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On the application of artificial intelligence in acute myeloid leukemia therapy

Jie Meng[1], Ruilan Zhong[1], Zhiqiang Wu[2] and Min Dong*[1]

[1]*Department of Hematology, The Second Affiliated Hospital of Hainan Medical University, Haikou 570000, China*
[2]*Department of Electrical Engineering, Wright State University, Dayton 45435, USA*

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Abstract. This study is a randomized pretest-posttest design that aims to investigate the effect of early entrepreneurship education on cognitive and non- early entrepreneurship education, non-cognitive skills, creativity, self-efficacy, Bizworld cognitive skills of male sixth-grade primary school students. A total of 45 students were selected by multi-stage random sampling method and were assigned randomly to experimental, active-control and control groups. The experimental group received entrepreneurship education based on the Bizworld entrepreneurship program. The results indicate that early entrepreneurship education had an effect on non-cognitive skills (such as risk taking propensity, creativity, self-efficacy, persistence and need for achievement. It seems that early entrepreneurship education is a proper strategy to develop children's non-cognitive skills in late years of primary school. These skills will affect children's individual, educational, social and occupational future and can have long term benefits for students, families and society.
Keywords: Bizworld; creativity; early entrepreneurship education; non-cognitive skills; self-efficacy

1. Introduction

Acute myeloid leukemia (AML) is a common acute leukemia in adults between 50-60 years old. This type of cancer rapidly developed if it is not treated in the early stages of the cancer. It is a result of making immature blood cells which are unable to become healthy cells (Dai and Safarpour 2021, Forsat *et al*. 2021, Ghamkhar *et al*. 2021, Khadimallah *et al*. 2021a, b, Kumar *et al*. 2021, Madenci 2021, Tlidji *et al*. 2021). Over time, this cells build up in the marrow and replace the healthy blood cells in the blood stream. Usually, if the count of immature leukemia cells become more than 20% percent of total counts of the cell it is regarded as AML and have to be treated as soon as possible (Yan *et al*. 2020, Lv *et al*. 2021, Wang *et al*. 2022a, Zhao *et al*. 2022). The acute term in AML refers to the rapid developing of the disease. Therefore, in the case of this cancer, and other cancers in general, rapid decision making for type, combination and dosage of drug treatment is vital. Studies on the application of artificial intelligence methods in cancer drug combination and therapy suggestions indicated that using these methods could effectually reduce the time and decision making. In recent years, great attention has put on the design and development of AI methods based on the previous dataset and experts' commands (Habibi *et al*. 2016, 2018a, b, c, d, e, Ebrahimi *et al*. 2019a, Esmailpoor Hajilak *et al*. 2019, Pourjabari *et al*. 2019, Safarpour *et al*. 2019a).

Two AI models were successfully employed to predict cancer relapse in the work by (Catto *et al*. 2003). They utilized three methods of linear regression, artificial neural network (ANN) and neuro-fuzzy modeling (NFM) in 109 patients with bladder cancer (Habibi *et al*. 2017, 2019a, c, Safarpour *et al*. 2018, b, 2020, Alipour *et al*. 2020, Ebrahimi *et al*. 2020a, Ghazanfari *et al*. 2020, Chen *et al*. 2022). Moreover, the clinicopathological data and molecular biomarkers were utilized as input data in their neural networks. The output of the neural networks was the possibility of relapse and the time of occurring relapse. They concluded that in addition to transparency, the presented results by NFM were superior to ANN and statistical methods (Ebrahimi *et al*. 2019b, c, Hashemi *et al*. 2019, Moayedi *et al*. 2019, 2020a, b, Mohammadgholiha *et al*. 2019, Mohammadi *et al*. 2019, Ebrahimi *et al*. 2020b, Habibi *et al*. 2020, Oyarhossein *et al*. 2020, Shariati *et al*. 2020a, b, Shokrgozar *et al*. 2020). Hirasawa *et al*. (2018) employed convolutional neural networks (CNN) (Hamidian *et al*. 2011, Shariati 2008, 2011c, Shah *et al*. 2015, 2016a, b, Khanouki *et al*. 2016, Toghroli *et al*. 2017, 2020, Shariati *et al*. 2018, Toghroli *et al*. 2018, Chen *et al*. 2019, Li *et al*. 2019, Shariati *et al*. 2019b, 2020d, Naghipour *et al*. 2020, Razavian *et al*. 2020, Hosseini and Toghroli 2021, Mehrabi *et al*. 2021) to detect gastric cancer from endoscopic images. In total, ~13000 images were used to train the CNN model and ~2200 images were employed to test the trained network. The outcome of the study showed the satisfactory efficacy in term of processing time and accuracy. The network specifically detected the invasive cancer satisfactorily. Rashid *et al*. (2018) utilized quadratic modeling to optimize cancer drug combinations to minimize overall toxicity. They considered only biological effects of the drugs and no molecular mechanisms and synergy data were included in the influencing factors. They found that using this model the treatment efficacy with suggested drug combinations were improved. Tsigelny (2018) reviewed several articles on the application of artificial intelligence algorithm in drug combination

*Corresponding author, Ph.D.,
E-mail: dm1175@sina.com

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procedure. The types of drugs and their dosage for different diseases were carefully addressed. It was showed that experts' rule-based approach and AI systems together could be a promising method in determination of drug combination. On the cancer diseases, Bi *et al*. (2019) reviewed application of AI methods in four common types of cancers. They collected articles of AI-based image processing to detect lung, breast, prostate and brain cancers. They also listed some limitations and challenges in the way of widespread utilization of AI methods in cancer detection. For an account, they argued about lacking of easy accessible reliable data to train the AI networks. Moreover, the ethical and legal issues in front of AI method in healthcare systems were revealed and discussed.

Diagnosis of skin cancer using combination of human and CNN methods were proven to have superior capability in comparison to other methods (2019). In this study, a vast image dataset labeled with 5 cancer level categories were utilized to train a CNN. Afterward, 300 additional images were examined by two expert groups and trained CNN. It was shown that using combination of human and AI-based method, more reliable and accurate results could be obtained. Rodríguez-Ruiz *et al*. (2019) used a pre-trained AI system to aid experts in breast cancer detection. It was observed that using the AI system along with radiologist's decisions provided more accurate results with insignificant change in reading time. Ho provided insight into the future applications and potential of AI in the cancer therapy (2020). Ström *et al*. (2020) trained an AI network to identify prostate cancer and its grades based on ~6600 image of needle biopsies. The trained AI network was capable of detecting prostate cancer with high accuracy comparable to expert's detections. It is extremely important since the large quantity of biopsy images with lack of urological pathologists necessitate reliable computer aiding software. Ryu *et al*. (2019) designed a deep neural network for prostate grading on the basis of Gleason's grading system. The network used near 1100 biopsy samples for training purpose and 700 samples for the validation process. The trained network showed high level of reliability in diagnosis and grading prostate cancer in comparison to expert's decisions. The trained network was further employed in an independent study by Jung *et al*. (2022) which confirmed the results of the original study (Hirasawa *et al*. 2018, Hekler *et al*. 2019, Horie *et al*. 2019, Patel *et al*. 2019, Ryu *et al*. 2019).

Artificial intelligence modeling itself divided in many sections with their respective capabilities. A type of neural network is the neuro-fuzzy networks which the layering pattern of the network and its mathematical relations and connectivity is completely transparent (Jang 1993). Using this type of network considerably reduces the effort to reach a solution and decision which takes extreme time and efforts in other methods (Zhang *et al*. 2012, Jiang *et al*. 2017, Rezkalla *et al*. 2017, Massoumi *et al*. 2018, Tsigelny 2018, Amelirad and Assempour 2019, 2021, Bi *et al*. 2019, Goldenberg *et al*. 2019, Patel *et al*. 2019, Rodríguez-Ruiz *et al*. 2019, Adir *et al*. 2020, Jin *et al*. 2020, Liang *et al*. 2020, Moradi *et al*. 2022). Besides, this type of network utilized fuzzy logic inside its layers which makes decision making more flexible. The vast employment of this networks in engineering healthcare predictions beside its transparency and accuracy makes one of the chief candidates of neural networks to investigate different problems (Catto *et al*. 2003, Abbod *et al*. 2007, Kantarjian and Yu 2015, Jiang *et al*. 2017).

AML cancer has received limited attention in the field of artificial intelligence. In the present study, we address an important potential application of the artificial intelligence method in tackling of acute myeloid leukemia (AML). In this regard, a detailed survey of employing artificial intelligence methods in the cancer diagnosis, therapy and solidification stage is presented. Afterwards, using databases of approved cancer drugs and their efficacy an adaptive neuro-fuzzy inference system (ANFIS) is trained and used for further prediction of the effects of drugs on the treatments of the AML cancer. Furthermore, nano-medicines made from these approved drugs are considered and discussed their potentials in AML cancer therapy. Using the available data on cancer drugs, a response surface method using quadratic equations is also designed for the purpose of combination optimization.

2. Materials and method

In this section, the methodologies in designing drug combination based on the both biological of the approved cancer drugs. In this regard, two methods of study for different purposes are employed here. First, the optimized drug combination condition is deduced using response surface method (RSM) and models for accurate prediction of drug combination is constructed using artificial intelligence (AI) methods. In the following both of this methods have been briefly introduced.

2.1 Response surface method (RSM)

Response surface method is a method of optimization processes based on fitting data using polynomial equations. The method is based on the data acquired from a set of experiments to obtain optimized condition for required outputs Adamian *et al*. 2020, Al-Furjan *et al*. 2020a, b, Li *et al*. 2020b, Liu *et al*. 2020a, b, Wang *et al*. 2020, Zare *et al*. 2020, Zhou *et al*. 2020, Dai *et al*. 2021a, b, Guo *et al*. 2021a, Habibi *et al*. 2021, He *et al*. 2021, Huang *et al*. 2021a, Liu *et al*. 2021b, Shao *et al*. 2021, Wu and Habibi 2021, Zhang *et al*. 2021). The inputs of this method could be from one factor to several factors. Also, the output could be one or more. In this method, the dependency of the output parameters on the input factors is commonly regarded to be quadratic. Since, the quadratic model is obtained using fitting data methods, it is expected that this method provides approximate values of the output data. However, the method could successfully give the behavior in behavior in outputs with respect to change in inputs and importance of each input factors.

In this study, the input factors are biological effect of each cancer drug which could be accessible from (Rashid *et al*. 2018). This valuable database presents effects of 5

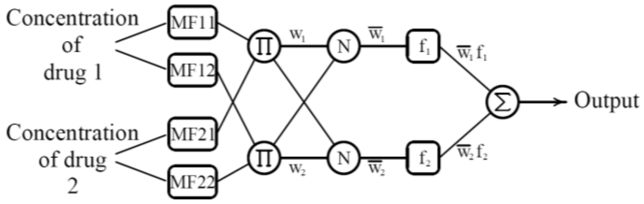

Fig. 1 Schematic of ANFIS network

selected drugs on the viability of the cells. In this regard, dependency of the IC_{50} on the concentration of each drug and their selected combination is modeled using quadratic model. This model is further utilized to find the optimum drug combination to IC_{50} to be maximize.

2.2 Artificial intelligence method

The RSM described in the previous section is indeed a rough approximation of the dependency of viability of AML cancer cell on the concentration of cancer nano-drugs. The AI-based modeling, however, provides more accurate output data using its advanced regression ability which enables it to follow highly nonlinear behaviors. In this section, a neuro-fuzzy system in Matlab software is designed based on the 75 sets of data acquired from the results of (Rashid *et al*. 2018). This dataset divide into 51 sets to train the ANFIS model in the Matlab (Ma *et al*. 2021, Zhao *et al*. 2021, Hou *et al*. 2021, Huang *et al*. 2021b, c, Jiao *et al*. 2021, Liu *et al*. 2021c, Moradi *et al*. 2021, Xu *et al*. 2021, Dong *et al*. 2022, Luo *et al*. 2022, Michael *et al*. 2022, Wang *et al*. 2022b, Yang *et al*. 2022, Yu *et al*. 2022) and 12 sets to validate the results. The other remaining 12 sets are employed for the purpose of testing. The ANFIS model utilized trapezoidal membership function (MF) in the fuzzification stage. For each input, i.e., individual drug concentrations, 3 level of concentration is assigned (Hashemi *et al*. 2019, Al-Furjan *et al*. 2020c, d, e, f, Bai *et al*. 2020, Cheshmeh *et al*. 2020, Li *et al*. 2020a, Lori *et al*. 2020, Najaafi *et al*. 2020, Shariati *et al*. 2020c, Xiong *et al*. 2020, Guo *et al*. 2021b, Liu *et al*. 2021a).

Training the model is performed using gradient decent back-propagation method to minimize mean square error between predicted results and actual provided data. The mean square error (MSE) is defined as (Arabnejad Khanouki *et al*. 2010, Mojtaba 2011, Shariati *et al*. 2011a, b, 2019a, c, d, e, f, 2020e, f, g, h, i, 2021, Sinaei *et al*. 2011, 2012, Mohammadhassani *et al*. 2013, 2014, Toghroli *et al*. 2014, 2016, Mansouri *et al*. 2016, Safa *et al*. 2016, Shahabi *et al*. 2016, Khorramian *et al*. 2017, Nosrati *et al*. 2018, Sadeghipour Chahnasir *et al*. 2018, Sedghi *et al*. 2018, Ziaei-Nia *et al*. 2018, Katebi *et al*. 2019, Milovancevic *et al*. 2019, Sajedi and Shariati 2019, Trung *et al*. 2019a, b, Afshar *et al*. 2020, Safa *et al*. 2020, Yazdani *et al*. 2020, Davoodnabi *et al*. 2021):

$$MSE = \frac{1}{n}\sum_{i=1}^{n}\left(\widehat{IC_{50}} - IC_{50}\right)^2 \qquad (1)$$

where $\widehat{IC_{50}}$ is the value predicted by the ANFIS. The back-propagation tuning the constants of the ANFIS in different layers to minimize MSE. One more merit of ANFIS network is the exact definition of each neuron and layers and their connectivity in the network which enables the user to change single parameters and see its influence on the values on each neuron in the calculating process. An schematic of the designed ANFIS is shown in Fig. 1.

Table 1 Analysis of variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Model	14	9.0669	0.647639	20.52	0
Linear	6	1.1199	0.186656	5.91	0
concentration	1	0.1512	0.151193	4.79	0.033
Bort	1	0.2956	0.295552	9.36	0.003
Dac	1	0.2957	0.295673	9.37	0.003
Dec	1	0.295	0.295044	9.35	0.003
Mech	1	0.2949	0.294892	9.34	0.003
MitoC	1	0.2953	0.295287	9.35	0.003
Square	3	0.8444	0.28148	8.92	0
concentration* concentration	1	0.0025	0.002466	0.08	0.781
Bort*Bort	1	0.1657	0.165664	5.25	0.025
Dec*Dec	1	0.6611	0.661133	20.94	0
2-Way Interaction	5	0.3866	0.07733	2.45	0.044
concentration*Bort	1	0.1514	0.151449	4.8	0.032
concentration*Dac	1	0.1515	0.151542	4.8	0.032
concentration*Dec	1	0.1518	0.151836	4.81	0.032
concentration*Mech	1	0.1517	0.151688	4.81	0.032
concentration*MitoC	1	0.1515	0.15154	4.8	0.032
Error	60	1.894	0.031567		
Total	74	10.9609			

3. Results

3.1 Optimized drug combination using RSM

Modeling of the behavior of AML cancer cell dependency on the nano-medicine concentration using RSM is conducted and the results of the statistical information of analysis of variance is presented in Table 1. The last column of this table devoted to the p-value which indicates the importance of each parameter. Lower p-values for a factor shows that that factor is more important than a factor with higher p-value. I this table it is seen that the square of Dec drug concentration is the most effective factor on the IC_{50}.

The residual plots as provided by RSM software is depicted in Fig. 2 It is seen that the difference between actual and predicted IC_{50}. It could be observed that the values of the residuals are small keeping in mind that the quadratic fitting is just a rough approximation of the actual value.

The Pareto graph for this RSM analysis is depicted in

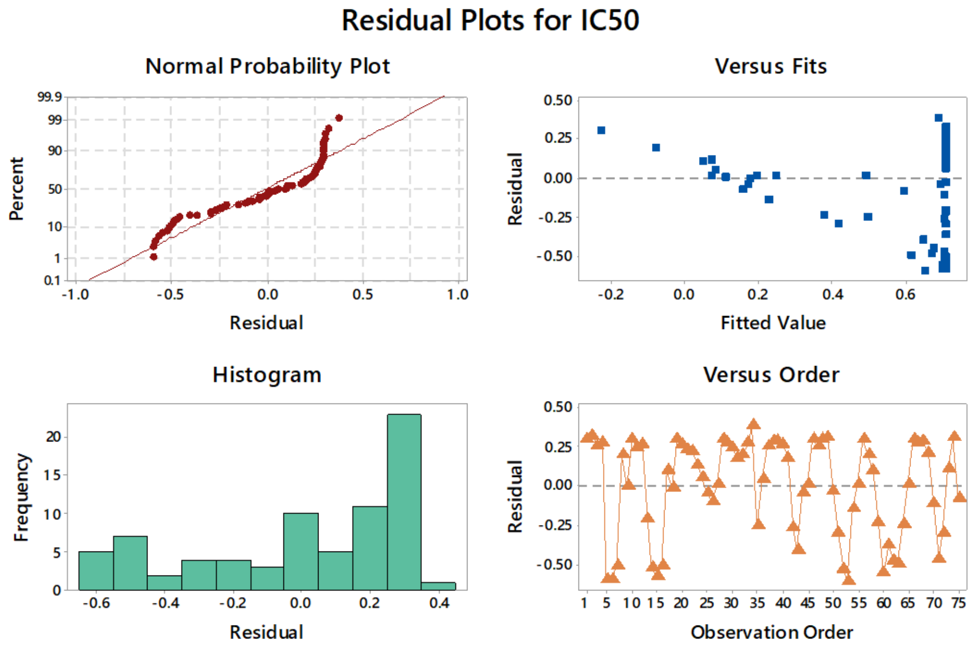

Fig. 2 Residuals of the RSM analysis

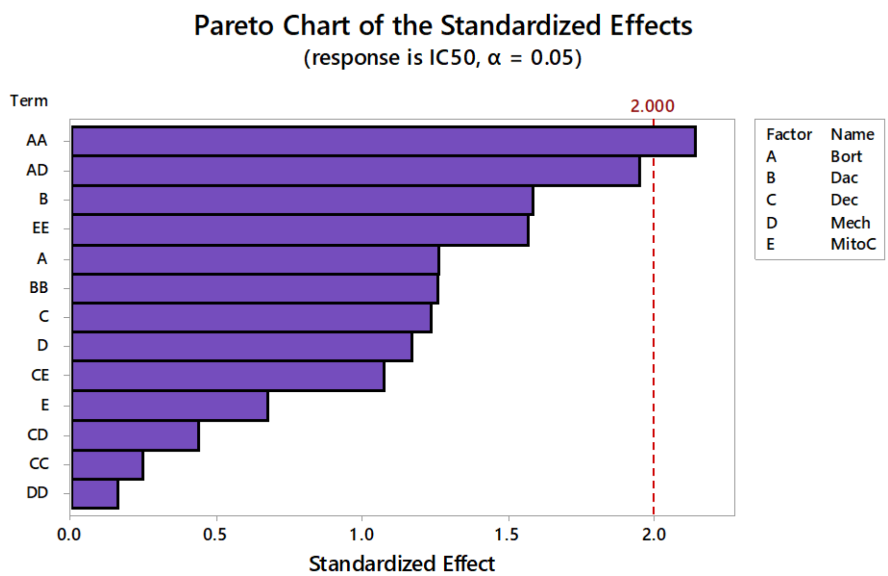

Fig. 3 Pareto graph of the RSM analysis

Fig. 3. In the present context, this type of chart is used to show the most effective factors on the output. In the case of the AML nano-drug influence and combination on the therapy of patients, it can be deduced that Bort inhibitor is the most effective drug and combinations of Bort and Mech follows. The less effective drug on the AML would be Mech individually or Dec individually. Thus, it can be deduced even when a single drug could not be effective its combination with other drugs produces highly effective treatment.

The three-drug combinations of the considered drugs is presented in the Figs. 4-6. In Fig. 4, combination of Bort/Dac/MitoC is depicted as calculated by RSM. It is seen that high concentration of both Bort and Dac in every concentration of the MitoC produces the favorable results. On the other hand, very low concentration of MitoC results in the highest results of IC_{50}. Therefore, combination of MitoC with Bort and Dac leads to negative effects on the treatment on AML cancer.

Fig. 5 presents combination of Bort/Dac/Mech effect on the IC_{50}. Similar to Fig. 4, in this figure it is also observed that high concentration of both Bort and Dac provides best results of this three drug. However, Bort and Mech drugs seemed to have concordance effects in term of increasing the concentration of Bort increase the effect of Mech and in low concentration of Bort, Mech inhibitor provided unsatisfactory effects. Thus, it is recommended that this two drugs to be administered together and at the same time.

The effect of combination of Dec with Bort/Dac is depicted in Fig. 6. It is seen that adding Dec to the

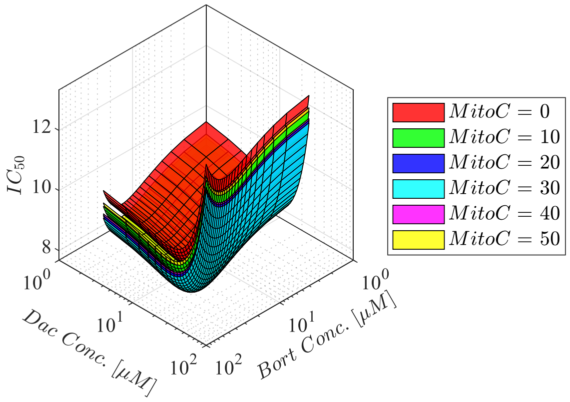

Fig. 4 Effect of combination of Bort/Dac/MitoC on the IC_{50}

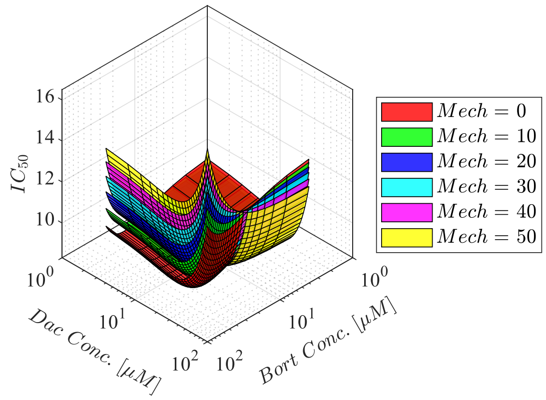

Fig. 5 Effect of combination of Bort/Dac/Mech on the IC_{50}

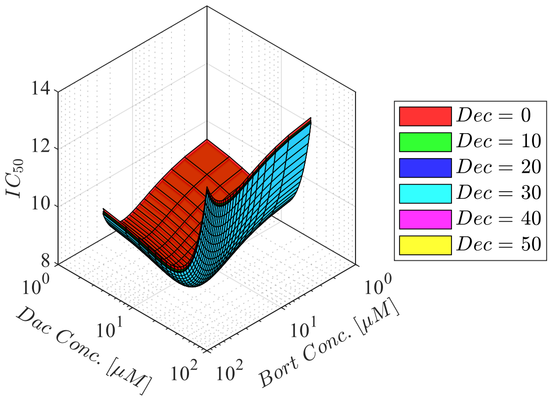

Fig. 6 Effect of combination of Bort/Dac/Dec on the IC_{50}

combination of Bort/Dac has a slight and negligible influence on the efficacy of the drug. Therefore, using Dec with Bort/Dac is not recommended since it has no effect on the effectiveness of the combination.

3.2 Predicted results using trained ANFIS

The ANFIS modeling could be regarded as a complementary modeling to RSM. The ANFIS modeling is flexible and could follow the high nonlinearity behavior in the effects of the results. After modeling Matlab, the

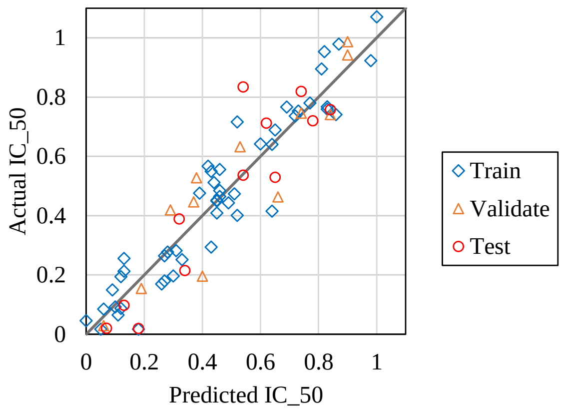

Fig. 6 Effect of combination of Bort/Dac/Dec on the IC_{50}

predicted IC_{50} and the provided values are compared together using a correlation factor. The correlation factors between the predicted values by ANFIS and the provided values is $R^2 = 0.932$, $R^2 = 0.915$ and $R^2 = 0.891$ for train, validate and test data. An illustration of the values obtained is depicted in Fig. 7.

The high values of correlation factor for three stages of train, validate and test in ANFIS indicates its high capability to model such problems and turn the AML nano-drug into mathematical and artificial intelligence problem which could be easily handled and would be a great and reliable aid to the experts in this field.

4. Conclusions

AML cancer has received limited attention in the field of artificial intelligence. In the present study, we aimed to address an important potential application of the artificial intelligence method in tackling of acute myeloid leukemia (AML). In this regard, a detailed survey of employing artificial intelligence methods in the cancer diagnosis, therapy and solidification stage was presented. Afterwards, using databases of approved cancer drugs and their efficacy an adaptive neuro-fuzzy inference system (ANFIS) was trained and used for further prediction of the effects of drugs on the treatments of the AML cancer. Furthermore, nano-medicines made from these approved drugs were considered and discussed their potentials in AML cancer therapy. Using the available data on cancer drugs, a response surface method using quadratic equations was also designed for the purpose of combination optimization. The main results could be summarized as follows:

• Combination of MitoC with Bort and Dac leads to negative effects on the treatment on AML cancer.

• It is recommended that this two drugs to be administered together and at the same time.

• Using Dec with Bort/Dac is not recommended since it has no effect on the effectiveness of the combination.

• The high values of correlation factor for three stages of train, validate and test in ANFIS indicates its high capability to model such problems and turn the AML nano-drug into mathematical and artificial intelligence problem which could be easily handled and would be a great and reliable aid to the experts in this field.

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