

Comparison of artificial neural network and ANFIS for parameter estimation of a tumor model

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Abstract—Cyber-medical systems are revolutionizing medicine. Mathematical therapy optimization is one of the main pioneering results of cyber-medical system approach. Mathematical therapy optimization is based on a mathematical model. A reliable model with personalized model parameters is crucial for generating optimal treatment. We discuss algorithms for estimation of tumor model parameters using artificial intelligence methods. We use in silico experiments to create a large set of training data in a span that covers real-life scenarios. Artificial intelligence-based systems may provide reliable estimation results in medical applications. In this research two different estimators will be introduced based on artificial neural network and fuzzy methods. The training data are generated on known parameter intervals, taking into consideration the experimental setup we use to validate our results. The estimated parameters can be used to track the change of the parameters and personalize the model for optimization algorithms. The two estimators are compared and shown that they compensate the weaknesses of each other.

Index Terms—tumor model, personalizing therapy, neural networks, fuzzy systems, identification

I. INTRODUCTION

Mathematical model based therapy generation may bring personalized and optimal treatments into practice. This approach can be used to minimize drug dosage, leading to less side effects and costs, and to prevent drug resistance [1]–[4]. There are several approaches to optimize therapy, starting from the application of classical results from optimization and

control engineering [5]–[9], to more sophisticated approaches using impulsive control, which deals with the impulsive nature of the input [4], [10]–[12]. In our work, we assume impulsive inputs, thus we use impulsive differential equations to model the tumor [13], [14].

Mathematical modeling of tumor growth have long been considered in literature, for a review the reader is referred to [15], [16]. Based on the modeled phenomena, some of them model tumor growth and supportive vasculature growth [17], others model the growth of tumor cells, healthy cells and immune cells [18], and there are tumor models which model tumor cell dynamics involving drug resistance [1]. The model use here describes the tumor proliferation, necrosis, dead cell washout, pharmacodynamics and pharmacokinetics of the drug [2], [19], described in Subsection II-A.

Personalizing therapy requires patient specific model parameters, thus identification has to be carried out. However, there are some parameters with low sensitivity, [20], making their estimation impossible. A possible way to solve such problems is generating virtual patient populations with realistic parameter values, generate offline therapies, and use these data to train estimators based on artificial intelligence [21]–[23]. The realistic parameters are acquired using mixed-effect models [2], [24], [25] applied on measurements from in vivo and in vitro experiments [26]. This approach use local search algorithms, requiring initial estimations for the parameters, and can not handle inpatient variability.

Pretrained expert systems can be used to get initial estimations for the model parameters. We use two different estimators, one is a neural network (NN) and the other is an adaptive neuro-fuzzy inference system (ANFIS). The NN has a four-layered, feed-forward architecture detailed in Subsection II-B. The ANFIS is a combination of the neural network and the fuzzy system, which has a five-layered, feed-forward architecture detailed in Subsection II-C. We solve two specific problems, first, we create a training dataset from which the systems can estimate the pharmacokinetic and pharmacodynamic

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parameters. Second, we create an other training dataset from which the systems can estimate the tumor growth parameters. The inputs of the estimators are the tumor volume measured every day for a week except the weekends and injections given two times a week based on the experimental setup discussed in Section III. We generate a large set of training data to cover real-life scenarios.

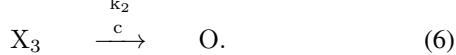
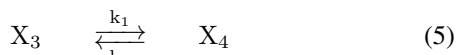
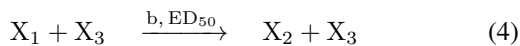
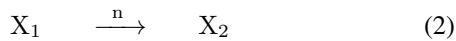
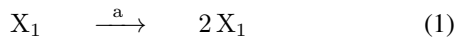
Both of the NN and ANFIS tend to be a reliable estimator for most of the training data which can provide accurately the tumor dynamics parameter values for most of the cases. The results of the estimation of pharmacokinetic and pharmacodynamic parameters show worse results on training data than the estimation of tumor dynamic parameters, but this is a very slight deterioration. The results of the estimation of parameters for most of the test data show that the estimators can also generalize to estimate the data not seen during learning. The NN shows better performance on training data, however, the ANFIS has larger generalization power.

II. PRELIMINARIES

A. Tumor model

We use a fourth-order differential equation to describe tumor dynamics and the pharmacokinetics and pharmacodynamics of the drug created by the authors [19]. Formal reaction kinetics analogy is used to interpret the terms in the differential equations [2]. Let X_1 , X_2 , X_3 and X_4 denote the fictive species representing the living tumor volume, dead tumor volume, drug level in central compartment and drug level in peripheral compartment, respectively.

The tumor dynamics and the drug pharmacokinetics and pharmacodynamics is described by the formal equations



where (1) is tumor proliferation with rate a , (2) is tumor necrosis with rate n , (3) is the washout (absorption) of the dead tumor cells with washout rate w , (4) is the drug effect (i.e., the pharmacodynamics) with maximal effect rate b and median effective dose ED_{50} , (5) is the drug transport between the central and peripheral compartment, while (6) is the depletion of the drug.

Mass action kinetics ([27], [28]) is considered to generate the corresponding terms in the differential equations, with the exception of (4), where Michaelis-Menten kinetics is considered with constant ED_{50} to model the saturated effect

of the drug. Thus, the mathematical model of the tumor growth is

$$\dot{x}_1 = (a - n)x_1 - b \frac{x_1 x_3}{ED_{50} + x_3} \quad (7)$$

$$\dot{x}_2 = nx_1 + b \frac{x_1 x_3}{ED_{50} + x_3} - wx_2 \quad (8)$$

$$\dot{x}_3 = -(c + k_1)x_3 + k_2 x_4 \quad (9)$$

$$\dot{x}_4 = k_1 x_3 - k_2 x_4, \quad (10)$$

where x_1 is the time function of the living tumor volume [mm^3], x_2 is the time function of the dead tumor volume [mm^3], x_3 is the time function of the drug serum level in the central compartment (blood) [$\text{mg} \cdot \text{kg}^{-1}$], and x_4 is the time function of the drug serum level in the peripheral compartment (tissues) [$\text{mg} \cdot \text{kg}^{-1}$]. The impulsive nature of the model is considered as impulsive effect on x_3 , which models injections into the central compartment. Let t_k , $k = 0, 1, 2, \dots$ be the time instants of injections, while u_k , $k = 0, 1, 2, \dots$ is the dosage of injections in $\text{mg} \cdot \text{kg}^{-1}$. Then the function x_3 has a discontinuity of the first kind at time instants t_k , modeled as

$$x_3(t_k^+) = x_3(t_k^-) + \kappa u_k. \quad (11)$$

Mixed-effect model was used to get the model parameters from mice experiments [2], [19], with the assumption that the parameters are constant. We accept these parameters as realistic values, and use them for virtual patient generation in Section III. The assumption that the parameters are constant limit the modeling power and application of the mathematical model, this problem can be solved using artificial intelligence, as shown in the following Sections.

B. Neural network

We use a four-layer feed-forward neural network to estimate the model parameters. The neural network has one input layer, two hidden layers and one output layer. The input layer of the neural network is composed of artificial input neurons. The hidden layers contains sigmoid activation functions and the output layer contains linear neurons, i.e., the outputs are weighted sums of the outputs of the neurons in the first layer and a bias [29]. The output of the r th neuron of the l th layer is calculated as

$$y_r^{(l)}(\mathbf{x}) = \varphi \left(\sum_{i=1}^{N_i^{(l)}} w_{r,i}^{(l)} x_i(p) + \underbrace{w_{r,N_i^{(l)}+1}^{(l)}}_{\text{offset}} \right), \quad (12)$$

where $r = 1, 2, \dots, R^{(l)}$ and $R^{(l)}$ is the number of neurons in the l th hidden layer, the superscript (l) refers to layer l , $\mathbf{x}$ is the input of the neural network, x_i is the i th input of the neural network, where $i = 1, 2, \dots, N_i$ and N_i is the number of inputs, $w_{r,i}^{(l)}$ is the weight of the i th input of the r th neuron in layer l , and $w_{r,N_i+1}^{(1)}$ is the weight of the bias of the r th neuron. The activation function of the neurons in the hidden layer is the sigmoid function

$$\varphi(\epsilon) = \frac{2}{1 + e^{-2\epsilon}} - 1 \quad (13)$$

because this activation function provided the best results during tests.

The m th output of the neural network is

$$y_m^{(3)}(x) = \sum_{r=1}^{R^{(2)}} w_{m,r}^{(3)} y_j^{(2)}(x) + \underbrace{w_{m,R^{(2)}+1}^{(3)}}_{\text{offset}}, \quad (14)$$

where the superscript (3) refers to layer 3, $w_{m,r}^{(3)}$ is the weight of the m th neuron and r th input in the third layer, and $w_{m,R^{(2)}+1}^{(3)}$ is the weight of the bias for the m th neuron in the output layer.

The neural network is trained with supervised learning utilizing error backpropagation using a Levenberg-Marquardt algorithm [30]. The training data are generated with in silico experiments from a large parameter set. We use 100 and 50 neurons in the hidden layers. We carried out some experiments with a different number of neurons in the hidden layers, and also increased the number of hidden layers, and the current setup turned out to be optimal in the view of complexity and accuracy.

C. Adaptive neuro-fuzzy inference system

We also use the ANFIS to estimate the model parameters. The adaptive neuro-fuzzy interface system (ANFIS) is a neural network based on fuzzy logic. It has a five-layered, feed-forward architecture that can have more input and a single output. The first layer is the fuzzification layer. We use in this layer fuzzy membership functions which are Gaussian functions. We could use other membership functions, like triangular or trapezoidal shaped ones. When we tried different types of membership functions we chose the Gaussian function because this choice gave the best result. The first layer defines the degree of membership for each input value as

$$w_{ij} = \exp\left(-\frac{(X_j - x_i)^2}{2\sigma_i}\right), \quad (15)$$

where w_{ij} is the degree of membership of the j th in the i th membership function, where $i = 1 \dots N$ is the number of functions and $j = 1 \dots M$ is the number of inputs. The variable X_j coefficient is the j th input value, x_i is the amplitude of the i th membership function, and σ_i is the i th variance of the function. The second layer nodes calculate the firing strength of rules. The third layer is normalized firing strengths. The fourth layer calculate the extent of rule contributions using the formula

$$\bar{z}_i = \sum_{i=1}^N w_i z_i. \quad (16)$$

The fifth layer summarizes the fourth layer outputs and normalize that to get

$$y = \frac{\sum_{i=1}^N \bar{z}_i}{\sum_{i=1}^N w_i}. \quad (17)$$

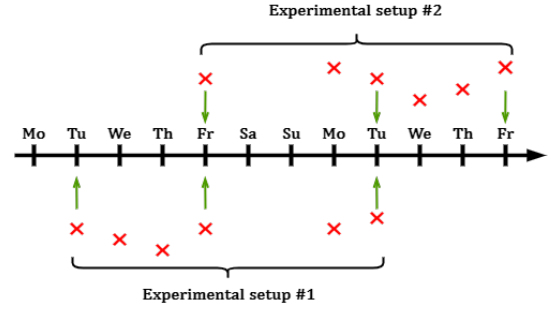


Fig. 1. The experimental setup with red crosses indicating tumor volume measurements and green arrows indicating injections.

We tried 8, 15 and 30 membership functions, we got the best result when we used 30 membership functions. The results detailed in Subsection IV-B. were obtained using 30 membership functions. We needed the same number of ANFIS as many parameters we have. So we trained 9 ANFIS.

III. TRAINING DATA

We generated training datasets for both the NN and ANFIS, the datasets consisted of 1000 variations for 100 different patients, i.e., 100000 training input-output pairs were generated. The parameters of the virtual patients are based on the results of the real animal experiments. We randomized these parameters in the ranges shown in Table I [29].

The trained experts will estimate the parameters using measurements from the last week, thus they can be used to track the changes of the parameters, handling inpatient variability and compensating the drawback of the identification algorithm based on mixed-effects. We will create experts based on NN and ANFIS, train them with the same data, and compare their performance.

There are two different measurement setups (Fig. 1.), the difference between the setups is in the start and end day of the estimation. In setup #1, the experts use measurements and injection doses from Tuesday to Tuesday, while in setup #2 the experts use measurements and injection doses from Friday to Friday. Tumor volume measurements are indicated with red crosses, while green arrows show the injections. Both experts have seven inputs: the five volume measurements and two injection doses [29].

The inputs of the NN and ANFIS are measurements of the total tumor volume and the injection doses. The measurements of the tumor volumes are done every day (except weekends). The initial conditions are different for all the patients. The living tumor volume at the time of the first treatment ($x_1(0)$) is a random number and the dead tumor volume at the same time is ($x_2(0)$) also a random number from the ranges shown in Table II. The initial values for x_3 and x_4 are considered to be zero. For both estimators, we prepare each training datasets with two experimental setups, but in this paper we will present those systems that learned with setup #1 (this experimental setup runs from Tuesday to Tuesday).

Parameter	a [day ⁻¹]	b [day ⁻¹]	n [day ⁻¹]	ED_{50} [ng · ml ⁻¹]	w [day ⁻¹]	c [day ⁻¹]	k_1 [day ⁻¹]	k_2 [day ⁻¹]
Minimum value	0.17888	0.09288	0.0036	0.0062	0.1126	0.1286	70.0957	0.5746
Maximum value	0.3990	0.64812	0.20784	0.1188	0.4147	12.8880	344.7991	4.9254

TABLE I

THE RANGES OF THE MODEL PARAMETERS FOR THE TUMOR DYNAMICS, PHARMACOKINETIC AND PHARMACODYNAMIC PARAMETERS

Parameter	$x_1(0)$ [mm ³]	$x_2(0)$ [mm ³]	dose [mg · kg ⁻¹]
Minimum value	100	10	0.2
Maximum value	1000	200	6

TABLE II

THE RANGES OF THE THE INITIAL CONDITIONS FOR THE LIVING ($x_1(0)$) AND DEAD ($x_2(0)$) TUMOR VOLUMES AND DOSE.

We generate noisy data to train and test the estimators. Since the tumor volumes in the real experiment are estimated from caliper measurements, we use a noise model tailored to this scenario. The width and the length of the tumor is measured during the experiments, and the volume is estimated using the formula

$$V = \frac{\pi}{2} (\text{width} \cdot \text{length})^{3/2}. \quad (18)$$

We add $\pm 10\%$ noise with uniform distribution to the measured length and width, and calculate the noisy virtual tumor volume measurement using (18) [29].

IV. TRAINING RESULTS

A. Estimated results for the NN

During the training, 70% of the 100000 training data was used for actual training, 15% for validation and 15% for test. We have also generated test data with 100 virtual patients and 10 different initial conditions for each patients, thus we used 1000 data to test the neural networks. The relative estimation errors are shown in Figs. 2-3. In these figures, the red horizontal curves show the median of the data, the blue rectangles show the range where the 25%-75% of the data are (thus, $\pm 25\%$ range around the median), the whiskers show data limit that are not considered as outliers, while the red crosses show the outliers.

Figure 2. shows the relative estimation errors in the range $\pm 50\%$ on training dataset. The percentages over the tumor dynamics parameters on the top of the figure show the how many of the total data from the dataset falls into this range. The results show that the parameters can be estimated within the 50% range for most of the data. If we want to highlight the parameters that are more difficult to estimate, these are the ED_{50} and n parameters with low sensitivity, according to [20]. These two parameters have lower percentages but still managed to give a good estimate of their initial value with NN on the training data.

The performance was also tested using the 1000 test data generated independently of the training data. These results are shown in Table III. The table shows the percentage of the total data that falls within the 50% error band for each parameter on both the training and test datasets. In the third row of the table, we indicated the estimation difference between the two

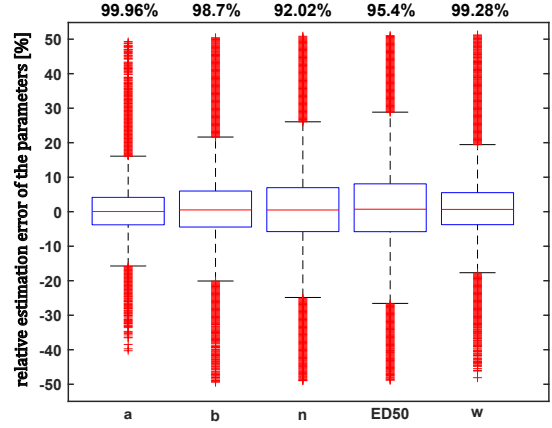


Fig. 2. The relative estimation error of the NN for the tumor dynamics parameters in the error range of $\pm 50\%$ on the training dataset, indicating the percentage of the samples in this range (on top of the figure for each parameter).

Parameter	Training Data	Test Data	Difference
a	99.96%	91.10%	-8.86%
b	98.70%	83.70%	-5.00%
n	92.02%	54.20%	-37.82%
ED_{50}	95.40%	49.60%	-45.80%
w	99.28%	81.10%	-18.18%

TABLE III

THE RELATIVE ESTIMATION ERROR OF THE NN FOR THE TUMOR DYNAMICS PARAMETERS IN THE ERROR RANGE OF $\pm 50\%$ ON THE TRAINING AND TEST DATASETS WITH THE PERCENTAGE OF THE SAMPLES IN THIS RANGE AND THE ESTIMATION DIFFERENCE BETWEEN THE TWO DATASETS.

datasets, i.e., the magnitude of the estimation deterioration on the test dataset compared to the training dataset. These results also show that it is difficult for the neural network to generalize to the values of the parameters that are hard to estimate (i.e., n , ED_{50}).

In order to estimate pharmacokinetic and pharmacodynamic parameters, we trained another neural network. Figure 3. shows the performance of this network on the training dataset. The relative estimation errors are shown for each pharmacokinetic and pharmacodynamic parameters in the error range of $\pm 50\%$. The percentage values show that the network could also learn these parameters efficiently. It can be seen that the value of the ED_{50} parameter can be estimated by both networks, whereas the network that estimates the tumor dynamic parameters can give a better estimation for the ED_{50} parameter.

We also examined the performance of this network on a test dataset and compared it with the results of the training dataset. The result is shown in Table IV. The results show that the estimation on the test dataset of the pharmacokinetic and

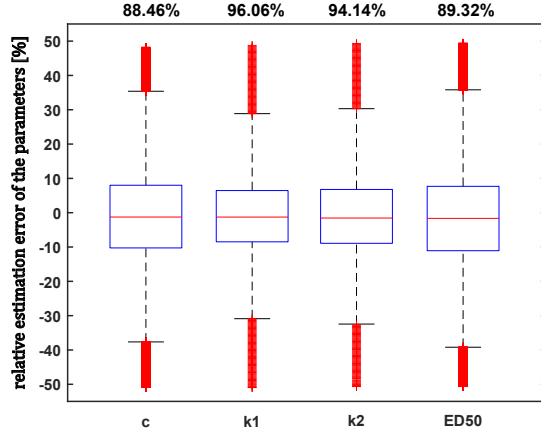


Fig. 3. The relative estimation error of the NN for the pharmacokinetic and pharmacodynamic parameters in the error range of $\pm 50\%$, indicating the percentage of the samples in this range (on top of the figure for each parameter).

Parameter	Training Data	Test Data	Difference
c	88.46%	52.70%	-35.76%
k_1	96.06%	60.80%	-35.26%
k_2	94.14%	53.00%	-41.14%
ED_{50}	89.32%	48.00%	-41.32%

TABLE IV

THE RELATIVE ESTIMATION ERROR OF THE NN FOR THE PHARMACOKINETIC AND PHARMACODYNAMIC PARAMETERS IN THE ERROR RANGE OF $\pm 50\%$ ON THE TRAINING AND TEST DATASET WITH THE PERCENTAGE OF THE SAMPLES IN THIS RANGE AND THE ESTIMATION DIFFERENCE BETWEEN THE TWO DATASETS.

pharmacodynamic parameters deteriorated to a greater extent than the estimation of the tumor dynamic parameters on the test dataset.

B. Estimated results for the ANFIS

We trained the ANFIS with the training dataset that includes 1000 variations for 100 different patients. After the training we tested the trained ANFIS on the training dataset and test dataset. We trained nine ANFIS because we had nine parameters which we had to estimate.

Figure 4. shows what percentage of errors fall within the $\pm 50\%$ error band when we estimated the tumor dynamics parameters. The higher percentage rates indicate better estimation. We can read from the statistic figure that the medians are near zero except for the parameter n . The n and ED_{50} parameters have the lowest percentage. The estimation of these parameters is difficult as mentioned in Subsection IV-A.

Table V. shows what percentage of the errors are in the $\pm 50\%$ error bar when we tested the ANFIS with training dataset and test datasets. According to the table, there is only a small difference between the two types of testing for parameters a, n, b , and w . The ED_{50} parameter estimation accuracy has 20% decrease when we tested the ANFIS with test data. For parameter a , almost all relative errors there are in the $\pm 50\%$ range.

We estimated the pharmacokinetic and pharmacodynamic parameters, the results are in Fig. 5., which shows that the

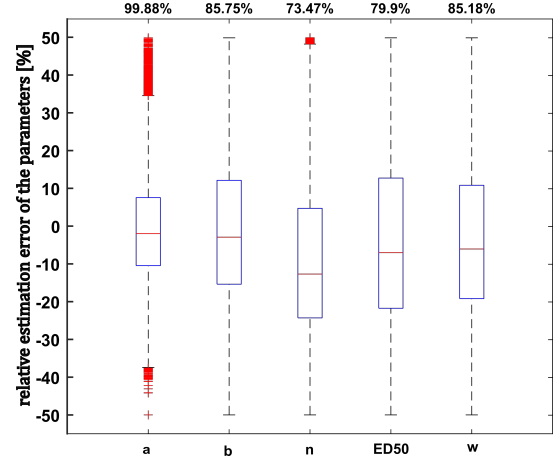


Fig. 4. The relative estimation error of the ANFIS for the tumor dynamics parameters in the error range of $\pm 50\%$ on the training dataset, indicating the percentage of the samples in this range (on top of the figure for each parameter).

Parameter	Training Data	Test Data	Difference
a	99.88%	99.90%	+0.02%
b	85.75%	83.27%	-2.48%
n	73.47%	64.86%	-8.61%
ED_{50}	79.90%	59.00%	-20.9%
w	85.18%	83.98%	-1.20%

TABLE V

THE RELATIVE ESTIMATION ERROR OF THE ANFIS FOR THE TUMOR DYNAMICS PARAMETERS IN THE ERROR RANGE OF $\pm 50\%$ ON THE TRAINING AND TEST DATASET WITH THE PERCENTAGE OF THE SAMPLES IN THIS RANGE AND THE ESTIMATION DIFFERENCE BETWEEN THE TWO DATASETS.

error medians under the zero. The relative error medians are located at around -10% . The worst estimation from these was the estimation of parameter c where 68.1% of the relative errors were in the $\pm 50\%$ error interval. In Table VI., we can see the two types of pharmacokinetic and pharmacodynamic estimator ANFIS tests, the test with training data and test with test data. Also we can see the difference between these two test data. The differences are lower than 20% and more than 50% of the relative estimation errors are in the $\pm 50\%$ interval. We estimated the ED_{50} parameter with tumor dynamics parameters and pharmacokinetic and pharmacodynamic parameters. The two estimations are almost equal so this does not influence the results.

C. Comparison of the two estimators

A comparison of the performance of the two estimators is shown in Table VII., containing training and test data for tumor dynamic parameters (a, b, n, w and ED_{50}) and pharmacokinetic and pharmacodynamic parameters (c, k_1, k_2 and ED_{50}). The difference between the two systems is also shown. Note, that the third and sixth columns show difference of the performance of the ANFIS and the NN, thus negative value means that the estimation with ANFIS was worse than the estimation with NN.

Based on Table VII., the performance of ANFIS on the training data was slightly worse compared to NN for all

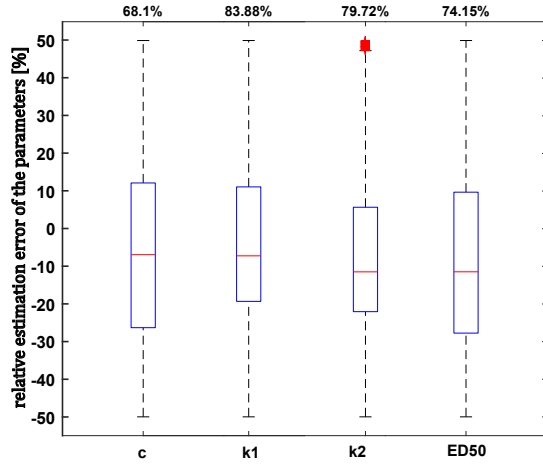


Fig. 5. The relative estimation error of the ANFIS for the pharmacokinetic and pharmacodynamic parameters in the error range of $\pm 50\%$, indicating the percentage of the samples in this range (on top of the figure for each parameter).

Parameter	Training Data	Test Data	Difference
c	68.10%	54.90%	-13.20%
k_1	83.88%	72.90%	-9.98%
k_2	79.72%	64.60%	-15.12%
ED_{50}	74.15%	60.80%	-13.35%

TABLE VI

THE RELATIVE ESTIMATION ERROR OF THE ANFIS FOR THE PHARMACOKINETIC AND PHARMACODYNAMIC PARAMETERS IN THE ERROR RANGE OF $\pm 50\%$ ON THE TRAINING AND TEST DATASET WITH THE PERCENTAGE OF THE SAMPLES IN THIS RANGE AND THE ESTIMATION DIFFERENCE BETWEEN THE TWO DATASETS.

parameters, but it nevertheless produced better results on the test data compared to NN. In the case of the tumor growth rate a , the performance is nearly the same in the training dataset. Here the difference between the two systems is only 0.08%. On the test dataset, ANFIS performs better for almost all parameters, with the exception of the necrotic rate n . The value of this parameter is better estimated by NN on the test dataset. So the ANFIS generalize better than the NN.

V. CONCLUSION

We trained two different estimators with given experimental setups with a large dataset acquired from in silico experiments. The datasets span a large set of realistic model parameters. The results show, that with the exception of a few cases, the systems are able to provide a reliable initial estimation of the parameter values that can be fine-tuned later by local search algorithms.

The NN performed better on the training data with performance over 90% for almost all cases. The performance of the ANFIS was worse on the training data, however, its generalization power is better. The analysis showed that both experts can be used to estimate the parameters.

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Parameter	Training dataset			Test dataset		
	NN	ANFIS	Difference	NN	ANFIS	Difference
a	99.96%	99.88%	-0.08%	91.10%	99.90%	+8.00%
b	98.70%	85.75%	-12.95%	54.20%	83.27%	+29.07%
n	92.02%	73.47%	-18.27%	83.70%	64.86%	-18.84%
w	99.28%	85.18%	-14.10%	81.10%	83.98%	+2.88%
ED_{50}	95.40%	79.90%	-15.50%	49.60%	59.00%	+9.40%
c	88.46%	68.10%	-20.36%	52.70%	54.90%	+2.20%
k_1	96.06%	83.88%	-12.18%	60.80%	72.90%	+12.10%
k_2	94.14%	79.72%	-14.42%	53.00%	64.6%	+11.60%
ED_{50}	89.32%	74.15%	-15.17%	48.00%	60.80%	+12.80%

TABLE VII

THE RELATIVE ESTIMATION ERROR OF NN AND ANFIS FOR TUMOR DYNAMICS PARAMETERS IN THE ERROR RANGE $\pm 50\%$ IN THE TRAINING DATASET (LEFT) AND TEST DATASET (RIGHT), THE PERCENTAGE OF SAMPLES IN THIS RANGE, AND THE DIFFERENCE IN THE ESTIMATION OF ANFIS COMPARED TO NN.

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