Evaluation of Different Learning Algorithms of Neural Networks for Drug Dosing Recommendations in Pediatrics

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Abstract. Publicly accessible databases with evidence-based information on drug dosages for children and adolescents are not available in Germany. In previous work a prototypical web-based online platform for pediatric dosing recommendation has been developed. Quality assured maintenance of such a database is a time consuming effort. Recent work has shown that it is possible to use routinely documented data for machine learning approaches in order to create models for future decision support tools. This work describes the development of a prototype for pediatric dosing recommendations on the basis of routine drug prescriptions. Since they are structured for daily clinical use, not for machine learning, they include a substantial proportion of narrative text that requires preprocessing with consideration of medical and pharmaceutical knowledge. Three different learning algorithms have been applied and compared. The genetic algorithm with backpropagation has achieved the highest accuracy in the predictions. Our study constitutes a first step towards pediatric dosing recommendations, but there are multiple additional steps to be taken before a routine use might be considered, such as an evaluation by experienced physicians.

Keywords. machine learning, neural networks, computer, drug dosage calculations, pediatrics

1. Introduction

In pharmacology, children cannot simply be seen as small adults, since they are subject to continuous growth and variation in drug-metabolizing enzyme activity. Age, weight and height are the most important parameters for correct dosing calculations, but many other factors are also influential, such as the development of specific organs, which may be difficult to assess. For various reasons, such as ethical concerns with respect to the inclusion of children or even infants in clinical trials, information on the efficacy of drugs in children is only available to a limited extent. In a previous project pediatricians have conducted continuous and comprehensive medical literature reviews to collect and quality assure evidence-based drug dosage information and to provide them on a web-based drug dosing recommendation platform [1]. The maintenance of the database, however, is a time consuming task, which requires continuous pediatric staff

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commitment. Big Data approaches, where new models have been trained on comprehensive sets of routinely documented clinical data, have proven successful in the past decade. Based on the continuously growing practical evidence of routinely documented medication therapies, researchers have applied various machine learning approaches in order to create models for dosage recommendations. Some approaches focus on specific active substances, e.g. warfarin [2,3], while others focus on specific diseases, e.g. cancer [4]; however, there is no general approach, especially in pediatrics. Similar to young clinicians, who continuously learn from experienced doctors, an artificial neural network (ANN) can also learn from the electronically documented prescriptions of experienced clinicians. At university hospital Erlangen (UHER), Germany, we investigated how such a learning process can be established based on routine documentation. The objectives of this work are to extract and transform the data for its application in artificial neural network training as a proof of concept, and to evaluate different learning algorithms for drug dosing recommendations in pediatrics.

2. Methods

The training and test data for this study originated from the mobile electronic patient charting system which has been applied in clinical routine at the pediatric clinic of UHER for about ten years. We established an ETL process (Extract-Transform-Load) to provide data for ANNs. We extracted prescription data from the year 2014 and de-identified them before further processing. These specific data included patients' age, weight, and full medication characteristics (e.g. dosage and route of application). Our investigation focused on three active substances, namely ibuprofen, paracetamol, and cefotaxim. The extracted data required essential transformation, since the original database structure of the patient charting system is not developed for data analysis but for daily clinical use. Consequently, the electronic medication documentation system does not strictly enforce structured documentation. Thus, the source data includes a substantial amount of drug prescription in the form of narrative text. For example, the route of application and even the dosage may be included in the name of the active substance and thus clinicians did not document this information separately in the respective input fields of the order entry module. While this might be useful for daily clinical work, it forms an obstacle for structured data analysis. Thus, we harmonized the heterogeneity of entries by means of a mapping schema. Eventually, we implemented the ETL process, which extracts required data from the underlying database of the mobile charting system and loads it into a separate database. As the technical platform, we used the open source web server *XAMPP*, which also provides a database. To evaluate the data and create the neural networks, we used *Python 2.7* with the *NumPy* library. To create the plots, we used the *Matplotlib* library.

To evaluate the three learning algorithms, we divided the data according to the holdout method [5] at a ratio of 2:1 (2/3 learning data, 1/3 test data). The age and weight of the patients are used as input values for the ANN. The output value is a dosing recommendation. We used 4 layer ANNs for each active substance, whereby the two hidden layers have four and two neurons. Every neuron of the hidden layers has a bias unit. This architecture remained unchanged in this analysis. The inputs of a neuron are added. The sigmoid function is used as the activation function of the neurons, whereby a neuron can only have values between zero and one.

The ANNs differ in their learning algorithms. We analyzed the following three algorithms: ANNs with backpropagation, ANNs with genetic learning algorithm, and ANNs with genetic learning algorithm and additional backpropagation on child population. All ANNs received a random initial weighting. In ANNs with backpropagation, the weightings were adjusted in order to minimize an error by the gradient method (Formula 1), where y is the real value and o is the output of the ANN. The learning rate was set to 0.01 and the number of iterations was 2000.

$$E = \frac{1}{2}\sum(y_i - o_i)^2 \tag{1}$$

The ANNs with genetic learning algorithm were optimized according to their fitness (Formula 2), which must be as high as possible. One population passes the genetic steps of variation, selection, crossover and mutation, after which a child population is created. The fitness of this new population was calculated and compared. If the fitness value was higher, the new network was included in the parent population, if it was lower, new child populations with the same parents were created.

$$Fitness = \frac{1000}{1+\sum|(y_i - o_i)|} \tag{2}$$

As third learning algorithm, children populations were also created with the same genetic steps and were additionally trained with backpropagation after the mutation step in order to increase their fitness.

3. Results

The predictions and the real dosages are visualized in Figure 1 in form of a 2D plot, using the dosage over age for ibuprofen as example. The recommendations are depicted in blue and the real dosages in orange. Even if the weight as input parameter is missing on this figure, it can be seen that the tendency (green: Fitcurve of predicted values, red: Fitcurve of real values) of the predictions is correct, i.e. a higher dosage with increasing age.

However, the individual predicted values differ from the corresponding real values. One can see that the fixed tablet strengths (600mg, 400mg, 300mg, etc.) are not recognized by the algorithm. This is one challenge to solve by using neural networks to create dosing recommendations. Table 1 shows the average deviations of the predictions of the networks with their different learning algorithms from the real dosages. For each dosage recommendation the percentage difference between prediction and real dosage is calculated; for example, 400mg (real) and 480mg (prediction) result in 20% deviation.

Table 1. Average deviations of the predictions of the networks with the different learning algorithms from the real dosages per active substance with number of the available data records of the respective drug.

Active Substance	Backpropagation	Genetic	Genetic with Backpropagation	Number of Data
Ibuprofen	15%	14%	13%	838
Paracetamol	45%	22%	20%	362
Cefotaxim	57%	32%	33%	135

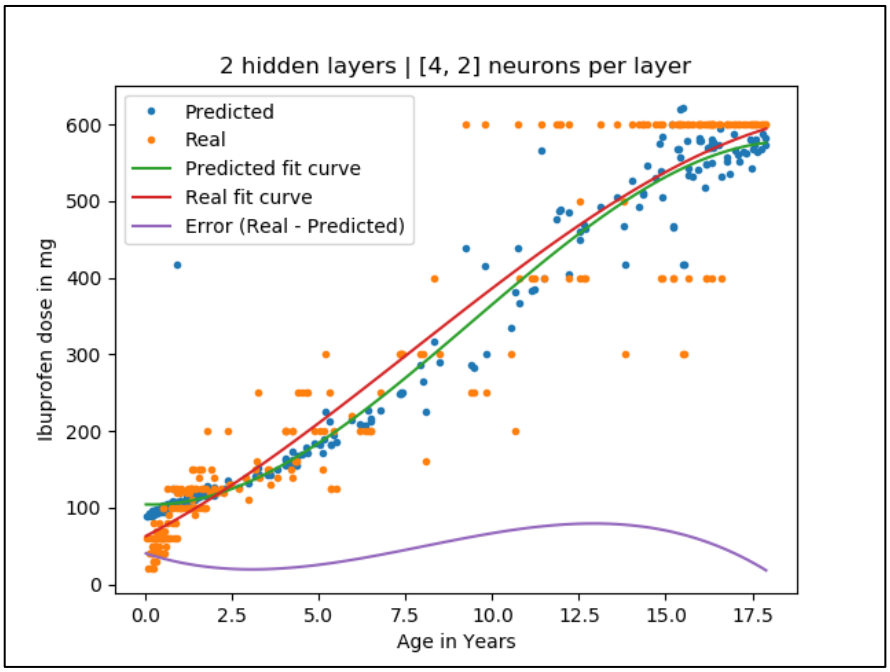

Figure 1. Example of visualization of predicted and real values; feedforward network with backpropagation.

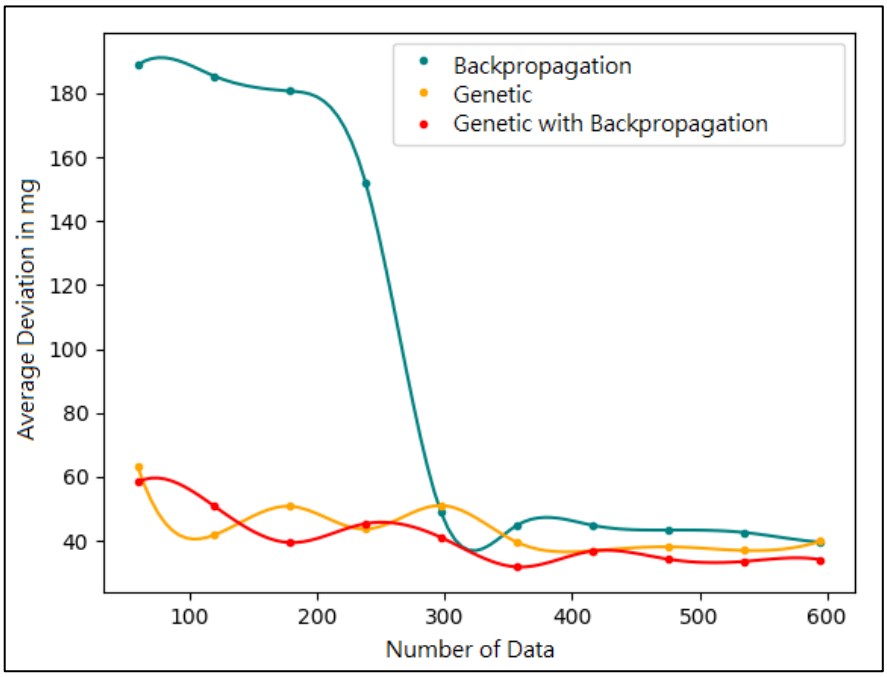

Figure 2. Dependency of accuracy on number of data.

Figure 2 shows the dependency of the accuracy on the number of available data. It can be seen that the deviation of the recommendations from the real values and therefore the accuracy is not linearly related to the number of data. Nevertheless, it can be seen that a higher number of data improves the accuracy, especially in ANNs with backpropagation.

4. Discussion

Our study shows that it is basically possible to create dosing recommendations for drugs in pediatrics with ANN from clinical medication documentation. To improve the drug dosing recommendations, many other parameters such as body surface, diagnosis, secondary diagnoses, previous treatments, allergies, compliance, even genomics [6,7] have to be considered. In future work, they have to be integrated as input values in order to achieve more personalized and more accurate dosing recommendations. So far, the networks do only have the dosage as learning parameter. Further indicators and outcome parameters, such as complications, patient drug rejection, improved patient's health, or lengths of hospital stay, have to be included.

Training ANNs inevitably requires a high quality of input data with respect to data structure. However, like in case of our study, clinical routine documentation data may not be sufficiently structured, which requires laborious data pre-processing during the ETL process to transform narrative prescription information to harmonize the data. Furthermore, this will likely require pharmaceutical knowledge as well as knowledge about the clinical documentation process in the individual hospital units. As a consequence, the dataset for the training of the ANNs in our study was of limited size. However, according to the results shown in Figure 2, a high number of input records for the ANNs is less important than we would have expected.

With respect to the training of ANNs for dosing recommendations, it must be taken into account that prescription behavior may improve over time due to new clinical evidence. Thus, it cannot be excluded, that the network could, at least to a certain extent, learn from outdated prescription information.

There are also indications that the architecture of the ANNs can have an impact on the accuracy of the predictions, i.e. a network with only one hidden layer with a few (4-7) neurons generated more accurate predictions than more complex networks with several hidden layers. However, this needs to be verified in more detail.

Our approach constitutes a first step towards ANN-based pediatric dosing recommendations, but there are still many steps to be taken before our prototype can be used in clinical routine. Further milestones would include an evaluation of the recommendations by experienced physicians and a strategy for dealing with exceptional scenarios in medication.

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