20	4.03	11.3	20.9	50.8	125
ADIPOSE	0.35	0.75	1.54	2.98	7.20	66.2	124	214	775
SKIN	1.12	1.25	1.80	2.28	2.30	14.7	15.6	117	394
HEART	0.55	0.72	1.24	3.08	4.84	12.7	23.5	55.8	130
BRAIN	0.60	0.76	1.42	2.57	2.51	12.8	14.9	79.4	275
TESTIS	0.69	0.79	1.63	2.59	3.95	8.22	20.9	42.9	129
RBC ^b	1.00	1.04	1.16	1.68	4.33	5.56	15.1	40.1	90.9

*From Blakey et al. [33] and P. Ballard (personal communication).

^bRed blood cell-to-unbound plasma concentration ratio.

that the training is stopped sooner, rather than later, after the plateau of the error is reached (i.e., in approximately 3000 epochs). The initial weight values were sampled from a random uniform distribution within the interval (-1, +1). The GDx optimization rule (adaptive learning rate, momentum fixed at 0.9) was found to perform better in our case. The training of the ANN was performed using the neural networks toolbox of Matlab 5.0 (39).

Mechanistically Based Model

The mechanistic model for this barbiturate series was developed and described by us before (34). Based on carefully defined assumptions regarding the water and lipid dissolution and the binding of the barbiturates in the various rat tissues, this model is expressed as:

$$Kpu_T = f_{w,T} [1 + a_T (nPROT_{t,T}) P^{b_T}]$$

where $f_{w,T}$ is the tissue water content, $(nPROT_{t,T})$ is the protein binding capacity of the tissue, n is the total number of the binding sites available in the tissue, a_T and b_T are the parameters of the relationship $Ka_T = a_T P^{b_T}$, P is the n-octanol-to-water partition coefficient for the particular barbiturate, and Ka_T is the binding association constant of each tissue. In order to estimate the unknown parameters of the mechanistic model $\theta_{1,T} = a_T (nPROT_{t,T})$ and $\theta_{2,T} = b_T$, Equation 5 can be linearized and fitted to the pre-determined Kpu values (Table 2).

Evaluating the Predictive Performance of Both Models

To measure the predictive potential of the derived relationship, a classical “leave-one-out” extrapolation exercise was carried out. At each step, all Kpu values for one of the homologues (one column) from Table 2 were dropped out. Then either the ANN was trained with, or the mechanistically based model (Eq. 5) was linearized and fitted to, the rest of the data to estimate the unknown $\theta_{1,T}$ and $\theta_{2,T}$ for each tissue separately (row-wise). Following this, using both the ANN and the mechanistic model, the Kpu values for all the tissues with the homologue, which was left out, were predicted. The predictive performance was measured by computing the mean prediction error (ME, a measure of the prediction bias) and the mean squared prediction error (MSE, a measure of the prediction precision) (35).

To illustrate further the predictive power of the parameter model derived, the resulting concentration time profiles of the PBPK model were simulated using the predicted Kpu values from both models and the profiles generated were compared. The simulations were performed in ACSL software (36).

The relative predictive performance of the two models is measured by computing the differences in ME ($\Delta ME = ME_{MECHAN} - ME_{ANN}$) and MSE ($\Delta MSE = MSE_{MECHAN} - MSE_{ANN}$) and their respective 95% confidence intervals (CI). The hypothesis that the two predictors are not different is tested, by observing whether the CI for the relative performance includes zero (35).

RESULTS AND DISCUSSION

The correspondence between the Kpu values, calculated during the “leave-one-out” extrapolation exercise using both the mechanistically based model (Eq. 5), and the ANN model is represented graphically in Figure 4: the upper panel shows two of the worst predicted tissues (in terms of MSE), adipose and skin; while the lower panel shows two of the best predicted tissues, muscle and testes. There is a good agreement between the predictions both with respect to the original Kpu values (represented by the line of unity), and between the two compared models, even for the worst predicted skin tissue.

To compare the predictive performance of the mechanistically based model and the ANN model, the percentage prediction errors of the Kpu values from the “leave-one-out” procedure are shown in Table 3 (results with the mechanistically based model, Eq5) and Table 4 (results with the ANN-based model). The column-wise and row-wise ME and MSE are shown in the last two columns and rows of the tables, respectively.

Figure 4. Correspondence between the original Kpu values and the ones predicted from “leave-one-out” exercise using both the mechanistically based model (triangles) and the ANN model (circles) for representative rat tissues.

Table 3. Prediction errors (in %) for the Kpu values of the different homologues and tissues, using the mechanistically based model (Equation 5) and a "leave-one-out" method

Tissue	C1	C2	C3	C4	C5	C6	C7	C8	C9	ME	MSE
LUNG	3.3	-30.0	-32.6	-9.1	67.9	124.0	113.3	-31.7	-51.1	17.1	42.8
LIVER	-57.6	-49.7	13.7	41.9	99.3	56.0	137.3	-18.1	-63.7	17.7	48.9
KIDNEY	-4.1	-7.5	-40.9	-31.5	81.2	87.8	49.4	-22.5	-31.6	8.9	23.3
STOMACH	201.4	191.7	60.5	-16.9	61.6	-33.2	-31.6	61.1	15.2	56.6	101.3
PANCREAS	73.4	55.6	10.2	-25.0	9.6	-11.5	31.8	-6.2	0.6	15.4	11.7
SPLEEN	3.5	-23.0	-25.1	-13.8	53.0	71.6	122.2	-3.0	-60.9	13.8	31.1
GUT	36.6	31.7	16.6	-36.8	15.5	-18.0	33.4	51.7	-33.1	10.8	10.5
MUSCLE	36.2	22.8	-29.2	-11.8	-1.6	-21.0	11.5	21.7	39.6	7.6	6.0
ADIPOSE	-8.4	-20.5	-0.3	46.6	74.1	-53.7	-24.0	49.6	14.9	8.7	15.9
SKIN	-34.4	-22.6	-13.2	39.1	230.2	5.8	180.1	-29.4	-62.8	32.5	104.1
HEART	53.4	39.9	34.1	-28.0	-0.8	-18.2	7.5	9.7	20.4	13.1	8.1
BRAIN	38.2	22.0	-23.1	-29.6	86.5	-25.8	94.8	31.8	-51.6	15.9	26.9
TESTIS	41.6	44.1	-10.8	-8.7	18.0	17.0	-0.4	14.8	-28.3	9.7	6.1
RBC	-1.8	10.5	32.6	45.2	4.6	69.1	36.8	17.2	18.7	25.9	11.1
ME	27.2	18.9	-0.5	-2.7	57.1	17.8	54.4	10.5	-19.5	18.1	
MSE	42.3	36.0	8.2	9.2	67.4	30.2	68.4	9.8	16.2		32.0

Table 4. Prediction errors (in %) for the Kpu values of the different homologues and tissues using the ANN-based model and a "leave-one-out" method

Tissue	C1	C2	C3	C4	C5	C6	C7	C8	C9	ME	MSE
LUNG	3.8	23.2	0.7	-11.6	-14.0	11.1	56.0	-38.5	-24.4	0.7	6.9
LIVER	33.1	-8.6	21.9	-0.1	-14.8	-24.3	108.0	-24.2	-40.1	5.7	18.1
KIDNEY	-2.8	54.1	-27.6	-39.1	20.4	49.6	26.2	-28.3	-20.1	3.6	11.1
STOMACH	-49.6	83.3	19.6	-25.6	-4.7	-24.5	4.8	81.8	-60.0	2.8	23.8
PANCREAS	-36.3	52.1	16.1	-11.8	-27.2	-23.3	80.0	-2.4	-37.1	1.1	15.0
SPLEEN	-13.6	22.7	11.4	-8.3	-14.7	-15.7	80.9	-14.0	-34.4	1.6	10.3
GUT	-49.3	56.8	31.3	-27.1	-19.7	-34.8	58.8	48.7	-58.8	0.6	20.3
MUSCLE	-36.3	33.5	-6.1	17.2	-19.6	-21.8	28.2	8.0	-27.0	-2.7	5.8
ADIPOSE	-20.0	10.7	-9.7	34.9	-9.5	-54.0	47.3	80.9	-61.8	2.1	19.4
SKIN	-26.1	18.1	-7.8	1.8	25.0	-63.6	216.3	-25.4	-31.7	11.8	60.2
HEART	-56.4	54.3	35.6	-21.3	-27.7	-15.8	41.4	9.0	-17.0	0.2	12.2
BRAIN	-26.0	52.2	-2.7	-23.0	22.1	-56.0	119.6	20.3	-61.6	5.0	29.0
TESTIS	-50.0	56.8	-5.2	-9.4	-22.5	2.3	5.2	20.5	-36.7	-4.3	9.1
RBC	-47.2	19.2	37.9	21.6	-54.5	22.7	16.5	-7.2	4.4	1.5	9.3
ME	-26.9	37.8	8.2	-7.3	-11.5	-17.7	63.5	9.2	-36.2	2.1	
MSE	13.2	19.8	4.2	4.5	5.7	12.2	70.0	14.5	16.6		17.9

Figure 6. Homologue C5 (one of the worst predicted in terms of MSE) simulations, generated using the original Kpu values and those predicted by the mechanistic and the ANN model. **Figure 5.** Homologue C3 (best predicted in terms of MSE) simulations, generated using the original Kpu values and those predicted by the mechanistic and the ANN model.

In order to illustrate how the predictions of the two alternative models translate into the dynamic behavior of the PBPK model, the simulated concentration-time profiles of representative tissues (venous blood, liver, muscle, and adipose) for the best (in terms of MSE) predicted homologue, C3, using the Kpu values predicted from the mechanistically based model Eq5 and the ones computed by the ANN, are shown in Figure 5. Figure 6 shows the same profiles for one of the worst predicted homologues, C5.

The simulated profiles almost coincide for C3. For C5, they are close for blood and muscle but quite apart for liver and adipose, reflecting the more than twofold difference in the Kpu values predicted by the mechanistically based model (for liver) and both models (for adipose), compared to the original values (Table 2). In general, because of the low-to-medium sensitivity of the PBPK model with respect to perturbations in most of its parameters (37), it can be expected that large differences in the predictions will not produce as large differences in the resulting concentration-time profiles (the liver and adipose with C5 being probably the extreme cases).

The calculated mean prediction error of the mechanistic model, with an average of 18% and a range between -20 and 57%, indicates a tendency for overprediction. This tendency arises in part because for some tissues (e.g., stomach, pancreas, spleen, gut, and heart), the Kpu values with the least lipophilic compounds (C1 and C2; Table 2) are below the respective water contents values. The latter cannot be explained by Equation 5. Although this

effect may be due to random factors in the original Kpu estimates, it deserves further research.

The ANN model has almost no bias: its ME is 2% (range -;36 to 64%).

The MSE for the mechanistically based model is 32% (range, 6 to 104%). The ANN is more accurate, with an MSE of 18% (range, 4 to 70%).

The results show that the overall predictive performance of the ANN model is marginally better than that for the mechanistically based model, regarding both the bias (Δ ME = 16% with a CI between 7.2 and 24.8%) and the precision (Δ MSE = 14.1% with a CI between 1.5 and 26.7%). The reason for this is that building of the ANN model is equivalent to fitting an arbitrary (and therefore more flexible) multivariate function to the data, whereas building the mechanistically based model is equivalent to selecting a particular function type (power function, (Eq5) as a result of the rigid modelling assumptions.

Table 5. Values and 95% confidence intervals of Δ ME and Δ MSE for different tissues

Tissue	Δ ME	CIlo	CIhi	Δ MSE	CIlo	CIhi
LUNG	16.5	-26.5	59.4	35.8	-6.1	77.8
LIVER	12.0	-36.2	60.2	30.7	<u>5.4</u>	<u>56.0</u>
KIDNEY	5.3	-21.6	32.2	12.2	-14.6	39.0
STOMACH	53.9	-14.0	121.7	77.5	-39.3	194.3
PANCREAS	14.3	-19.9	48.4	-3.3	-23.2	16.5
SPLEEN	12.3	-23.8	48.3	20.7	-2.2	43.6
GUT	10.2	-17.3	37.7	-9.8	-19.7	0.1
MUSCLE	10.2	-18.6	39.0	0.2	-4.8	5.2
ADIPOSE	6.6	-33.6	46.9	-3.5	-26.7	19.7
SKIN	20.7	-39.2	80.6	43.9	-101.2	189.0
HEART	12.9	-19.4	45.2	-4.1	-12.7	4.6
BRAIN	11.0	-16.7	38.6	-2.1	-28.1	23.9
TESTIS	14.0	-11.7	39.7	-2.9	-7.2	1.3
RBC	24.4	<u>6.7</u>	<u>42.1</u>	1.9	-15.0	18.7

Table 6. Values and 95% confidence intervals of Δ ME and Δ MSE for different homologues

Homologue	C1	C2	C3	C4	C5	C6	C7	C8	C9
Δ ME	54.2	-18.8	-8.8	4.5	68.6	35.6	-9.1	1.3	16.6
CIlo	<u>8.9</u>	-42.6	-20.5	-7.1	<u>34.2</u>	<u>14.2</u>	-35.7	-7.3	-5.2
CIhi	<u>99.4</u>	4.9	3.0	16.1	<u>103.1</u>	<u>57.0</u>	17.5	9.8	38.4
Δ MSE	29.1	16.2	4.0	4.7	61.7	18.0	-1.7	-4.7	-0.4
CIlo	-27.8	-29.7	-1.6	<u>0.6</u>	-15.5	-8.1	-43.6	-11.9	-12.4
CIhi	86.1	62.0	9.5	<u>8.8</u>	138.8	44.1	40.2	2.4	11.5

The CIs of Δ ME in regard to tissues given in Table 5, show that in terms of the bias, the ANN model predicts significantly better only for red blood cells. All other CIs of Δ ME include the zero. Therefore, the hypothesis that the predictive performance of the two alternative models with respect to the prediction bias is the same cannot be rejected. Similarly, all confidence intervals for tissues (except for liver) of Δ MSE include the zero. Therefore, the hypothesis that the predictive performance of the two alternative models with respect to the prediction precision is the same cannot be rejected for all listed tissues, except the liver. The fact that the constructions of both the mechanistically based model and the ANN model are tissue oriented (i.e., aimed at predicting a Kpu value of a single tissue at a time) may be considered to be the most important result of the comparative study.

Table 6 shows that, in regard to compounds, the ANN model predicts better with respect to bias only for homologues C1, C5, and C6, and in terms of precision for homologue C4. For all other homologues, both with respect to bias and precision, neither model appears to be a significantly better predictor.

It should be noted once again, however, that in our case, the overall performance of the models is not as important as their tissue-by-tissue performance, as rated in Table 5. In this connection, the general conclusion can be made that neither of the alternative models can be considered an undisputedly better predictor of the tissue-to-unbound plasma distribution coefficients for the rat tissues than the other. This conclusion is supported further by the virtual coincidence of the resultant PBPK model profiles simulated using the Kpu values, predicted by the mechanistic and the ANN models, as shown in Figures 5 and 6.

The current comparison between the two alternative models is by no means intended to discriminate against either of them. On the contrary, its aim is to validate both approaches by illustrating their potential and limitations.

The mechanistically based model is based on our current knowledge of the underlying mechanisms of drug distribution within various rat tissues. It is built on sound and well-defined assumptions (34). This circumstance can be viewed both as an advantage and a defect of the approach, as the assumptions may not always be practically validated for a new drug of

interest. Therefore, despite the theoretically superior predictive potential, mechanistically based models may fail to extrapolate successfully, if their assumptions are not verifiable.

With no or very limited a priori knowledge about the processes studied, the empirical ANN model compensates for its inherent information inadequacy by requiring fairly large and well-spread training sets (38). Once a good training set of input-output data is available, however, ANN models can prove useful for specific applications.

The failure of the comparison to show a marked superiority of either model shows once again that the controversy between the empirical and mechanistic schools of thought is only superficial. In fact, in this argument, the empiricists often fail to define the particular application of the model they have in mind (especially whether it will be used for interpolation or extrapolation), while the rationalists often do not specify whether there is a need to generate new knowledge every time a model is used.

In conclusion, the similar predictive performance of the mechanistic and the empirical model in our case proves once again the well-known principle, often neglected by modelling zealots, that any model is only as good as the available information about the system of interest. With the chronic insufficiency of information inherent to many pharmacokinetic studies, neither of the approaches should be considered inferior and discarded as useless. A much more pragmatic, positive attitude should be adopted, considering both models as complementary and, consequently, adapting and adjusting both of them with the accumulation of new information and knowledge.

We totally agree with and advocate Siegel's opinion (4) that a perspective is drawn only after a considerable experience has been accumulated. The present article compares the performance of a particular mechanistically based model and a particular empirical ANN model on a particular data set. Many more well-designed and well-executed studies are needed before a fairly confident perspective of both approaches can be attained. We view our study as a step in this direction.

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