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An Artificial Neural network Model to predict the Activity data of ITK Inhibitors

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ABSTRACT

Interleukin-2 inducible T-cell kinase (ITK) is a tyrosine kinase expressed in T-cells, NK cells and mast cells. Experimental evidence suggests that inhibiting expression of ITK has prominent role in the treatment of asthma. In this study, we presented the efficacy of the artificial neural network (ANN) in predicting the activity data of ITK inhibitors. Apart from ANN, multiple linear regression model was also constructed. A Multilayer Perceptron MLP neural network trained back propagation was chosen for the bioactivity estimation problem. The sufficient number of hidden neurons and learning rate was estimated based on variation of RMSE. Therefore, the final neural network has six input variables with 8 hidden neurons and three nodes accounting for bias, a 0.55 learning rate with one output variable as output layer. To assess the robustness of neural network model, test set data was predicted and the accuracy was estimated. From the output of ANN it was evidenced and suggested that considering influential parameters such as Balaban index, logP, LUMO, HOMO, KC3 index and shape index on these set of ITK inhibitors enhanced biological activity.

Keywords: neural network, backpropagation, neurons, hidden layer.

1. INTRODUCTION

Artificial neural networks (ANNs) are one of the most powerful tools that have been widely employed in recent years in various fields such as sensors [1] measurement and control [2], and engineering [3] due to their computational speed, ability to handle complex non-linear functions. A neural network is a model characterized by an activation function, which is used by interconnected information processing units to transform input into output [4]. A neural network has always been compared to human nervous system. Information is passed through interconnected units analogous to information passage through neurons in humans. The first layer of the neural network receives the raw input, processes it and passes the processed information to the hidden layers. The hidden layer passes the information to the last layer, which produces the output [5]. A perceptron, viz. single layer neural network, is the most basic form of a neural network. A perceptron receives multidimensional input and processes it using a weighted summation and an activation function. A major limitation of perceptron model is its inability to deal with non-linearity. A multilayered neural network overcomes this limitation and helps solve non-linear problems. The input layer connects with hidden layer, which in turn connects to the output layer. The connections are weighted and weights are optimized using a learning rule [6].

Experimental evidence suggests that inhibiting expression of ITK has prominent role in the treatment of asthma [7]. The main aim of the work is to develop a neural network model to estimate the biological activity of ITK inhibitors as a way to assess predictive capability of the model by using specific influential physico-chemical variables versus experimental data. Of all the machine learning methods, neural networks and support vector machines deal with function approximation problems [8]. Several regression techniques have been applied and put forward to predict activity data of biologically relevant inhibitors against many protein targets. Although regression models trained on a machine learning concept appear simpler, it remains tough to control many parameters and understand the domain knowledge as the number of independent variables increases, which further increases dimensionality of the dataset. Therefore, it is essential to develop a lighter prediction model, such as an empirical approach [9]. Among the empirical approaches, the artificial neural networks (ANNs), in particular, multilayer perceptrons (MLP), were widely applied in the last decades in the fields of bioinformatics [10]. In this study, we evaluate the validity of neural networks for forecasting ITK inhibitor activity data.

2. MATERIALS AND METHODS

Neuralnet package is used to train neural networks using backpropagation, resilient backpropagation (RPROP) with [11] or without weight backtracking [12] or the modified globally convergent version (GRPROP) by Anastasiadis et al. [13]. The function allows flexible settings through custom-choice of error and activation function. Furthermore the calculation of generalized weights [14] is implemented. The possible algorithms in neural net are 'backprop', 'rprop+', 'rprop-', 'sag', or 'slr'. 'backprop' refers to backpropagation, 'rprop+' and 'rprop-' refer to the resilient backpropagation with and without weight backtracking, while 'sag' and 'slr' induce the usage of the modified globally convergent algorithm (grprop).The globally convergent algorithm is based on the resilient backpropagation without weight backtracking and additionally modifies one learning rate, either the learning rate associated with the smallest absolute gradient (sag) or the smallest learning rate (slr) itself.

2.1 Dataset

A set of 133 ITK inhibitor data from multivariate regression analysis outcome was selected as dataset in neural network analysis. The dataset was conveniently divided into training and test sets, given in Table-1, with bioactivity as dependent variable and six independent variables are selected such as, Balaban index, logP, LUMO, HOMO, KC3 index and shape index, respectively. These variables explain how the response variable is influenced by the change in property values.

Table 1: ITK inhibitor training and test set data.

Training Set

Activity	BALABAN	LOGP	LUMO	HOMO	KC3	SHAPE
-0.10607	1.26758	1.7469	-0.83198	-8.46474	3.39466	6.12690
-0.60264	1.09088	3.9511	-0.65749	-8.49199	3.50835	7.40238
0.011762	1.07498	3.5897	-0.58275	-8.45258	3.31011	7.16509
-0.00581	1.09088	3.8545	-0.49918	-8.33252	3.50835	7.96828
0.307417	1.07498	3.4931	-0.51726	-8.36368	3.31011	7.73093
-0.21542	1.27798	1.4997	-0.60697	-8.4041	3.10599	5.88807
0.071021	1.2752	1.908	-0.6324	-8.47381	3.10599	6.39383
-0.11919	1.27719	2.2694	-0.57413	-8.37499	3.51423	6.63225
0.300448	1.0553	3.6846	-0.6371	-8.47916	3.31011	7.67591
0.287611	1.07309	3.199	-0.50533	-8.37269	3.59878	8.15593
0.029969	1.25813	3.1322	-0.62515	-8.46272	3.39466	7.68693
-1.71238	1.08549	4.1983	-0.94919	-8.51629	3.79703	7.64039
-0.74179	1.07012	3.8369	-0.97376	-8.50695	3.59878	7.40238
-0.62054	1.08549	4.1017	-0.90497	-8.45064	3.79703	8.20638
-1.69808	1.28997	1.8975	-0.52544	-8.81458	2.13435	7.42828
-2.21908	1.28189	2.6058	-0.53495	-8.97438	2.13435	7.50228
-2.72048	1.27434	2.3531	-0.5249	-8.95243	2.33847	8.25666
-2.13636	1.2801	3.3976	-0.52906	-8.95976	2.42302	8.1119
-2.06593	1.2801	2.7453	-0.82046	-9.04527	2.42302	7.68087
-1.70939	1.28372	2.7453	-0.50005	-8.78236	2.42302	7.68087
-3.09565	1.2967	3.073	-0.17675	-8.93134	2.33947	7.73496
-1.4344	1.28997	0.874801	-0.95814	-9.09837	2.13435	7.38148
-1.49069	1.28189	1.7588	-0.46428	-8.70377	2.13435	7.76101
-3.65154	1.54713	1.7763	-0.53487	-8.9766	2.30102	6.94553
-2.25535	1.29945	2.9483	-0.21375	-8.8672	2.07798	8.05816
-2.53876	1.31015	3.3464	-0.77193	-9.0172	2.07798	8.41538
-1.64129	1.29716	3.7401	-0.88868	-9.03766	2.36666	8.67633
-2.10408	1.30775	4.1382	-0.93898	-9.03583	2.36666	9.03661
-2.16347	1.28189	2.7024	-0.56805	-8.73479	2.13435	6.91128

-2.03164	1.29681	2.144	-0.95517	-8.94298	2.01478	7.98461
-1.88687	1.30674	2.3905	-0.92366	-8.9407	2.29514	8.21582
-1.81604	1.28751	2.1492	-0.88734	-8.99535	2.13435	7.98461
-1.4609	1.28054	2.5455	-0.89697	-8.96169	2.13435	8.55479
-2.5088	1.2652	3.8503	-0.90043	-8.86662	1.7261	6.93611
-2.80119	1.12762	5.0675	-0.93322	-8.90224	1.93023	7.68592
-1.90875	1.2652	2.5961	-0.66216	-8.77583	1.7261	6.90508
-1.60784	1.27608	2.6482	-0.90693	-8.89762	1.7261	7.45743
-2.62081	1.27608	2.3007	-0.8565	-8.88731	1.7261	7.45743
-2.50794	1.28997	1.8975	-0.96046	-8.97064	2.13435	7.42828
-2.67356	1.52085	0.9858	-0.90684	-8.76119	1.41612	4.58915
-0.64103	1.28997	1.6134	-0.60404	-8.43434	2.13435	7.12725
-1.04978	1.28189	1.818	-0.6762	-8.51866	2.13435	7.76101
-0.855	1.28189	2.665	-0.49816	-8.42218	2.13435	7.50228
-0.67562	1.28372	3.4568	-0.71358	-8.47871	2.42302	8.1119
-0.1985	1.2801	3.4568	-0.7897	-8.48865	2.42302	8.1119
-0.28513	1.2801	3.183	-0.43036	-8.35614	2.42302	7.96142
-0.67908	1.28102	2.4123	-0.09543	-8.2552	2.33847	8.25666
-0.75826	1.27434	2.4123	-0.4087	-8.41383	2.33847	8.25666
-1.41247	1.28372	3.1322	-0.6359	-8.47246	2.42302	7.73496
-1.25874	1.28997	1.9567	-0.86522	-8.41884	2.13435	7.42828
-1.20835	1.2801	3.1322	-0.09647	-8.30285	2.42302	7.73496
-0.27655	1.28102	2.53	-0.65463	-8.46496	2.33847	7.88787
-0.27655	1.27434	2.53	-0.8457	-8.47154	2.33847	7.88787
-1.52238	1.27287	1.9735	-0.77731	-8.43864	2.63435	8.26046
-2.04998	1.18918	3.6717	-1.13856	-8.4535	1.98659	6.33283
-0.86463	1.25719	4.8791	-1.11953	-8.43565	1.93023	7.94663
-1.19106	1.25222	4.4273	-1.11724	-8.42493	2.23859	7.09057
-0.48202	1.12181	5.7	-1.12411	-8.46655	2.13435	8.14399
-1.67831	1.12308	5.4473	-1.13821	-8.45702	2.33847	8.88345
-0.87956	1.26589	3.559	-1.03258	-8.50194	1.93023	8.4804
-1.52473	1.26637	2.3487	-0.85795	-8.61768	2.33847	7.34606
-0.64144	1.28505	2.7765	-0.82453	-8.43437	2.2189	8.44328
-0.84567	1.29802	3.023	-1.10143	-8.53537	2.49926	8.67395
-1.50775	1.1242	3.4521	-1.02214	-8.46359	2.42302	8.90883
-0.43279	1.11075	3.5042	-1.11652	-8.46122	2.42302	9.45957
-0.43275	1.1326	2.4629	-1.10592	-8.54341	2.33259	9.2
-1.00015	1.13325	2.8243	-1.10753	-8.5407	2.62127	9.43237
-0.5323	1.29704	2.8725	-0.84435	-8.55392	2.28211	8.44328
-1.87563	1.32171	3.2856	-0.7875	-8.82661	2.59047	8.67395
-1.37774	1.52639	0.6545	-1.13808	-8.54863	2.31269	6.549
-2.12685	1.52843	1.2827	-1.31081	-8.60159	2.21506	7.10276
-1.97844	1.53574	1.8451	-0.77413	-8.44031	2.50514	7.33373
-1.29674	1.29037	1.3411	-1.12847	-8.53095	2.33847	6.30554
-0.551	1.28921	1.7374	-0.80488	-8.53199	2.33847	6.81842
-0.96992	1.27434	2.5674	-1.12666	-8.5531	2.33847	7.29772
-0.15162	1.27434	2.53	-0.77256	-8.43386	2.33847	7.88787
-0.35081	1.28189	1.818	-0.82922	-8.47782	2.13435	7.76101
-0.64201	1.28997	0.934001	-0.88141	-8.50452	2.13435	7.38148
-1.19391	1.2268	3.9775	-1.10931	-8.75121	1.90892	8.52657
-1.53333	1.47045	2.3295	-1.13417	-8.83484	1.70479	8.35404
-1.71778	1.18237	2.5134	-1.12838	-8.82231	1.90892	9.08199
-1.334	1.2392	4.7131	-0.69814	-8.67145	1.90304	8.61412
-0.96346	1.24157	4.0601	-0.94311	-8.71582	1.81848	8.52657
-1.30109	1.2455	2.4641	-0.95824	-8.76279	1.61436	8.02367
-1.19542	1.23926	3.3481	-0.66473	-8.72431	1.61436	8.42545
-1.32519	1.23509	4.0601	-1.11645	-8.72935	1.81848	8.52657
-1.27424	1.24361	3.0311	-0.76663	-8.56313	2.22673	7.91494
-1.17233	1.09096	4.511	-1.2464	-8.89489	2.02261	8.58563
-1.08033	1.22583	3.7818	-1.12105	-8.73857	1.81848	7.9504

-1.33639	1.09369	2.915	-1.10031	-8.91465	1.81849	8.0852
-1.27719	1.2209	2.1027	-0.98399	-8.81722	1.41612	7.80056
-0.08511	1.2209	2.1993	-0.89591	-8.33401	1.41612	7.15524
-1.80735	1.48362	2.1136	-1.13289	-8.80379	1.41612	6.96325
-1.30218	1.21296	3.6987	-1.12324	-8.81087	1.62024	8.30363
-1.32426	1.21296	3.7953	-1.18437	-8.36369	1.62024	7.66475
-1.90023	1.28189	3.1332	-0.38474	-8.44161	2.13435	6.91128
-2.71402	1.09412	4.8176	-0.47078	-8.43816	2.46768	7.90825
-3.08954	1.15343	4.1354	-0.51713	-8.44388	2.40652	7.07671
-1.66933	1.12184	4.1354	-0.59074	-8.43217	2.46768	7.07671
-1.41427	1.28997	2.4249	-0.50908	-8.43755	2.13435	6.8336
-1.40672	1.28997	2.6607	-0.39326	-8.3917	2.13435	6.8336
-2.18328	1.28997	1.7589	-0.69007	-8.5025	2.13435	7.0816
-1.76574	1.28997	1.5889	-0.76896	-8.53348	2.13435	7.0816
-2.28918	1.28997	1.9927	-0.78192	-8.66806	2.13435	6.78908
-1.86641	1.28997	1.4156	-0.60993	-8.54527	2.13435	6.78908
-1.89124	1.28997	1.2456	-0.68865	-8.53768	2.13435	6.78908
-1.63597	1.28997	1.4022	-0.9087	-8.69184	2.13435	6.78908
-0.82917	1.28648	2.5577	-0.69444	-8.50205	2.42302	7.28563
-0.89744	1.28648	2.8583	-0.74794	-8.51795	2.42302	7.43018
-0.83596	1.27657	1.4976	-0.96971	-8.57262	2.63435	7.58818
-1.48203	1.08094	3.4105	-0.94644	-8.56378	2.66013	8.34595
-1.87824	1.06848	3.7966	-0.61675	-8.44727	2.5426	8.3252
-1.28733	1.05073	3.8915	-0.4863	-8.43947	2.5426	8.86054
-1.31011	1.08925	3.8735	-0.71483	-8.4432	2.46768	7.83112
-0.99862	1.08925	3.4256	-0.84731	-8.47274	2.46768	8.07208
-0.76621	1.09992	3.0763	-0.99062	-8.50343	2.46768	7.99825
-0.73694	1.09436	2.2358	-0.91769	-8.43903	2.75636	8.20462
-0.01167	1.09992	1.9651	-0.91097	-8.5135	2.46768	7.7125
-1.6217	1.09992	2.4852	-0.38262	-8.23103	2.46768	7.85093
-1.59569	1.08925	1.817	-0.49858	-8.37667	2.46768	8.34746
-0.64318	1.09495	2.8915	-1.28495	-8.49203	2.60377	8.45603
-0.21163	1.09373	3.166	-1.03364	-8.53224	2.6728	8.25585
-0.93285	1.2801	3.6512	-0.58081	-8.49654	2.42302	7.36109
-0.89934	1.27434	2.9982	-0.83904	-8.57572	2.33847	7.29772
-1.90399	1.27434	2.8805	-0.40552	-8.41085	2.33847	7.65006
-1.13133	1.2801	3.925	-0.57696	-8.52532	2.42302	7.50475

Test Set

Activity	BALABAN	LOGP	LUMO	HOMO	KC3	SHAPE
-1.5733	1.27287	2.5594	-1.43531	-8.89371	2.63435	8.17491
-1.97552	1.28102	2.4708	-1.06036	-9.10845	2.33847	7.88787
-2.115	1.29775	3.1365	-0.71665	-8.91311	2.01478	8.55479
-0.85055	1.27904	2.0541	-1.01295	-8.62032	2.33847	7.21907
-1.01507	1.2689	2.6882	-0.94374	-8.55525	2.8268	8.3625
-0.61456	1.09992	2.733	-0.9535	-8.5341	2.46768	7.7125
-0.5013	1.09436	2.4481	-1.00614	-8.49699	2.75636	7.94854

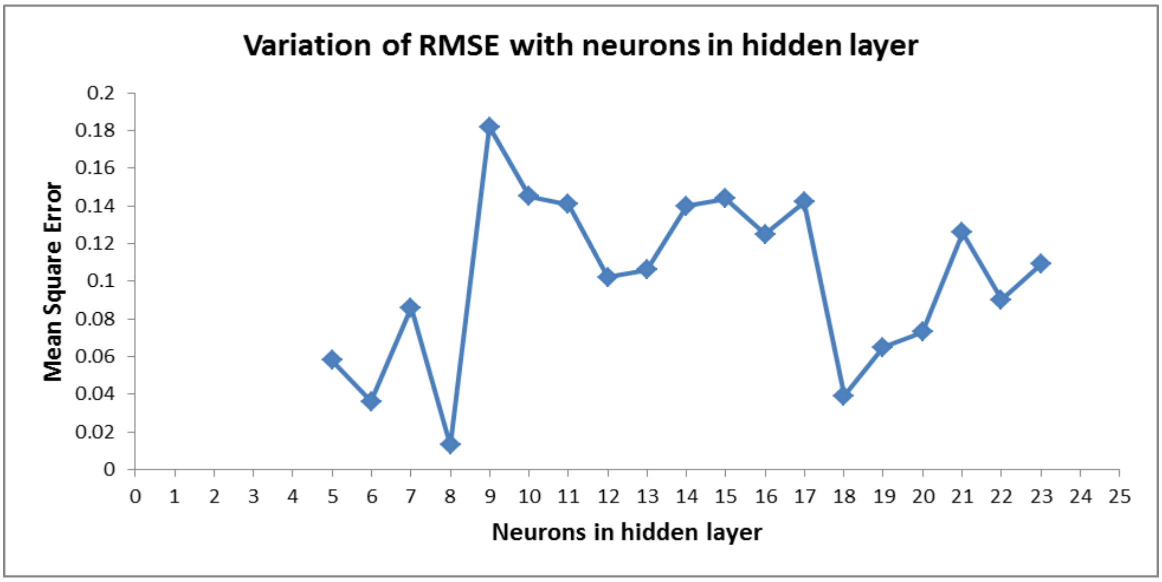
3. RESULTS AND DISCUSSION

The data was normalized using the min-max normalization where it transforms the data into a common range, thus removing the scaling effect from all the variables. Unlike Z-score normalization and median and MAD method, the min-max method retains the original distribution of the variables. The normalized data set comprising 133 data points against six variables (BALABAN, LOGP, LUMO, HOMO, KC3 and SHAPE) has been divided randomly into training (95%) and testing (5%) subsets. A Multilayer Perceptron MLP neural network trained backpropagation was chosen for the bioactivity estimation problem. The nonlinear association between input and output data for a given network necessitates a function that can appropriately relate all variables under study. Therefore, for the hidden neurons in a network, nonlinear transfer functions are required to introduce non-linearity into the network. It has been reported that an MLP network, with enough number of neurons satisfies the universal approximation property [15, 16].

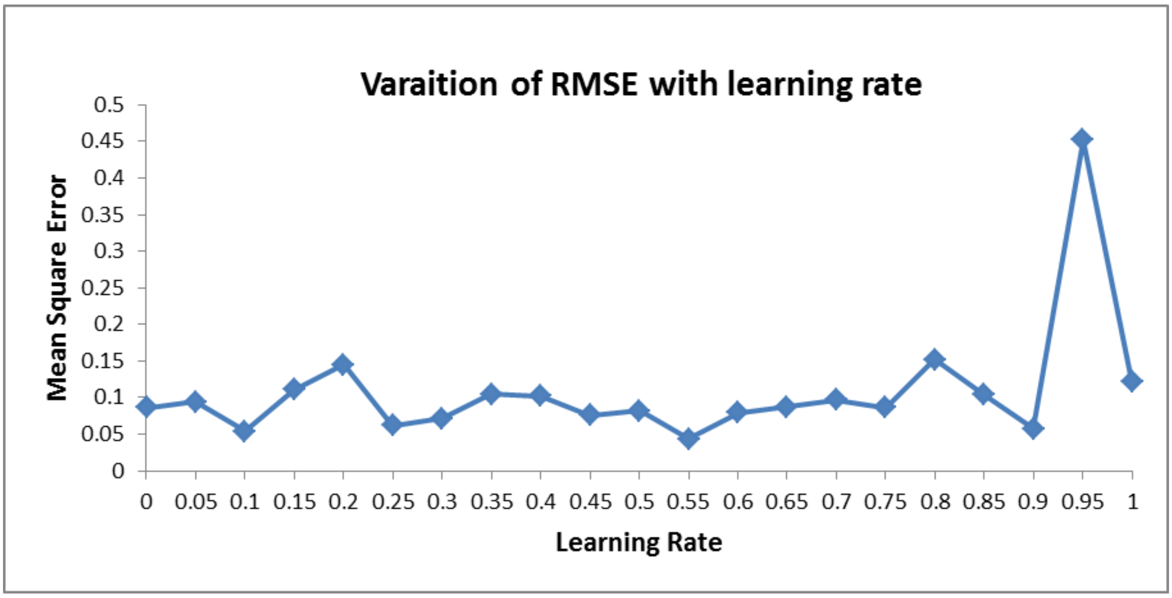
Several neural networks are available for function approximation problems. A Multilayer Perceptron MLP neural network trained with backpropagation was selected as it can efficiently learn large data sets when compared to Radial Basis Function (RBF) networks and Generalized Regression neural networks (GRNN) [17]. MLP was shown to be effective for function approximation problems and can efficiently establish a nonlinear relationship between groups of variables. As the backpropagation learning algorithm was more familiar, extensive research efforts have been made to accelerate its convergence because the basic algorithm is too slow for most practical applications. Several algorithms were put forward along with backpropagation such as resilient backpropagation with and without weight backtracking, globally convergent algorithm with the smallest absolute gradient (sag) or the smallest learning rate (slr). All these algorithms were tested on training set to achieve minimum RMSE to assess the performance of different training algorithms.

In certain cases, when a particular training algorithm could not achieve desired result on an MLP, it might be due to the convergence failure of the learning rule to reproduce values of the network parameters and the inability of a given network to implement the desired function, perhaps due to insufficient number of hidden neurons [18]. However, the required hidden neurons needed to approximate any given function has not been ascertained theoretically. If the hidden neurons are few then a high training error and high generalization error would result due to underfitting and high statistical bias. On the other hand, if the hidden neurons are much more than the variables, this might result in a low training error, but there would still be a high generalization error, due to overfitting and high variance [18]. In most situations, there is no way to determine the best number of hidden neurons without training several networks and estimating the generalization error of each [19, 15].

The neural network requires learning rate, number of nodes in a single hidden layer, and maximum number of training epochs [20]. In this work, the network growing technique [15, 19] is applied by varying hidden neurons sequentially from 5 to 23 and comparing the generalization (testing) RMSE error and the learning rate was varied from 0.01 to 1.0 in increments of 0.05 [21]. For each configuration, the mean square error (MSE) between the model output and the measured data was calculated. Figure1 illustrates the optimal number of neurons in the hidden layer and the optimal learning rate having the maximum model performance as indicated by MSE. The number of neurons in the hidden layer and the optimal learning rate were selected using a trial-and-error method.



A



B

Figure 1: Mean square error calculation between data and output from variation with the number of neurons in the hidden layer (A) and variation with the learning rate (B).

The criterion employed was to find the optimum number of hidden neurons which equals to the number when the testing RMSE decreases. As soon as the optimum number of hidden neurons attained, a neural network with that optimum number of hidden neurons is trained several times in order to determine the best learning parameters. Therefore, the final neural network has six input variables with 8 hidden neurons and three nodes accounting for bias, a 0.55 learning rate with one output variable as output layer (Figure 2).

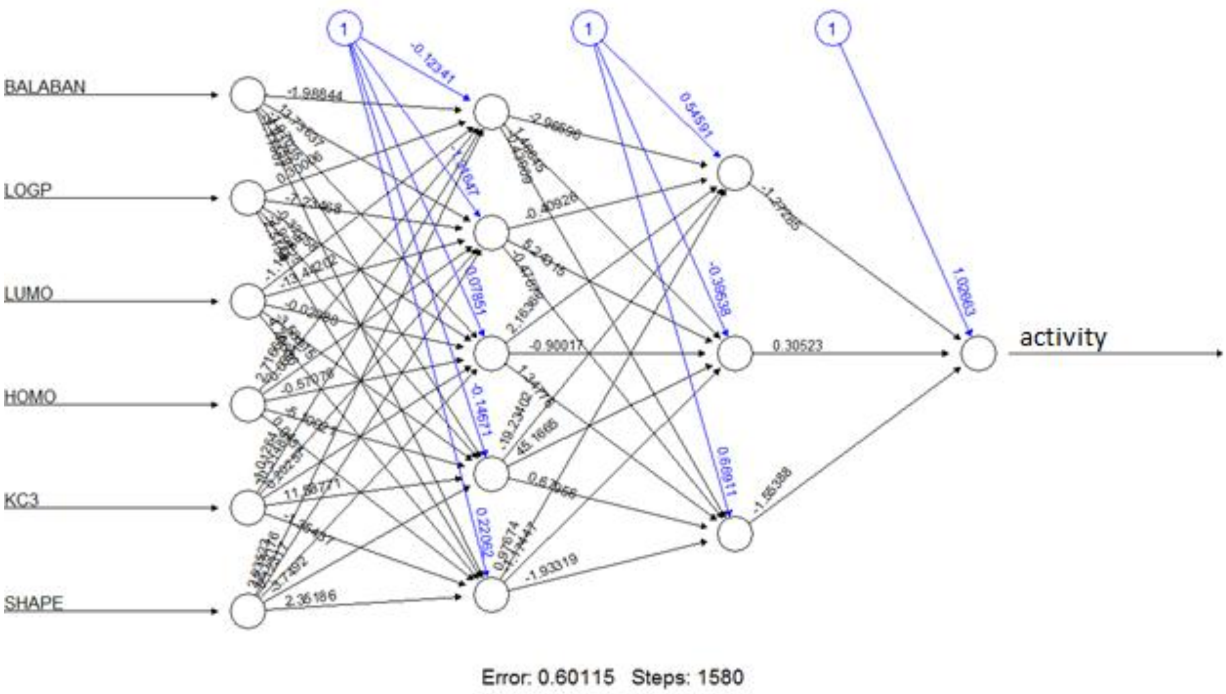


Figure 2: Presentation of neural network with backpropagation algorithm.

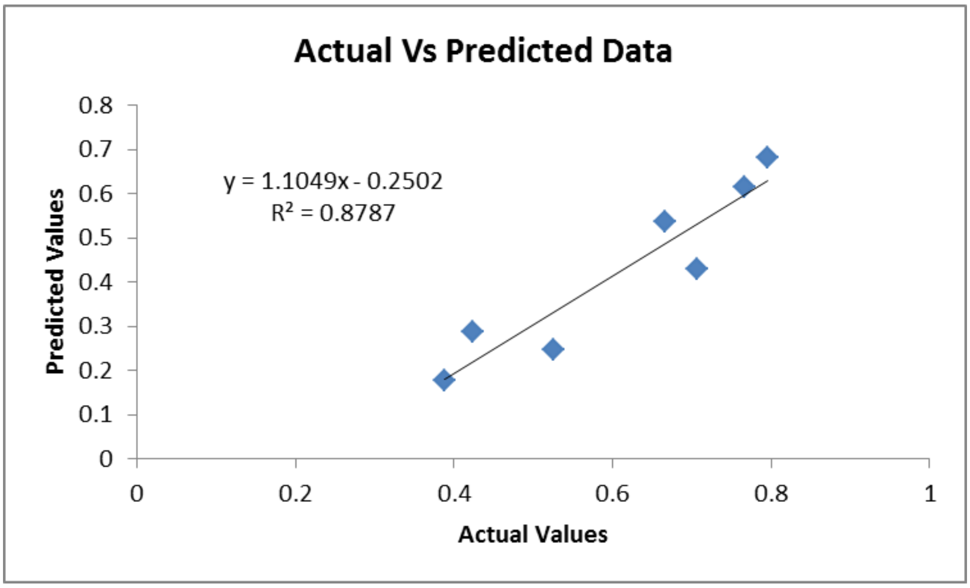


Figure 3: Prediction of test set data by neural network.

In order to assess the robustness of neural network model, test set data was predicted as the most significant property of a model should be its ability to generalize. Such generalization ability of the model indicates its power to perform well on test set data which was not used to train the model, however, overfitting prevents model generalization [22]. Therefore to avoid overfitting, the data set was randomly split into two sets, 95% data being set to train the model which computes the gradient and updates network parameters, such as weights and biases representing the training set and 5% data used to test the model. The weights were initialized at random and the model training procedure was stopped when the network tried to overfit the data, i.e. error on the dataset. From figure-3, it is evidenced that the model predicted test set with much reasonable accuracy (78% accuracy) with correlation coefficient being 0.8787 which justified the predictive ability of the neural network model.

In order to develop a robust neural network model, it should be noted that one has to consider the selection of the number of layers, the number of neurons in the hidden layer, the learning rates, and the number of epochs for model training. Hence, in this case, the number of hidden layers and learning rates were optimized based on mean square error calculation. Further, if insufficient number of neurons in the hidden layer is considered, then the model may not reflect nonlinearity. On the other hand, if too many neurons are selected, then the model might result in overfit which leads to lack of generalizability [23].

Further, a multivariate linear relationship analysis on training set resulted in low r2 value of 0.49 with better F-statistic and low p-values which suggests that the proposed model estimates the activity with low accuracy than neural net model, however, it has better predictive ability on the test set. A cross-validated mean square error plot given in Figure 4 represented 0.24 as error. A subset of training set has been plotted to study the variation of RMSE with length of the training set, given in Figure 5 displays that RMSE values are below 0.3 respectively.

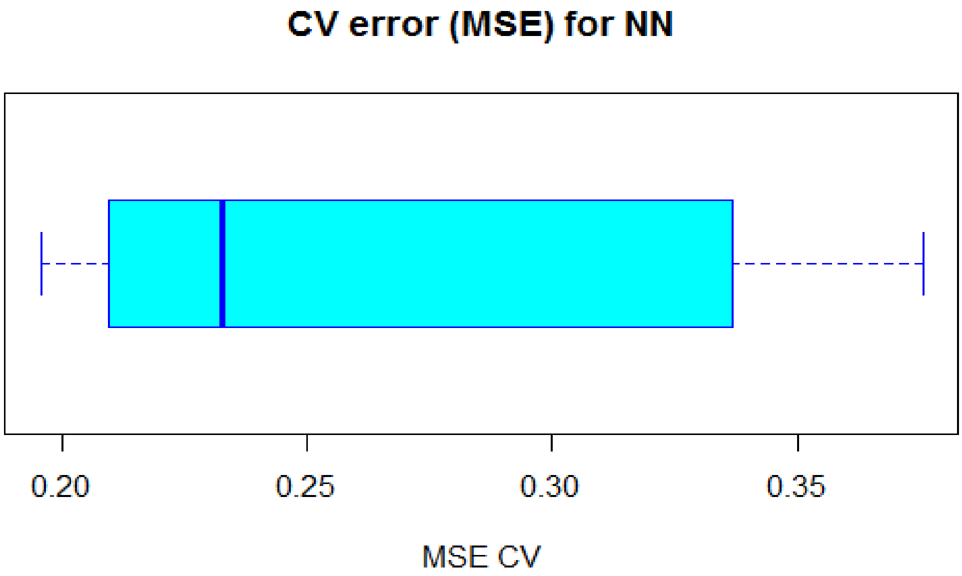


Figure 4: Cross-validated mean square error of the dataset.

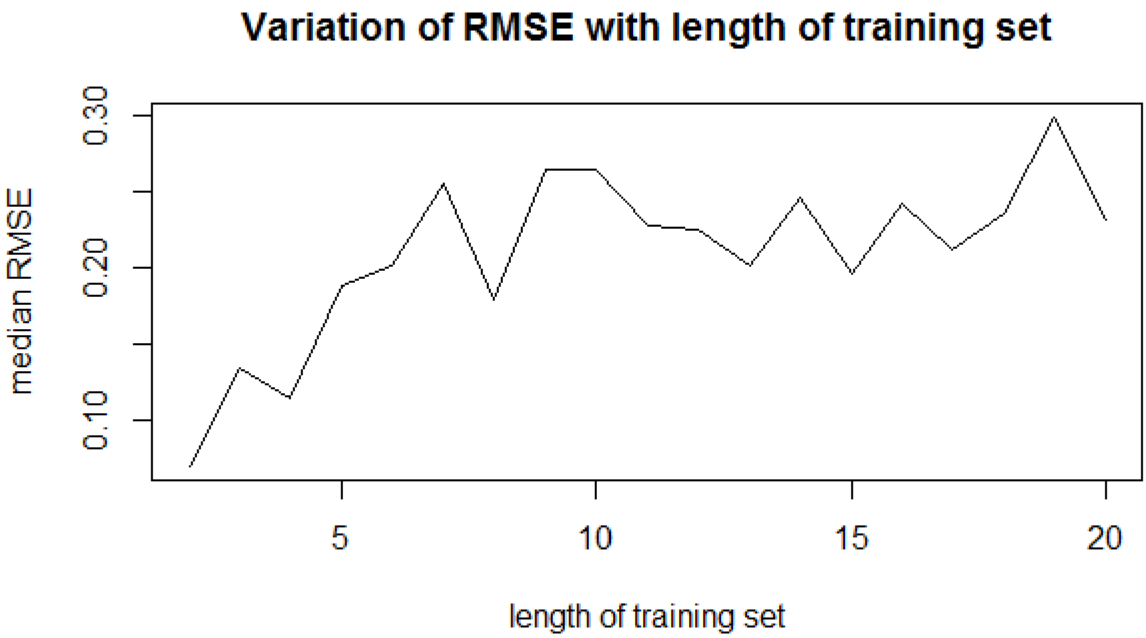


Figure 5: Variation of RMSE with length of the training set.

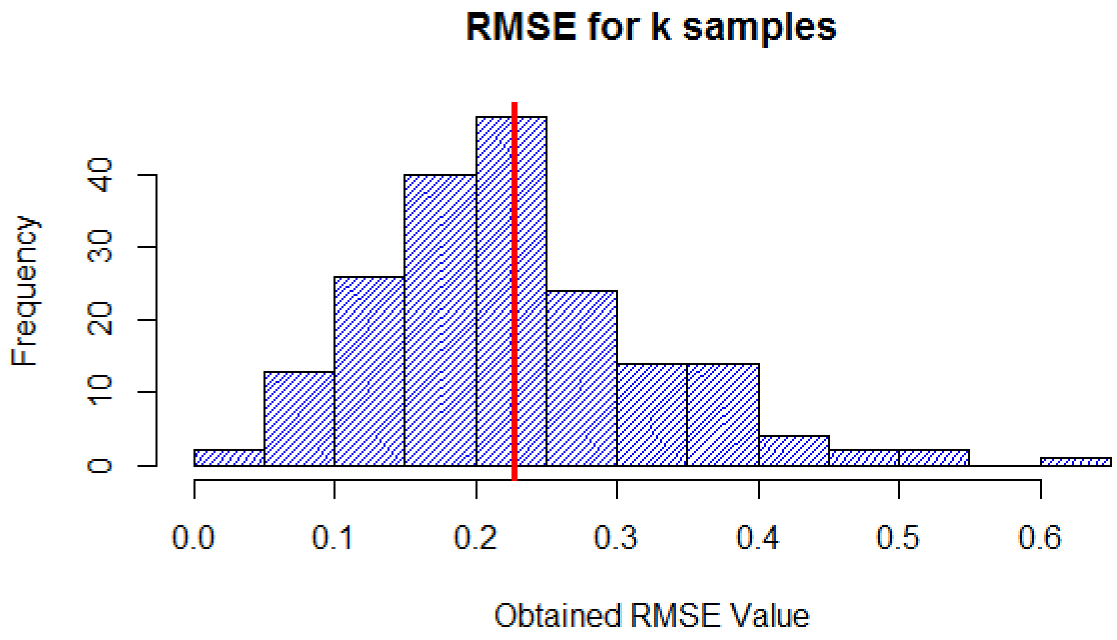


Figure 6: Obtained RMSE values for k sample size.

The histogram given in figure 6 highlights the average RMSE (vertical red line) across k different samples and displays the RMSE spread of the dataset. The RMSE of the activity variable obtained range from zero to 0.6. These represent relatively low RMSE values.

4. CONCLUSION

In summary, both neural network and linear regression models provided reasonable accuracy of their respective models for training and test set data of ITK inhibitors used in this study. A network growing technique implemented here suggested 8 neurons in hidden layer and learning rate being 0.55 based on mean square error calculation. Further, the neural network model predicted test set with 78% accuracy and 0.8787 as correlation coefficient justified the predictive activity data by considering logP and indices such as Balaban, KC3 and Shape index, as well as LUMO and HOMO as molecular orbital features explained biological activity of ITK inhibitors. Therefore, it has been suggested from the investigational work that considering these variable features on a set of ITK inhibitors would increase positive hits in achieving better inhibition against ITK.

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