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ESTIMATION OF BLOOD DRUG CONCENTRATION WITH NEURAL NETWORK MODEL

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Abstract. *Treatment cannot avoid the risk of side effects and sequelae. Appropriate dosages and dosing intervals will typically vary among patients. The most important consideration in administration design is blood drug concentration of the patient, and it is necessary to estimate the concentration beforehand for the administration plan. However, it has been difficult to predict individual blood drug concentration. Also, administration design is extremely difficult. In this study, we construct a model for predicting personal blood drug concentration with neural network mixing equations which has been defined in pharmacy field. Our proposed method is compared and examined with previous method. It is a statistical model proposed in previous study. As results of the experiments, our model outperformed the method.*
Keywords: Neural network, Prediction, Blood drug concentration, Pharmacology

1. **Introduction.** Recently, variational medicines are used as antimicrobial for people who have diseases. However, its treatment cannot avoid the risk of side effects and sequelae since precisely making an administration plan before beginning treatment is extremely difficult. In general, appropriate dosages and dosing intervals may vary among patients. The most important consideration in administration design is a change of blood drug concentration of the patient, and it is beneficial to precisely estimate the concentration beforehand for the administration plan. However, in current way, administration plans cannot be completely decided in advance. Choosing optimal doses requires knowledge of pharmacokinetics (the process of absorption, distribution, metabolism and excretion of drugs within the human body) and pharmacodynamics (the drug action: how the body is affected by the drug). According to Marsot et al. [1], several pharmacokinetic studies

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in various patient populations use in particular nonlinear mixed-effects modelling, a commonly used population-based modelling approach, to identify the covariates that could influence the dose-concentration relationship. In 2000, Tolle et al. suggested artificial neural networks as an effective replacement for those "complex computation models and/or cumbersome statistical prediction applications" [2]. They concluded that their predictions for concentrations of the drug tobramycin by a neural network were as good as or better than the predictions by statistical analysis methodologies done with NONMEM®, the current industry standard application for pharmacokinetic data analysis. Yamamura et al. also showed some potentials of aritificial neural networks [3]. In recent studies, the effectiveness of machine learning models for predicting serum concentration levels is performed for vancomycin, too. For example, Hu et al. proposed machine learning models (SVM and M5) to predict the vancomycin peak (maximum concentration after dose administration, approximately examined after 1-2 hours) and trough (minimum concentration before next dose is administrated) concentrations [4]. Since they limit their research to the peak and trough concentrations, they leave out all other observations. Hua et al. compared some typical machine learning methods in a warfarin dosage prediction problem [5]. They also showed the superiority of machine learning methods copmared to statisitical methods.

Indeed some efficient machine learnig methods have been proposed, but all previous studies used a plenty of data, at least more than 500 data. In most cases, it is really difficult to collect enough data to learn models because the number of clinical cases is small. In conventional study, to address the few data problem, an equation to predict personal deference was generated with population pharmacokinetic analysis [6]. That equation can estimate personal clearance (CL) from Age and Total Body Weight (TBW). CL is deeply involved with change of drug concentration in blood. The previous statisical approach can handle few data, typically less than 100 data. The accuracy of the previous model is higher than typical population model by virtue of personalization.

In this study, we aim further improvments of the accuracy by utilizing artificial neural networks. In pharmacokinetics, a mathematical model calculating blood drug concentration independent on personal characteristics has been defined [7]. To cope with the few data problem, we incorporate the mathemactial model to a neural network model. The utilization of the mathematical model can result in the small number of parameters to learn the model, and the model can handle a nonlinear model with the small number of clinical data.

The remainder of this paper is organized as follows. In Section 2, the statistical pesonalization model is briefly introduced as the conventional study. In Section 3, a mathematical notation of neural network model is described. In Section 4, phatmacokinetics considered in this study is described. In Section 5, we propose a neural network model incorporating phamacokinetics-based mathematical model. In Section 6, we demonstrate the validity of our method by numerical experiments with clinical dataset. Finally, conclusions and some remarks are given in Section 7.

2. **Conventional Study.** In pharmacokinetics, an equation to calculate blood drug concentration in case of oral administration has been defined as Equation (1). Also, meaning of each variable is shown in Table 1

$$DV = \frac{Dose * K_e}{V * (K_a - K_e)} * \left(e^{-K_e * Time} - e^{-K_a * Time}\right) \tag{1}$$

$$K_e = \frac{CL}{V} \tag{2}$$

V, K_e, CL and K_a vary among patients. However, these values cannot be got unless blood is sampled after starting a treatment. For this reason, changes of drug concentration in blood can be precisely estimated in advance. Therefore, Equation (1) cannot consider personal differences before starting a treatment. In conventional research, population

TABLE 1. Meaning of variables

Variable name	Meaning
DV	Blood drug concentration
$Time$	Elapsed time after administration
V	Distribution volume
K_a	Absorption rate constant
K_e	Elimination rate constant

pharmacokinetics analysis was adopted to generate an equation for prediction of CL as Equation (3). This model consists of Age and TBW.

$$CL = 17.8 * \left(\frac{Age}{60}\right)^{-0.269} * \left(\frac{TBW}{46.9}\right)^{0.408} \tag{3}$$

3. **Neural Network.** In this study, we adopt a neural network as a non-linear regression model. A neural network consists of matrix operations [8, 9]. In the neural network, relationship between output and input of the j-th neuron in each layer is represented as follows:

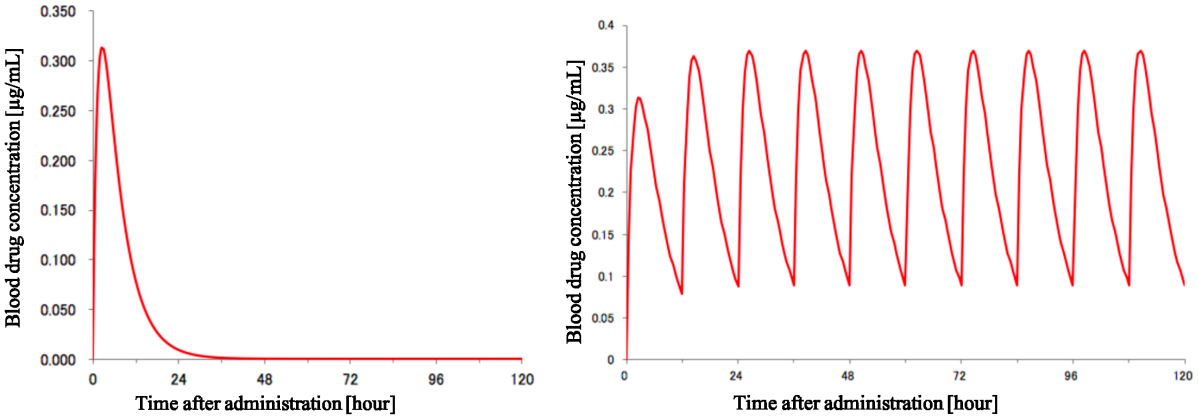
$$y_j = f\left(\sum_{x_i} w_{ij} + b_j\right) \tag{4}$$

where x_i is the i-th value input to the layer. Also, w_{ij} is weighting factor of the j-th neuron against the i-th neuron, and b_j is bias of the j-th neuron. Therefore, output $y = [y_1, y_2, \ldots, y_M]$ of the layer against input $x = [x_1, x_2, \ldots, x_M]$ of the layer is represented as the following when the number of neurons of the layer is M.

$$y = \left(\begin{bmatrix} w_{11} & \cdots & w_{1N} \\ \vdots & \ddots & \vdots \\ w_{M1} & \cdots & w_{MN} \end{bmatrix} \begin{bmatrix} x_1 \\ \vdots \\ x_N \end{bmatrix} + \begin{bmatrix} b_1 \\ \vdots \\ b_M \end{bmatrix}\right) = f\left(Wx + b\right) \tag{5}$$

4. **Pharmacokinetics.** How to change drug concentration in blood after oral single-dose administration is shown in Figure 1(a). A vertical axis is blood drug concentration, and a horizontal axis is time after an administration. That concentration tends to sharply increase up to after about 15 hours. In contrast, that becomes 0 after about 30 hours. In other words, the administered medicine disappears from blood at that time. In case of Mixed Connective Tissue Disease (MCTD), repeated oral administration is widely applied. In repeated administration, medicine is administered regularly in accordance with administration plan. For example, Figure 1(b) shows how drug concentration changes in blood by repeated oral administration when dose interval is assumed 12 hours. A horizontal axis is time after first administration. Considering dose interval and when an administered medicine would disappear from blood in Figure 1(a), a medicine administered a certain time ago would be no amount in blood at that time. Specifically, in repeated administration case, when blood drug concentration would be estimated at t time, the concentration does not depend on administration more that 30 hours ago since there is nothing to affect by the old administration at t time. Therefore, in this research, we consider that only 3 administration is directly involved in prediction of blood drug concentration at t time. Furthermore, total of concentration which is calculated by each administration is defined as t time drug concentration in blood. This definition is represented as the following.

$$DV_t = \sum_{i=1}^{3} DV_{t-T} \tag{6}$$



(a) Single administration (b) Repeated administration

FIGURE 1. Examples of changes of blood drug concentration after administration

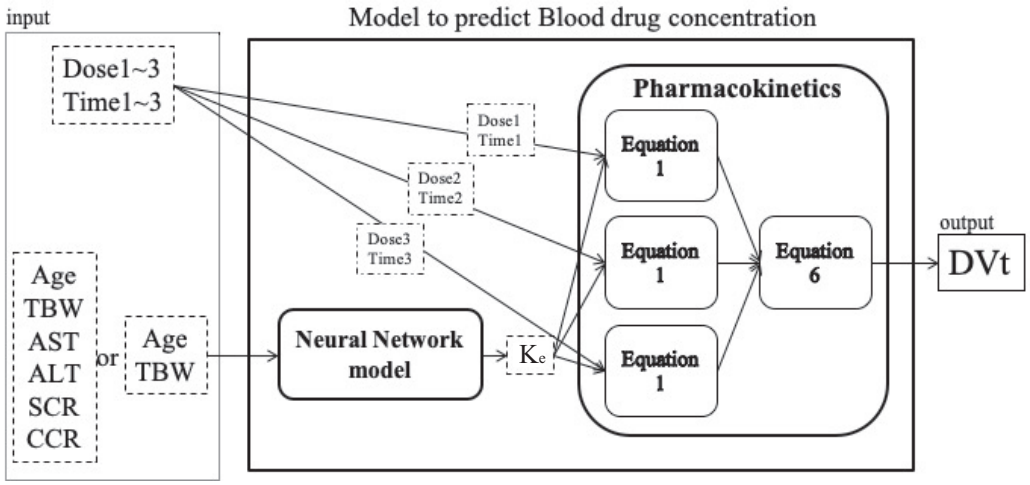


FIGURE 2. Our proposed model

5. **Proposed Method.** In this study, a model in Figure 2 is constructed with neural network. This is mixed model and completely designed according to pharmacokinetics model, mixing neural network, Equations (1) and (6). First, K_e would be predicted through neural network part by input of personal items (Age and TBW, etc.). Secondly, blood drug concentration would be calculated by substituting personalized K_e, 3 Dose and Time after each administration into Equation (1). Finally, drug concentration in blood at t time would be predicted summing up each concentration with Equation (6). When Equation (1) is used, V and K_a are contents ($V = 98$, $K_a = 0.67$). Equation (1) is used for training of neural network part as well. An image of training is shown in Figure 3. At that training, loss of output gained through Equations (1) and (6) is used for backpropagation. Neural network typically carries out backpropagation with loss of direct output. However, precise K_e to be target data of our neural network part cannot be obtained, though precise blood drug concentration can be obtained. For that reason, it is necessary to utilize Equations (1) and (6) for training of neural network. Also, to generate equation by statistics as Equation (3) is difficult and cannot easily change the structure of that. However, it is possible to change a neural network structure easily. In this study, first of all, a model personalized by Age and TBW is generated, which condition is the same as previous study. Additionally, a model personalized by 6 items is generated, which is added 4 items about liver functions to Age and TBW.

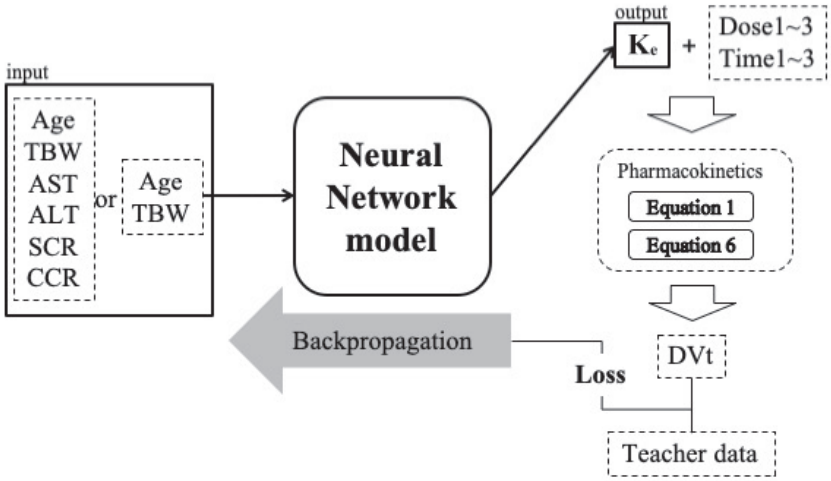


FIGURE 3. Image of training for neural network

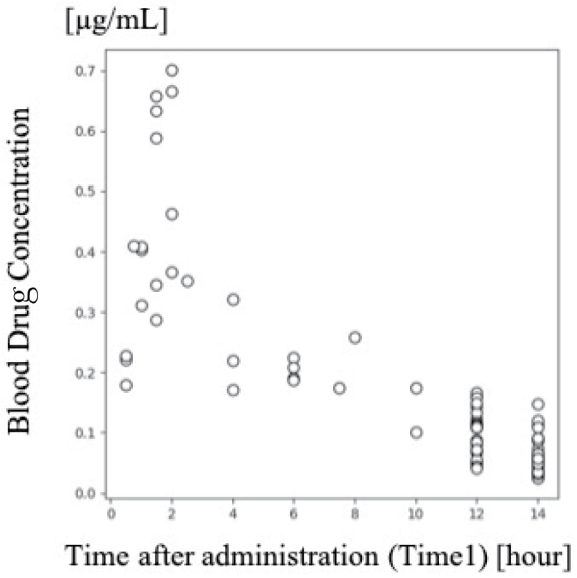


FIGURE 4. Distribution of datasets (blood drug concentration vs time after last administration)

6. **Experiments.**

6.1. **Explaining dataset.** Data used in this experiment is what used in previous study. Patients in the data had been administered cyclosporine for treatment, and disease they have is MCTD. The data was obtained from 36 patients and has 89 drug concentration in blood. Distribution of the data is shown in Figure 4. A vertical axis is blood drug concentration, and a horizontal axis is time after latest administration. As Figure 4 shows, the data is biased.

6.2. **Normalization.** First, data is normalized for neural network. Basic range of data is known since our data is clinical. Therefore, data is normalized in accordance with that range and Min-Max normalization. The reason why we adopt Min-Max normalization is to avoid that any data does mean outlier. When certain input x_i would be normalized, the normalized input x_{norm} is calculated with maximum $x_{\max}$ and minimum $x_{\min}$ as the

following.

$$x_{norm} = \frac{x_i - x_{\min}}{x_{\max} - x_{\min}} \tag{7}$$

6.3. **Procedures.** Personalized model to predict blood drug concentration is trained. Input data for overall of model is administration data ($Dose$1-3, $Time$1-3) and individual data (Age and TBW, etc.). Regarding to neural network part, inputs are only individual items. In 36 patents data, 35 data sets are assigned to training data, and 1 data is used as testing data. The number of epochs is 1000, and there are 2 or 3 hidden layers in our structure. Also, activate function is sigmoid function. Furthermore, as per the previous paragraph, another personalized model is trained, adding AST, ALT, SCR and CCR to Age and TBW as individual data.

6.4. **How to evaluate.** In order to evaluate losses of prediction, cross validation and Root Mean Squared Error (RMSE) are applied. Neural network models are generated trained with all combination of 35 training samples and 1 testing sample. Losses by testing in each model are evaluated (cross validation). Finally, loss got by cross validation is evaluated by RMSE. That would be calculated with predicted values $y_{0,1,\ldots,n}$ and answer values $t_{0,1,\ldots,n}$ as the following.

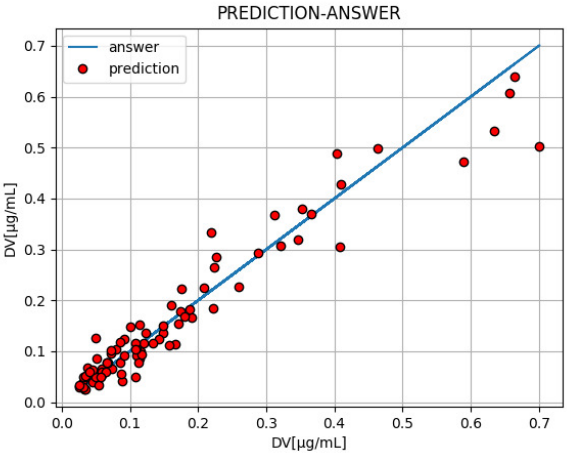
$$RMSE = \sqrt{\frac{1}{n}\sum_{k=1}^{n}(y_i - t_i)^2} \tag{8}$$

6.5. **Results.** As Table 2 shows, model personalized by 6 items is best in all models. Also, model personalized by 2 items is better than population pharmacokinetics analysis. These models were generated under the same conditions, namely, neural network is more effective than that analysis. Considering only our proposed model, increasing the number of personal data items made neural network model more accurate. From this result, it was found the more feature vector is, the better neural network is. Figure 5 shows results of prediction to drug concentration in blood by each method. Compared to the conventional method, our proposed models estimated blood drug concentration for low value range better, though losses of predictions for high value range were comparable. Nevertheless, there was a problem on training process. For example, one of history of losses during training is shown in Figure 6 (case of when the 35th patient was assigned to test data with model personalized by 6 items). Training loss is lower and becomes clearly stable, though it is confirmed test loss starts to increase at early epoch. This problem was found sometimes. It seems that over-fitting tends to occur in case of several cases and it is caused by biased datasets.

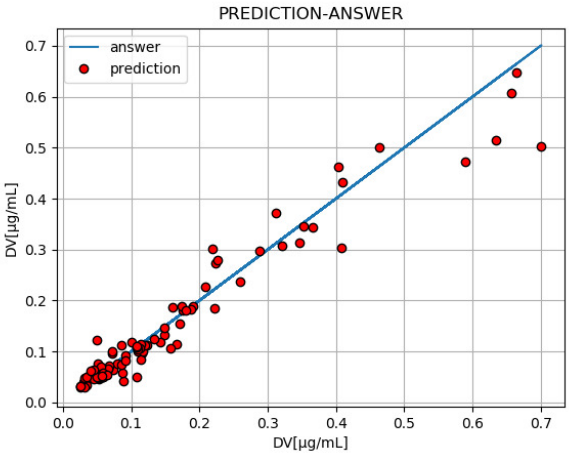
Table 2. Comparison of RMSE

Model	RMSE [ng/mL]
Previous model	41.13
Personalized model by 2 items	38.66
Personalized model by 6 items	37.06

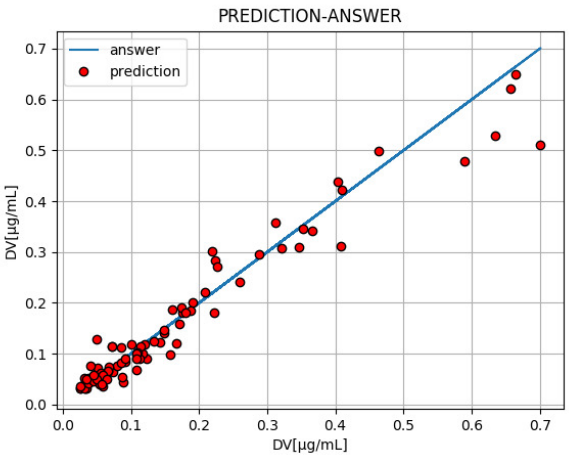
7. **Conclusion.** In this study, our proposed models outperformed population pharmacokinetics analysis. Eventually, prediction of blood drug concentration was personalized by 6 individual items with our model. Therefore, it was found that neural network and increasing individual items are effective to the solution of this research. Namely, it is likely that accuracy of prediction would get higher when that item would increase, e.g., sex (male or female) and measured data such like ALT. Also, as mentioned in previous paragraph, over-fitting happened by bias of data in some cases. Additionally, used data



(a) Population pharmacokinetics analysis



(b) Model personalized by 2 items



(c) Model personalized by 6 items

FIGURE 5. Results of prediction to drug concentration in blood by each method

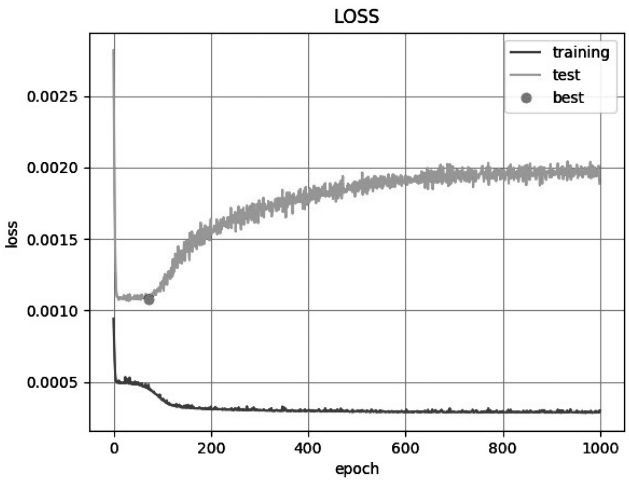


FIGURE 6. History of losses during training (case of when the 35th patient was assigned test data with model personalized by 6 items)

was few for neural network model. However, it needs to solve these problems in the future since real clinical data cannot be got easily. We would like to adopt Generative Adversarial Network (GAN) [10] and Variational Auto Encoder (VAE) [11], which can generate similar data.

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