Neural Network Prediction Model to Explore Complex Nonlinear Behavior in Dynamic Biological Network

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Mohammad A. Alsharaiah[1(✉)], Laith H. Baniata[2], Omar Al Adwan[1], Orieb Abu Alghanam[1], Ahmad Adel Abu-Shareha[1], Laith Alzboon[1], Nedal Mustafa[3], Mohammad Baniata[3]
[1]Al-Ahliyya Amman University, Amman, Jordan
[2]Gachon University, Seongnam, South Korea
[3]Ubion, Seoul, South Korea
m.sharaiah@ammanu.edu.jo

Abstract—Organism network systems provide a biological data with high complex level. Besides, these data reflect the complex activities in organisms that identifies nonlinear behavior as well. Hence, mathematical modelling methods such as Ordinary Differential Equations model (ODE's) are becoming significant tools to predict, and expose implied knowledge and data. Unfortunately, the aforementioned approaches face some of cons such as the scarcity and the vagueness in the biological knowledge to expect the protein concentrations measurements. So, the main object of this research presents a computational model such as a neural Feed Forward Network model using Back Propagation algorithm to engage with imprecise and missing biological knowledge to provide more insight about biological systems in organisms. Therefore, the model predicts protein concentration and illustrates the nonlinear behavior for the biological dynamic behavior in precise form. Also, the desired results are matched with recent ODE's model and it provides precise results in simpler form than ODEs.

Keywords—artificial neural Feed Forward Network, prediction, Back Propagation, organism, progression process, synthesis, degradation, Cyclin, Ordinary Differential Equations model (ODE's)

1 Introduction

Organism has progression process which organized through involving synthesis/degradation proteins. Therefore, a significant component from protein regulator has been chosen as a case study to develop the proposed work. For illustration, we carefully picked CycE and their synthesis/degradation sub network form mammalian cell system. Cyclin concentrations make a variation in a cyclical way through cell cycle. Cyclins has an oscillations or fluctuations behavior, this attitude is made through variants in cyclin gene expression and degradation. We analyzed the relations between CycE subnet work components systematically; we based on the available literature for the biological knowing that was transformed into two model segments such as a Boolean

rule and ODE model. Depending on the lately obtainable biological knowledge from numerous sources such as [1] [2] systems to describe CycE sub network behavior. Consequently, Cyclin E (CycE) requires transcription factors like TFE to initiate its synthesis in presently way over cell cycle system [3]. Yet, another element are involved in this sub network such as ubiquitin-ligase (SCF), this element halts CycE accumulation since it's a degradation factor, and has an impact on CycE [4]. Furthermore, P27 has a harmful influence on Cyclin E therefore its existence in lowers levels of CycE [5] as displayed in Figure 1.

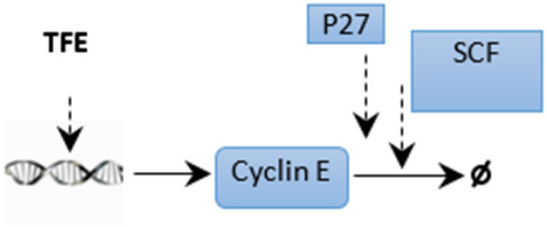

Fig. 1. Cyclin E sub network

It can be noticed that the discrete models like Boolean model has the capability to express the standing for each protein by which ever ON/OFF, present/absent or (0, or 1). On the other hand, ODE model is complex mathematical model and hard to be implemented due to the fact that many Kinetic parameters are missing, further details in the literature review section.

The main contribution for this paper are as follows:

1. Applying feed forward neural networks in modeling mammalian cell cycle system. For illustration, formulation and modeling the CycE sub network. One of the most significant intentions of this study is to comprehend the activities of complex biological systems like CycE subnetwork. To gain insights into this system and how the mechanisms in interacting, this evidence can improve our awareness to recognize and create our model and introduce enhancements to it.
2. Predicting and investigating the nonlinear behavior for proteins during their collaboration by applying neural Networks.
3. This research introduces a simpler method such as neural network to be an alternative technique to ODE models in modeling and prediction the concentration levels for proteins, also this alternative method provides precise results. However, this research paper are organized in the following sequence, section two presented for the literature review. Then, section three encloses the employed method, model architecture and implementation. Section four contains the results and discussions. Section five represents the research conclusion and future works.

2 Literature review

The investigation of biological systems can offer more comprehension of a system's configuration and its dynamic behavior [6] [7] [8] [9]. Essentially, the literate has

classified the functionality for the models within two classes – simple implementation model – Boolean model such as [10] and complex implementation – continuous model such as [2]. Several models have been introduced to study and investigate the biological network such as [11] [12] who investigated the relation between CycE and other species. However, Boolean-Discrete-model has the capability to express the standing for each protein through whichever (1 or 0) present/active or ON/OFF respectively. In this situation, the Boolean functions that be able to organize Cyclin E activity be able to utilized in the arrangement presented in Equation 1.

$$\text{CYCE} = \text{TFE} \mid (!\text{SCF} \ \& \ !\text{P27}) \tag{1}$$

Essentially, the disadvantage for Boolean system, they cannot elucidate the intermediate states of proteins concentrations, it provides simply qualitative result. Therefore, a quantitative results are more required. As a result, moreover promising quantitative models were developed, like rule based modelling that utilized a numeral of rules to express a system in qualitative form. For instance, Danos [13] utilized a type of modeling such as rule-based to restrained dual ODE models for EGF receptor signaling pathway through 70 rules Brightman [14], Schoeberl [15] and Fauré et al. [16]. Further, more recent ODE models have developed to model biological systems such as Iwamoto [2] and Ali [17]. Mainly, the ODE models provide more realistic results, as they can produce the intermediate states of protein concentration and their nonlinear dynamics in the system. More recent models, such as that published in [18], recommended additional continuous model aimed at the yeast cell cycle constructed on biochemical rate equations. [19] Similarly offered mathematical based model to elucidate the oscillatory biochemical paths [20]. Certainly, each ODE equation includes a set of components such as an activator and a deactivator besides a set of kinetic parameters. It organizes the conversion in protein concentrations close. The general form for the popular ODE model is that simulates CycE activity, which denoted underneath in equation 2 [2]. Mainly, continuous models have track the fluctuations in concentration for proteins, such as $C_j\,(t)$ *for* $j = 1, 2, \ldots, N$ by resolving a group of nonlinear (ODEs) model- ordinary differential equations- of the arrangement:

$$\frac{d\text{Ci}}{dt} = \sum_{r=1}^{R} V_{jr}\, P_r \left(C_1, C_2, C_3, C_N\right) \tag{2}$$

The P_r that appears in the equations denotes the rate for the *rth* reaction also V_{jr} represents the stoichiometric coefficient for the species *i* for the reaction named *r*. To separately rate, term is interrelated one or other kinetic constants which control carefully in what way express the reaction conducted in exact situations. The kinetic constants essential be expected by trial data, and usually an existing scarce kinetic data to define their amounts. As stated before, this kind of model is deliberated as problematic in computer programing, plus the Kinetic parameters quantities are actual inflexible to be obtainable where specifies the variations in the concentration level during time. Besides, it depends on the values for the Kinetic parameters to clarify the oscillations in concentration level during the time. The supreme obvious struggle is the scarcity in Kinetic values. Hence, a significant concern is how to facilitate the modelling of complicated quantitative models of biological networks that can predict and elucidate

the outcomes of biological experimentations. Further, although large amount of data is generated from microarray and similar experiments, protein data needed for the development of complete continuous models are lacking. Consequently, there are another attempt to model cell cycle system with new methodology. Scientists have attempted various modelling approaches to represent the mechanics of interaction of cell cycle species. For instance, merely a limited cell cycle models related is available in the literature. Fujita et al. [21] Established a Mixture (discrete enclose continuous) Useful prototypical intended for cell cycle system in Fission yeast. While they combined continuous and discrete in integrated form. This model has not explained diverse levels of abstraction which make it inflexible to realize the model. Herajy et al. [22] [23] familiarized a mixture Petri Net model designed for Eukaryotic, the model applied on cell cycle system and was a PN imitation of an ODE model. The model mimics the cooperation of cyclin such as cyclin B protein kinase. [24] explain the character of noise in the cell cycle system for the eukaryotic.

Consequently, recent biological research considered the Neural network as alternative assortment for predicting and exploring the nonlinear behavior for proteins in organism. There are numerous methodologies utilized for biological data investigation in which employment of Neural Network (NN) is a common choose for the scientists [25] [26] [27]. Essentially, several approaches have been utilized for biological data investigation through investigators in which efficiently of (NN) is conventional and superlative selection for the researchers among the diverse techniques. For instance, in Widespread Regression [28], data mining with biological in systems biology [29]; they introduced a multivariate biological model to accomplish different biological data mining investigation on a set of biological data. [30] Provided a comprehensive review analysis on DNA microarray experiments for gene expression over the biological. [31] Another techniques such as Pearson Coefficient Technique [32], Focused Time Daley Neural Network, Fuzzy Inference System [1] [33] [34] etc. In [28] the researchers recommend to apply the standardized regression-based method to identify the breakpoints also the corresponding sectors from date that has a type of multivariate time-series. In preparation with methods from clustering, the method as well authorities estimating the importance of the selected breakpoints and the key mechanisms concerned in the appearance of the breakpoints. Prorated investigation with the standing substitutes validates the influence of the method to discovery biologically significant breakpoints in varied time-resolved transcriptomics datasets through the cell cycle in the yeast. Mainly, researchers have done few analysis works on mammalian cell data biological. For instance, [35] presented an adaptive neural fuzzy inference system aimed at predict the concentration for protein and disclosures the complex and nonlinear behavior with regard to protein. In addition, neural network are used in Bioinformatics fields such as [36], cancer classification and discoveries [37] and other diseases such as blood illness [38]. Therefore, in this article we examine the neural network to be an alternate technique in investigating and predicting the dynamic behavior with nonlinear activity for proteins in organism in simpler form to cross over the drawbacks for the aforementioned models.

3 Model architecture and implementation

The supervised learning technique encloses several techniques, and one of the most promising techniques is the Back propagation algorithm. This algorithm consist of multilayer feed-forward networks and it's a part from the Artificial Neural Networks filed. Feed-forward neural networks are stimulated thru the information management process in a single cell or more neural cells, named a neuron. A neuron can receive input signals through specific part called dendrites, which permit the signal in electrical form toward the cell bulk. Besides, the axon brings the signal out to another part called a synapses, these are the links of a cell's axon toward further cell's dendrites. The standard of the backpropagation method is to constitute a specified purpose by adjusting interior weightings of input signals to provide a probable output signal. The proposed model is trained through supervised learning technique, also, the error amongst the system's output and an identified estimated output is offered to the system and applied to adjust its interior state. Precisely, the backpropagation algorithm is a technique for exercise or training the weights inside a multilayer feed-forward NN. Typically, it needs a well-defined network structure with one or extra layers where one layer is completely connected to the next layer. A regular network structure has only three different layers organized as follow, one input layer, the second layer enclose single or further hidden layers, and one output layer, this simple architecture is illustrated in Figure 2a.

The crucial goal of this study is to introduce a novel method to predict Protein concentration for the several species who present a sub biological network and investigate the dynamic behavior-based synthesis/degradation proteins. The proposed Artificial Neural Network (ANN) Model was established and fulfilled through MATLAB. A Feed Forward Neural Network (FFNN) by Backpropagation Algorithm and with specific training function called Levenberg-Marqurdt [39]. The training function also called damped least-squares (DLS) method, is utilized to elucidate non-linear least squares problems [40]. These minimization problems arise particularly in least squares curve fitting. In addition, the model has a set of training parameters and they specified in Table 1. At the end of the training an important process executed; this process was concerned on experiments; the experiments are carried out by arbitrary selection for the number of processing unit. Also, we utilized Mean Squared Error (MSE) to check the weather of how near to estimates or predicts are to actual values; since the lower value of MSE indicates the closer is predict to actual values. Mean squared error (MSE) is a systematic squared difference amongst targets and productions. Regarding to the errors the adjustment of the network is prepared. Therefore, based on Mean Squared Error, performance will predicted in the developed model. During the simulation, several experiments have been done to check the performance of the model and analyses the outcome of the predictions. However, the selection of the processing elements narrows down. We notices that the model produces a precise prediction for the domain of 5- to 45 neurons. Concerning to the number of hidden layer in the model, it is composed of hidden layers and a changing quantity of neurons within the hidden layer. The most optimal configuration is obtained as shown in Figure 2b. Furthermore, the relation between the protein CycE and the synthesis and degraded fundamentals were categorized via FFNN model Figure 2b. the proposed model mimics CycE vitality; it

comprises of three input variables whereas has single one output variable as presented in Figure 2a. The figure clarifies the input variables for cycE; its shows the CycE regulators for activation and degradation. The best finest configuration is acquired through employing the trial and error method.

Table 1. Parameters used for model training

Network Type	FFNN has Back Propagation
Functions for training	The (LM) function – Levenberg-Marquardt
Function for Adoption learning	Learn GD and Learn GDM
Function related to Performance	The (MSE) – Mean Square Error
The Transfer function	In the Hidden Layer – Tansigmoid In the Output Layer – Linear
The number of Neurons used in Hidden Layers	5–50

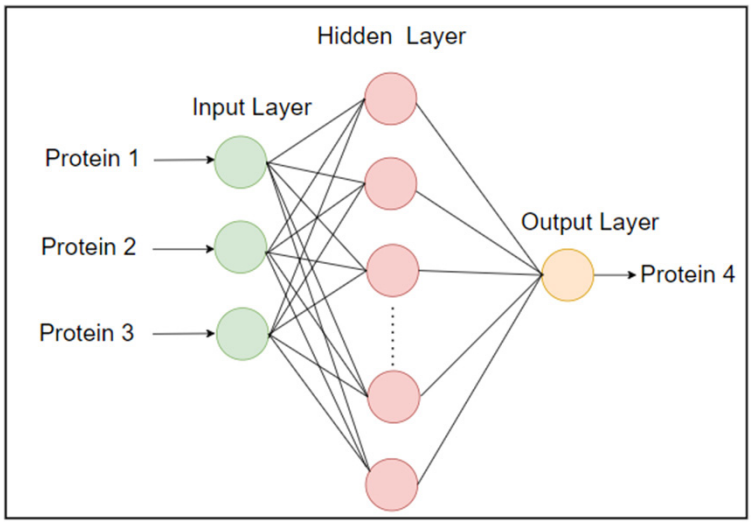

Fig. 2a. The proposed Feed Forward Neural Network model (FFNN) employing Backpropagation

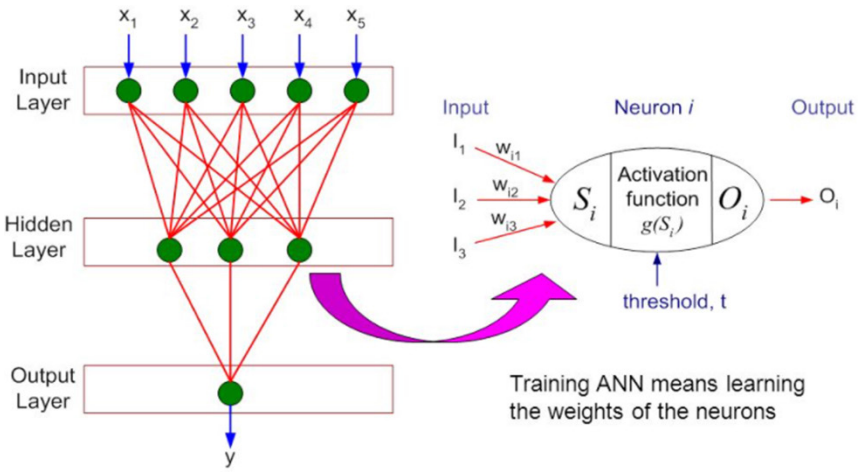

Fig. 2b. The architecture of the Feed Forward Neural Network (FFNN)

3.1 Dataset selection

Backprobogation algorithm needs perfect parameter values for the entire model. Therefore, we relied on secondary data set that offered in the literature [2]. This biological data consists of 1200 records for three inputs proteins such as (TFE, SCF, P27) respectively which control the dynamic behavior and the protein synthesis and degradation for the output variable CyCE. These secondary data was selected because the availability of fairly long series of biological data during the life cycle for the mammalian cell. Afterward investigated data, certain data was picked to train ANN models, and the rest part was utilized as a testing set. The data utilized to fed the proposed model for input variable with the output variable; this step can finest model development, both input and output variables are specified in Table 2. We developed a model with different configuration regarding the numeral of neurons within the hidden layer. In the developed model, three input variables have been used which are the readings of protein 1, protein 2 and protein 3. The developed model will predict the output of protein 4. As shown in Table 2.

Table 2. Model description

Model	Inputs Proteins	Predicted Protein
FFNN	P1 = TFE	**P4 = CYCE**
	P2 = SCF	
	P3 = P27	

4 Results and discussion

The artificial neural networks are engaged due to their efficiency in undertaking a enormous size of data per the relief and worthy convergence rate during which it be capable to be trained. This assistances in several aspects such as the prediction of identification and classification of chief particle out of the library of an associated class of complexes, which essentially supports new drug sighting. The main goal of the proposed work is to develop a neural network model for precise identification and predication to the select case study. During the simulation, we have been keen to analysis the network performance over time in every experiment. For instance, we analyzed some of factors such as the hidden layer components, especially, the number of neurons, the best network structure and least MSE values in comparison to other configurations. The network performance of the model is given in Table 3 below. In Table 3, the amount of neurons in the hidden layer is settled in ascending demand. Furthermore, their validation performance is measured accordingly. It is noticed that for FFNN Model, the optimum network structure is 3-40-1. Further, as displayed in Table 3, the FFNN model provides the best results in 3-40-1 configuration, with least MSE values of 1.3e-06 in comparison to other configurations. The validation for machine learning model is devoted to as the practice where a trained model is assessed through data set testing. However, in concern to best validation performance regarding to the model, the Figure 3 exposes the relation against MSE vs. epochs. In addition, the performance for the model was clarified and it was explained by the diagrams, the plotted diagrams between 27 epochs and mean squared error (MSE). As shown in Figure 3, the model shows in for the modeling that the best validation performance is obtained at epoch 27 which is 2.1997e-06. Besides, it is found out that when the network error is low the performance is not essentially enhanced.

Table 3. Model performance

Neurons Used	Model Performance	Epochs	Stopping Criteria	Model Configuration
5	3.4e-06	112	Maximum epochs for Validation	3-5-1
10	1.94e-06	182	Maximum epochs for Validation	3-10-1
15	4.42-06	57	Maximum epochs for Validation	3-15-1
20	1.57e-06	172	Maximum epochs for Validation	3-20-1
25	1.61e-06	40	Maximum epochs for Validation	3-25-1
30	1.45e-06	109	Maximum epochs for Validation	3-30-1
35	6.01e-06	23	Maximum epochs for Validation	3-35-1
40	**1.3e-06**	**33**	**Maximum epochs for Validation**	**3-40-1**
45	1.95e-06	83	Maximum epochs for validation	3-45-1
50	1.37e-06	156	Maximum epochs for Validation	3-50-1

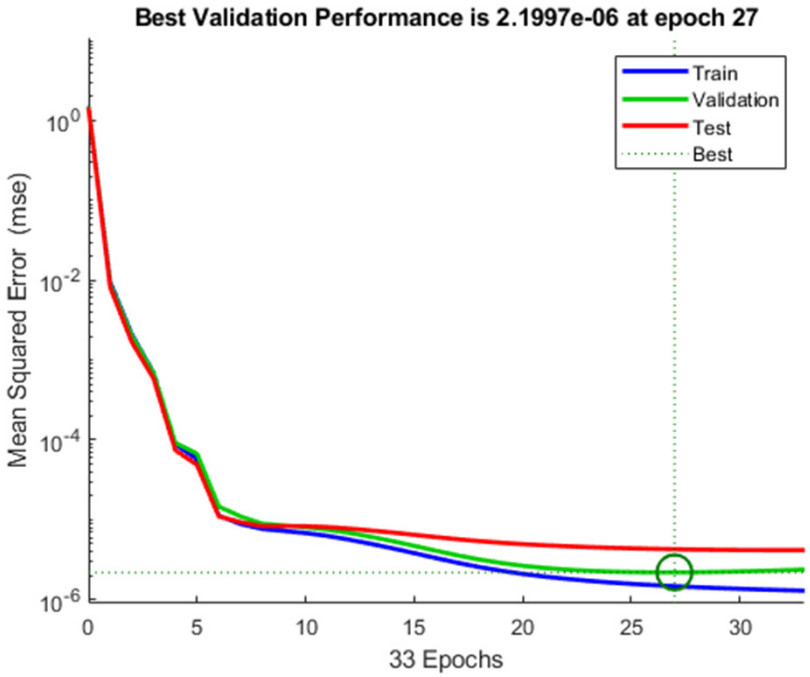

Fig. 3. Best validation performance

Obviously Figure 4 shows that after 166 epochs for the 3-20-1 configuration, the performance of training, as well as the testing and the validation errors were stagnant. this mean afterward epochs 166 there is definitely not additional enhancement in the performance of the network and the network looks to have saturated.

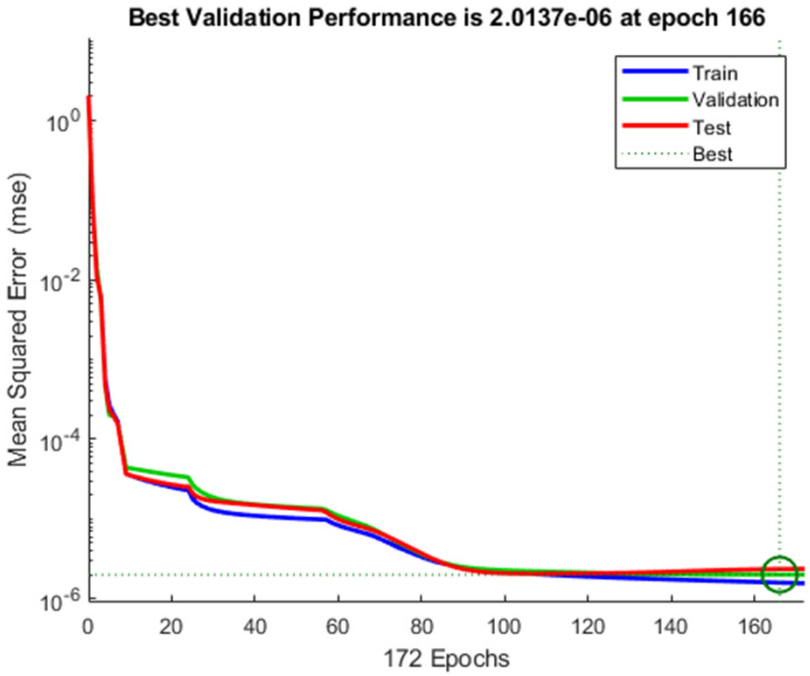

Fig. 4. Best validation performance

It can be specified about the FFNN model provides a great mapping as the investigation among model output and model responses; investigation is exposed in Figure 5. For illustration, Figure 5 explores several significant things such as the relation between the training target and training output, as well as signifies the state among the validation target and validation output. In addition, the figure explain the relation between the output values, the tested and targeted values. Also, the relation between errors and response. Principally, the model shows convenient results over time.

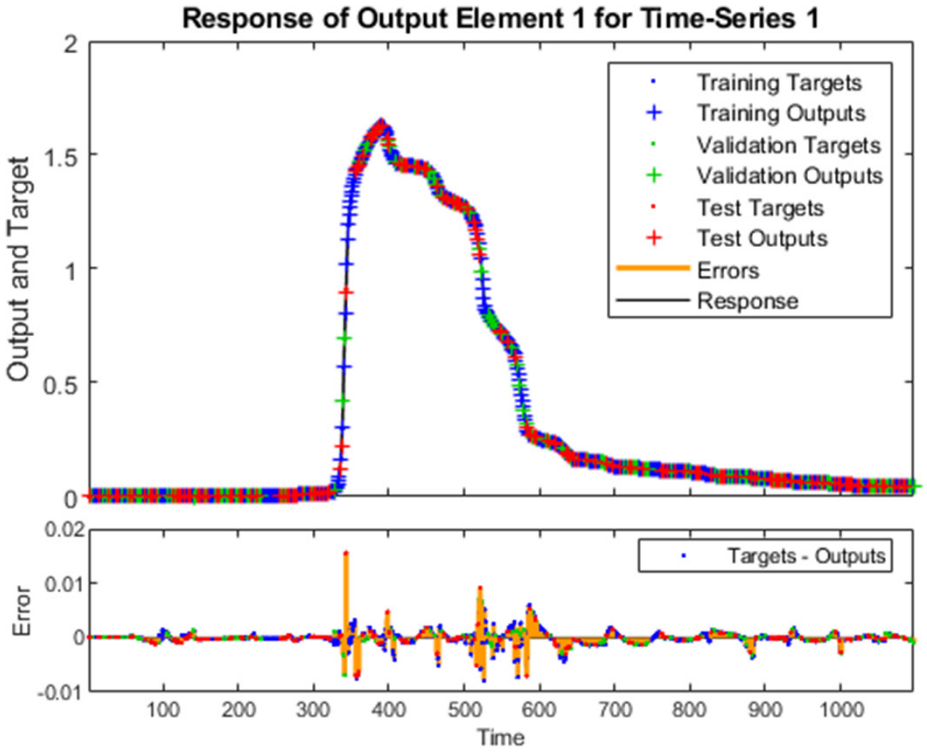

Fig. 5. Response of output for biological data

In this research project, 15% of data is used for validation, 15% for testing and 70% for training. Figure 6 illustrate the error histogram with 20 bins. It can be concluded that for 470 instances of the training data, 100 of instances of validation data and 100 instances of testing data, the FFNN model obtained the least error value which is –0.00026.

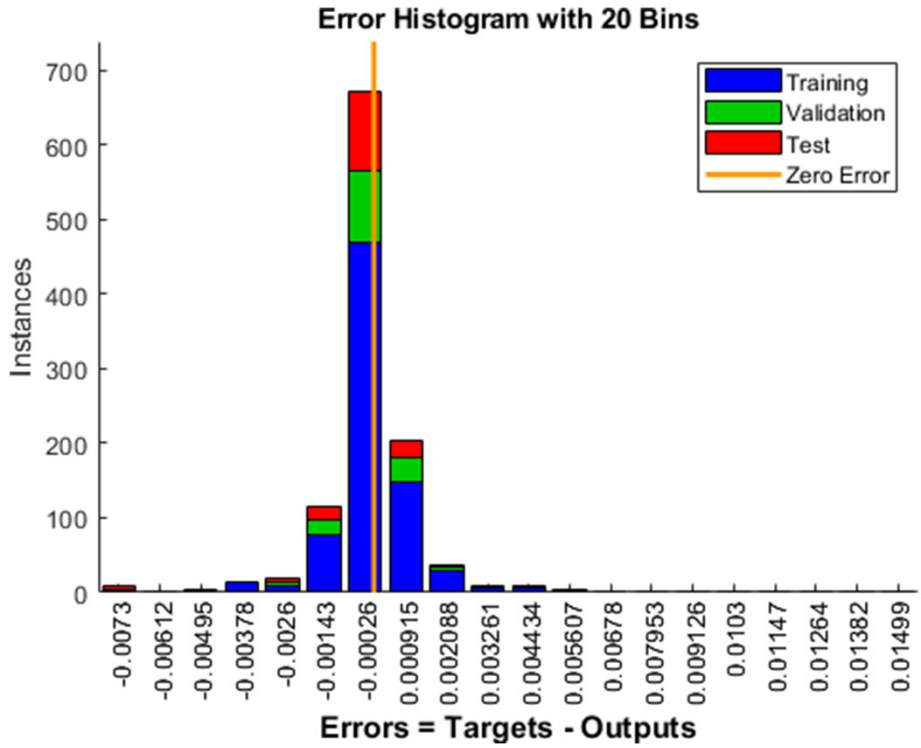

Fig. 6. Error histogram with 20 bins

To improve and measure the efficiency for the developed we applied the autocorrelation. It's a delay function to specify the correlation in the model within discrete time, it also provides the signal's correlation with the late copy for it. It is the likeness among observations as a function of the time lag amongst them. Autocorrelation is a mathematical analysis to discover the repeating patterns, comparable to the presence of periodic signal becloud through noise, or recognizing the lost essential frequency in a signal implied via its organized frequencies. Its s regularly utilized in signal handling for investigating functions or series of values like time domain signals. Precisely, the lag denotes to how far the series are offset, and its sign defines which series is shifted. We have to be aware that as the lag increases, the number of likely matches decreases since the series "hang out" at the ends and do not overlay. The value of the lag with the maximum correlation coefficient characterizes the finest fit between the two series. Also, the lag times the sampling interval offers the duration through which one series dominates or trails the other—how long it takings the effect to propagate from one variable to the other. If you have per hour data and the finest lag in 12, the time variance between the two series is 12 hours. Figure 7 shows the Autocorrelation for the FFNN model and the best Correlation occurs at 0 Lag and the pattern is not symmetrical. It shows how the noise effects on the occurrence of a periodic signal and how its obscured through noise, or recognizing the lost essential frequency in a signal implicit by its harmonic frequencies.

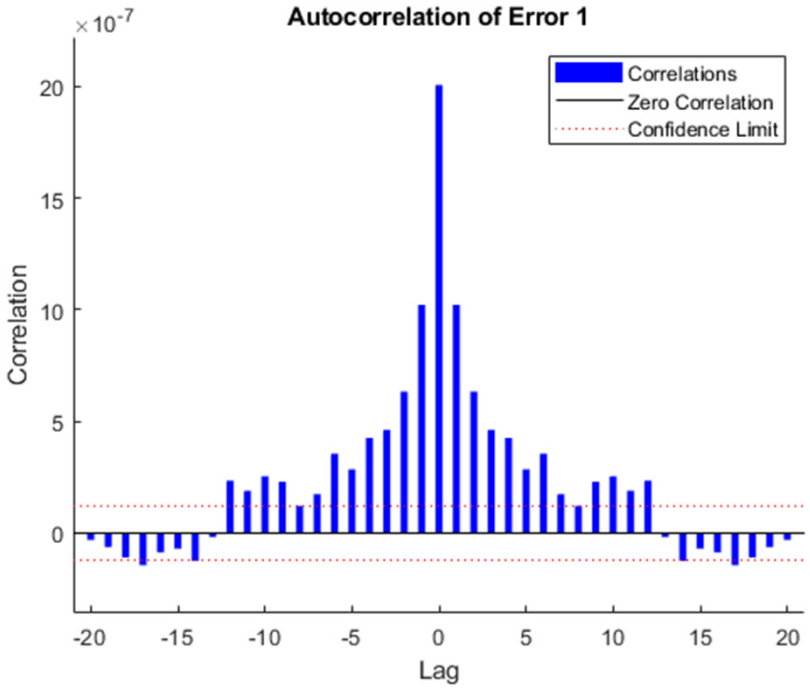

Fig. 7. Autocorelation of error1

The input-error cross-correlation function defines how the input sequence are correlated with the errors. For the value 252, the optimum prediction model, all correlations must be zero, excluding for the one at zero lag. As illustrated in Figure 8, the input-error correlation was fundamentally within the 90% confidence limit, and the FFNN model accomplished the optimum predictions.

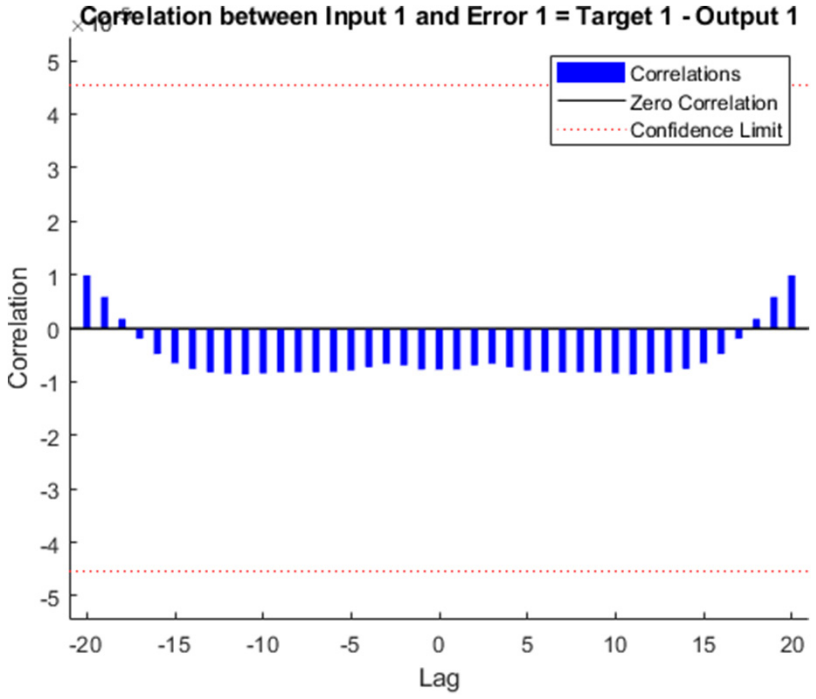

Fig. 8. Input error correlation

FFNN model simulation results, exposed and explained the problem of predicting proteins concentration levels in organism. Precisely, the simulation offered a satisfactory results to explore and predict the concentration measurements and the dynamic behavior for proteins as shown in Figure 9. For illustration, when P27 must be miniature to a low level once triggering it prevents CycE production. Also, TFE is the most important activator for CycE construction. The amount of TFE concentration essential be on low level at the establishing, yet when TFE during the time becomes accumulates, it effects positively on CycE to be accumulated rapidly. Conversely, during the cell progression other CycE degraders with negative effects may become active suitably to convey CycE level decreased down. For incident, SCF concentration gradually reductions of CycE level as explained in Figure 9. The blue line signifies the crisp values provided by the FFNN model for CycE activity (concentration). The rest of lines signify input variables and their activity during CycE subnet wok. The model mimics the biological activities CycE activity as can be found in the biological literature [2].

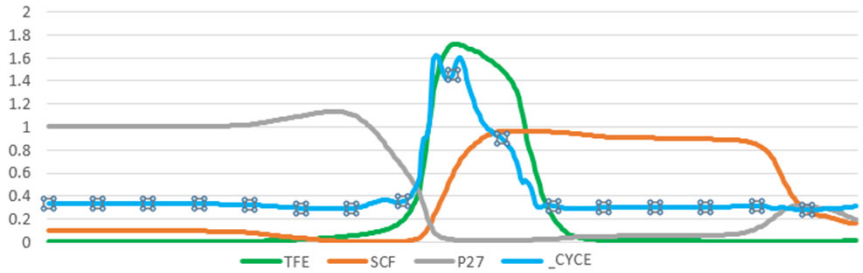

Fig. 9. The FFNN model results simulating CycE activity

In addition, FFNN model have been compared with recent available ODE model in the literature [17]. We accomplished a comparison study to be assured and proven that the proposed FFNN model can simulate the interactions between elements, behaviors and offer precise results for protein synthesis and degradations. Certainly, the FFNN model results have been accurate and well-matched with results from a certain ODE model such as Ali Abroudi (2017) model as shown in Figure 10. The FFNN model is simpler in implementation than the aforesaid ODE model and it drop off all Kinetic parameters since it does not required like ODE's model. However, the result in both model are satisfactory and accurate. The ODE model is considered as one of the most important methods in modeling biological systems. Therefore, here we introduce a novel method, which can produce a precise result in simpler form.

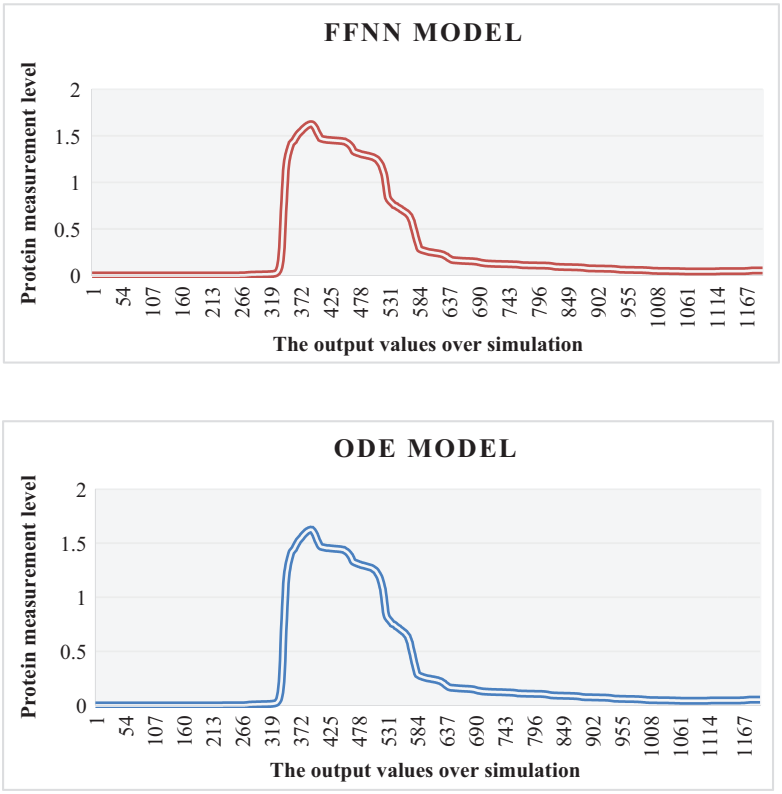

Fig. 10. The FFNN CycE model outcomes and CycE ODE model outcomes to explain and predict proteins concentrations

5 Conclusion

Herein, we introduced a novel method to employ neural networks for biological data investigation and prediction in biological systems. The Backpropagation algorithm is involved to train layered, feed-forward networks to model biological data which has a complex and non-linear features. It is accomplished of "learning" a target function from a set of "training examples" deprived of robust assumption about the function. It depends on intelligent neurons to mimic and control nonlinear system accomplishments. Also, predicts and computes protein concentrations for biological species in a simple manner. The limitations that found in classical biological models such as ordinary differential equations (ODE) have been crossed over by FFNN model. For instance, the FFNN model can figure the crisp values depended on uncertain and information and without requisite for kinetic parameters such as ODE's Model, which face lack limited in certain organism. Besides, the FFNN model has been compared with recent available ODE model in the literature. Certainly, the simpler FFNN model can

offer reasonable results similar to the ODE in clarifying the dynamic behavior and protein concentrations; it provides a novel view for Cyclin E function and regulations in cell progression. However, biological data analysis for biological filed is one of the furthermost critical aspects of the applied usage. Accurate predictions and computing with the assistance of biological data analysis will support in estimating drugs and treatments in illnesses advancement.

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8 Authors

Mohammad A. Alsharaiah is a Department Head of Data Science and Artificial Intelligence at Information Technology Faculty – Ahliyya Amman University He received a Ph.D. degree in Computer Science and Information Systems from Lincoln University, Christchurch, New Zealand in Dec. 2018. His research interest includes Data Science and Artificial intelligence fields such as Machine Learning and Deep Learning, Data mining, Big data., Bioinformatics, and Modeling complex systems.

Laith H. Baniata received a Ph.D. degree in Computer Science and Engineering from Kyungpook National University, Daegu, South Korea, in 2019. From 2021 January till 2022 January, he was a Post-doctoral Research Fellow with NLP and Deep Learning Laboratory, Kyungpook National University. Since April 2022, he has been a research professor in Computational Intelligence and NLP Laboratory, Gachon University. His research interest includes Natural Languages Processing and Deep Learning.

Omar Yousef Adwan is a Professor Dean of Information Technology Faculty – Ahliyya Amman University. He received all his qualifications from George Washington

University, USA. His research interest includes Software Engineering, Data Science, Artificial intelligence, Big data, and Modeling complex systems.

Orieb Abu Alghanam is an Assistant Professor at Information Technology Faculty – Ahliyya Amman University. She received all her qualifications from the University of Jordan, Jordan. Her research interest includes Computer Networks and Security, Data Science, Artificial intelligence, and Modeling complex systems.

Ahmad Adel Abu-Shareha is an Assistant Professor at Information Technology Faculty – Ahliyya Amman University. He received his PhD from the University of Science Malaysia, 2012. His research interest includes Computer Science, Data Science, Artificial intelligence, and Information Retrieval.

Laith Alzboon is an Assistant Professor at Information Technology Faculty – Ahliyya Amman University. He received his PhD from the Eastern Mediterranean University. His research interest includes applied mathematics and Computer Science.

Nedal Mustafa is a Professor at Information Technology Faculty – Ahliyya Amman University. He received his PhD from Bucharest Politechnic University. His research interest includes Computer Networks and Security.

Mohammad Baniata received a Ph.D. degree in Computer Science and Engineering from Soongsil University, Seoul, South Korea, in 2019. From 2019 till 2020, he was a plant manager at Mathevon Company in France, currently Dr. Baniata works as a project manager in Ubion Company in Seoul, South Korea.

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