

Original Research Article

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## ADAPTIVE NEURAL FUZZY INFERENCE SYSTEM FOR PREDICTING PROTEIN ACTIVITIES

Mohammad A. Alsharaiah<sup>1\*</sup>, Majdi Sawalha<sup>1</sup>, Mutaz KH. Khazaaleh<sup>2</sup>, Nafea S. Alkharabsheh<sup>1</sup>

1. Computer Information Systems Department, The University of Jordan, Jordan.
2. Library and Information Technology Department, Al-Balqa Applied University, Jordan.

**ABSTRACT:** Organism species activities can be exposed by protein concentration level. These activities produce nonlinear and complex behavior, therefore, Mathematical and computational modelling methods are becoming significant tool to elucidate this complex behavior. Moreover, these methods can be utilized to compute, predict and uncover the veiled knowledge. Unfortunately, most of the aforementioned approaches face the scarcity and the ambiguously in the biological knowledge to figure and expect protein concentrations measurements. Consequently, the purpose of this research introduces a computational model has the ability to work with vague and missing biological knowledge we derived a fuzzy logic model which predict protein concentrations; this research presented a new adaptive neural fuzzy inference system for predict protein concentration measurements level and exposes the nonlinear and the complex behavior for protein. The concern research utilize both fuzzy inference systems and artificial neural network which is identified as neuro fuzzy technique for elucidate the problem of predicting organism proteins concentration levels.

**Keywords:** Neural Network, Fuzzy Logic, protein concentration level, Sugeno fuzzy inference system, ANFIS, Mathematical and computational modelling, Genetic algorithm, Particle swarm optimization.

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**Corresponding Author: Mohammad A. Alsharaiah \***

Department of Computer Information Systems, The University of Jordan, Amman, Jordan.

Email Address: Modsharaiah@gmail.com

### 1. INTRODUCTION

Organism Progression process is systematized by applying synthesis/degradation proteins. Herein, an important element from protein regulator is selected as a case study to implement our work. For

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instance, we selected SCF in mammalian cell since it controls the transitions between G1/S and G2/M phases [1]. SCF has a crucial roles in degrading mammalian cell proteins plays, this element has quintessence on cyclins activity, such as CycD and CycE. SCF activity is controlled by two species such as CycE and CDH1. SCF is active in the presence of CycE and absent in the presence of CDH1 since CDH1 can inhibit SCF activity [2]. Numerous modelling approaches have been developed to recognize, explore and examined biological system behavior and activities. Mainly, literature models have classified the functionality into two categories - discrete model such as Clare E. Giacomantonio [3] and continuous model such as Iwamoto [4]. For illustration, Discrete model be able to only define the status for each protein by either present/active or absent/not active (1 or 0 respectively), this mean it cannot clarify the intermediate states of proteins concentrations. Nevertheless, The ODE models deliver supplementary realistic outcome than discrete models, it can explicate the intermediate states of proteins concentrations. Definitely, every ODE equation involves of an activator and a deactivator and a set of kinetic parameters. These mechanisms regulator the transformation in protein concentrations level. The recent ODE model is Iwamoto [4] that mimics SCF activity which is represented below in equation

$$\frac{d[aSCF]}{dt} = k_{92} \cdot [aCycE\_Cdk2] \cdot [iSCF] - k_{91} \cdot [aSCF] \cdot [aAPC\_Cdh1], \dots\dots (1)$$

Mainly, this type of model is measured as difficult to be implemented, and the Kinetic parameters values are very hard to be obtainable Where  $d[aSCF]/dt$  signifies the variations in the concentration level over time, and this ODE equation involves of the activator as CycE and the inhibitor as CDH1 for SCF. Besides, it depends on Kinetic parameters values like  $k_{92}$  and  $k_{91}$  to express the fluctuations in protein level over time. Yet, the most evident conflict is the scarcity of Kinetic values. To cover the aforementioned shortcoming, fuzzy inference system can be utilized to characterize and process imprecise information common to most real-life complications in Practical means [5]. These methodologies depend on the use of simple language such as in the IF-THEN rules in the elucidation of the crucial system response as a function of numerous linguistic variables. It relies on the regular human language to denote the problem and discover the solution [6]. As established, fuzzy logic models have been employed in many parts such as industrialized and technical software [7]. Furthermore, it can effort with uncertainties and nonlinearities behavior for any complex system. However, in fuzzy system modelling there is several issues can be appear [8]. For instance, the difficulty of tuning membership functions and appropriate rules is commonly a challenging process. Therefore, to cover this gap, developers lead to the idea of engaging knowledge algorithms to the fuzzy system models. For illustration, neural networks can be utilized in tuning fuzzy system since they have competent learning algorithms. So, neural networks can be considered as an alternative computerize to maintain the development of fuzzy systems. Recently, neural networks are involved in almost research and industrial fields. For example, data analysis, data classification, decision

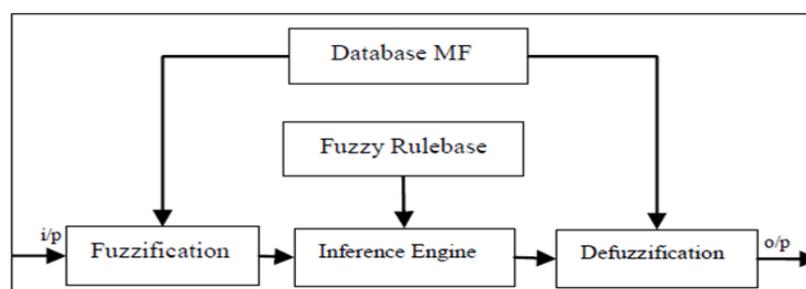
making and imperfection detection [9]. To find out more about the applications that have been used the Neuro-Fuzzy Inference (NFI) see [10-18]. We developed a new productive fuzzy model to predict protein concentration measurement to elucidate organism biological species activities. This method can be an alternative method to Ordinary differential equations (ODE's) which utilized to compute and predict proteins levels. The ODE's functionality based on kinetic parameters that discovered from biological research and wet-lab experiments. However, this types of models face a scarcity in the Kinetic parameters due to the biological knowledge is incomplete and vague. Therefore, fuzzy logic can an alternative option in computing and predicting the nonlinear behavior for proteins in organism. Herein, we introduce an Adaptive network based fuzzy inference system called (ANFIS), it is a technique based on intelligent neuro-fuzzy to model and control nonlinear system activities. Mainly, integrating a powerful fuzzy model form available data using the Adaptive Neuro-Fuzzy Inference System (ANFIS).

## 2. MATERIALS AND METHODS

### 2.1 Fuzzy inference system and ANFIS structure

#### 2.1.1 Fuzzy system

Fuzzy system has several main significant components such as fuzzification, which interprets the inputs crisp (real-valued) into fuzzy values. The second component is, rule base reasoning, it is an inference engine which employees a special mechanism called fuzzy reasoning to acquire a fuzzy output utilizing rules. Then, defuzzification part, this part translates this latter output into a crisp value. The crucial task of fuzzification is to map system input values from 0 to 1 through defined input membership functions. in addition, in rule-based reasoning, the fuzzy input values membership values are mapped to classify fuzzy output by a specific table inclosing set of rules (if-then rules). All rules are stated as a logic implication  $p \rightarrow q$  where  $p$  is termed the antecedent of the rule and  $q$  is termed the consequence of the rule [19]. Mainly, Defuzzification is a process that produces single system output (crisp) values via utilizing a defuzzification formula. In addition to fuzzy output membership outputs; the aforementioned components are shown in (fig-1).



**Figure 1: Fuzzy inference system components.**

The fuzzy inference system is a common computing framework depended on several concepts such as fuzzy set theory, fuzzy if-then rules, and fuzzy reasoning. It has been applied in several wide fields, such as decision analysis, expert systems and data classification [20]. However, further details

information that related to fuzzy logic can be available in R. Neuro-Fuzzy Modeling [21].

### 2.1.2 Adaptive neuro fuzzy inference system

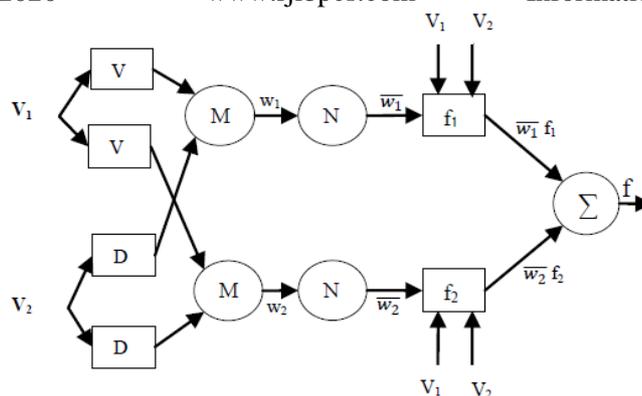
Adaptive neuro fuzzy inference system (ANFIS) was implemented in the early 1990s. [9], it's a type of artificial neural network which is depend on Takagi–Sugeno fuzzy inference system [22]. Mainly, this technique integrates in cooperation neural networks and fuzzy logic principles; all benefits from these two methods are captured and become in a single framework. The inference system corresponds to a set of fuzzy rules that take IF–THEN format. It has learning capability to estimate nonlinear functions [23]. Therefore, ANFIS is considered to be a universal estimator [24]. This section explores the architecture and basic learning process underlying ANFIS (adaptive-network-based fuzzy inference system). In this method fuzzy inference system is implemented in the framework of adaptive networks. Precisely, the adaptive neuro fuzzy inference system (ANFIS) is a combined approach that involve two techniques like neural network and fuzzy logic to create a new powerful and efficient shell [25]. Mainly, the system of ANFIS employs the feature of the artificial neural network learning rules to accomplish and tuning the fuzzy inference system components such as structures, parameters and rules. As a consequence, ANFIS features have the ability to support and develop the system intensely. For example, ANFIS features are considered as fast and precise learning, simple to implement, exceptional clarification abilities, robust generalization over fuzzy rules. ANFIS can integrate the linguistic and the numeric acquaintance for problem solving [9, 21, 25, 26, 27 and 28]. Typically, ANFIS extract an adaptive fuzzy inference system (Sugeno- type fuzzy systems) through the proficiency of learning fuzzy rules from data and as a connectionist method delivered with linguistic meaning. Recently, Takagi-Sugeno (T-S) fuzzy models are playing a significant role in mimicking the problems class of nonlinear systems. Several experts system had been developed by hybrid neuro-fuzzy inference such as [29 and 30]. Also, this joint influential method has seen enormous preferences newly from researchers working in enormous domains. A comprehensive study which related to the combination between fuzzy logic and neural network can be found in [9]. During the development process, developers defined the number and the type of fuzzy system membership functions while ANFIS is utilized as a teaching technique for Sugeno-type fuzzy systems. ANFIS structure consist of multilayer feed-forward network with set of nodes that connected together in complex form by directed links, each node operates a specific function on its incoming signals then generate a single node output [9]. In concern to the links inside the adaptive network they determine the direction of signal flow from one node to another; the links inside this network has no weights. In more details, n ANFIS the incoming signals performs a statics and fixes node function to generate a single node output, and each node function has a parameterized function with modifiable parameters. The changing process include these parameters and the node functions overall behavior of the adaptive network. ANFIS consist of five layers such as fuzzy layer, product layer, normalized layer, de-fuzzy layer and total output layer respectively, as shown in (fig-2). In

general form, ANFIS network structure consist of two parts, premise and consequence parts. Also, the architecture is composed by five layers. The first layer includes the input values and defines the membership functions fitting to them. This layer can be called fuzzification layer. Each function has membership degrees and they are computed by utilizing the premise parameter set. The second layer called rule layer, the main function for this layer is generating the firing strengths for the rules. The computed firing strengths are normalized in the third layer, this can be done by dividing each value for the total firing strength. In the next layer, the normalized values become as input for the layer four with the consequence parameter set. In this layer, the values are become defuzzified then passed to the last layer to return the final output [20]. ANFIS method generates a fuzzy inference system (FIS) to the input/output data for given set of parameters. This FIS has a set of membership function parameters (the premise parameters, these parameters define the shape of the membership functions [20] which tuned by utilizing either a back propagation algorithm only, or in permutation with a least squares type of method. This method used to define the optimum values of the comparable fuzzy inference system parameters by employing a learning algorithm. Optimizing parameters sets can be done during the training session, in this session the amount of error between the target and actual output have to be minimized. To achieve this point a hybrid algorithm is utilized for optimization, which is the mixture of gradient descent method and least square estimate. Achieving the minimum value for the error ensure several optimization routines can be applied after constituting MFs. Also, the parameter set of an adaptive network consents fuzzy systems to learn from the data they are modeling. In this research we selected the SCF protein activity which predicated and mimicked by mathematical ODE model in equation 1, this SCF has two proteins such as CYCE and CDHL protein as demonstrated in equation 1 that controls SCF activity. Therefore, in the adaptive system under consideration has two inputs V1 and V2 and one output f. furthermore, lets study a first order Takagi, Sugeno and Kang (TSK) fuzzy inference system comprehending two rules:

$$\text{Rule 1: If}(v \text{ is } V1) \text{ and } (d \text{ is } D1) \text{ then } f1 = p1v + q1d + r1 \dots\dots\dots (2)$$

$$\text{Rule 2: If}(v \text{ is } V2) \text{ and } (d \text{ is } D2) \text{ then } f2 = p2v + q2d + r2 \dots\dots(3)$$

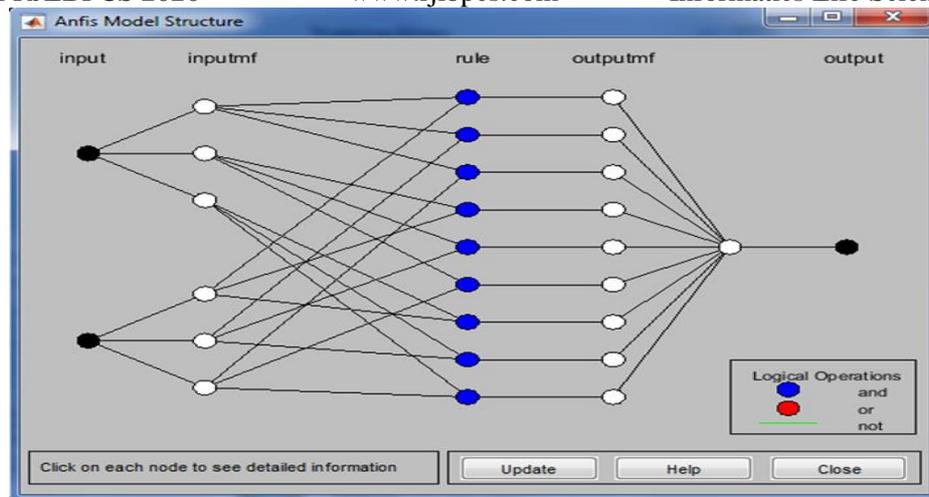
In the two aforementioned rules the parameters are either linear parameters or nonlinear parameters. For instance, p1, p2, q1, q2, r1 and r2 are linear parameters and V1, V2, D1 and D2 are nonlinear parameters, the V1 and D1 are the membership functions of ANFIS (antecedent), while p1, q1, r1 are the consequent parameters [31]. As shown in (fig-2) we employ both circle and square to reflect the adaptive capabilities. For illustration, circle indicates fixed node while square indicates adaptive node, this explains how the parameter can be changed through adapting or training.



**Figure 2: General form for ANFIS network structure and functionality.**

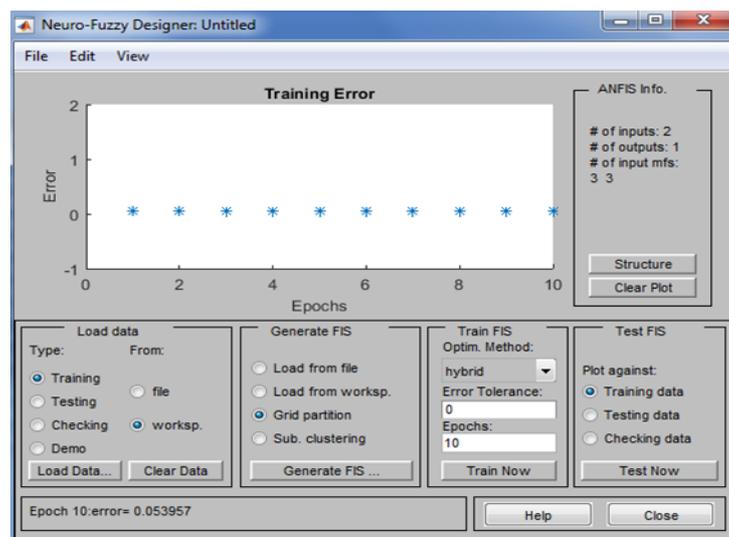
## 2.2 Adaptive neural fuzzy inference system for predicting proteins measurement to explore biological species activities

Essentially, organism species activities can be exposed by protein concentration level. Therefore, this paper presented an innovative adaptive neural fuzzy inference system for biological proteins activities with the support of some neuro fuzzy rules. As demonstrated before, ODE models provide accurate and realistic result to predict and compute protein concentration measurement, but, ODE functionality rely on kinetic parameters, but it face a limitation in a scarcity of kinetic parameter. However, fuzzy inference model can work in missing and vague knowledge and provides a promise result, so, herein by selecting fuzzy inference models we dropped all the kinetic parameters. Based on the available data in the literature. For example, we depended on transcriptomic and proteomic expression data are available (see TCGA: <http://firebrowse.org/>) and (TCPA: <https://tcpaportal.org/tcpa/>), the ANFIS method exacted and constructed a rule-based reasoning system that takes into account the gene from the microarray data and searches for activator-repressor regulatory relationships The proposed method uses the ways of predicting changes in expression level in the target gene based on input expression level. This method removed the probable false predictions from the traditional fuzzy model and offered an open search space to infer the regulatory relations. An activator-repressor relationship was shown by the genes that most like fit the model. All simulation part was corroborated under MATLAB. Furthermore, ANFIS is generated from incorporation of fuzzy logic and neural network, as demonstrated before it's called. Therefore, Neural system has numerous inputs and also has multiple outputs, nevertheless the fuzzy logic has many inputs and single output, accordingly the blend of this two is known as ANFIS. The constructed ANFIS which utilized as a teaching technique for Sugeno-type fuzzy systems has a powerful structure as shown in (fig-3). ANFIS structure consist of multilayer feed-forward network with set of nodes that connected together in complex form by directed links. These links determine the direction of signal flow from one node to another; and these internal links has no weights.



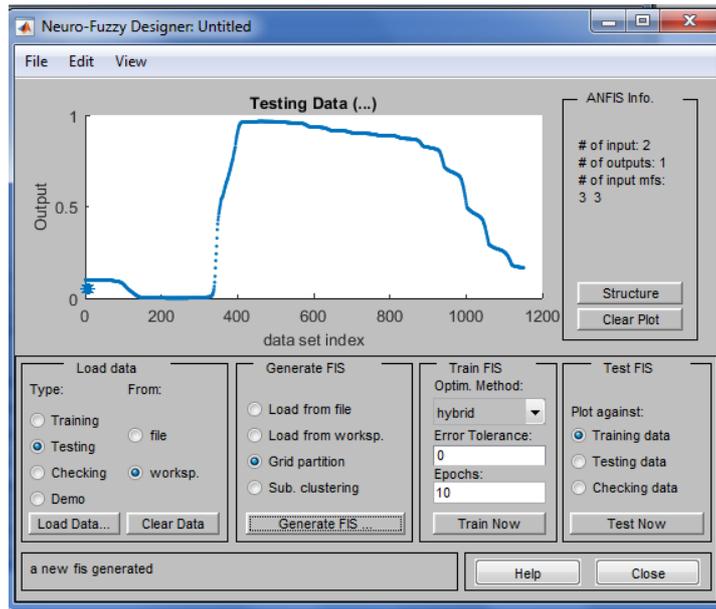
**Figure 3: ANFIS structure with multilayer feed-forward network.**

Creating an efficient fuzzy inference system from the ANFIS structure required several constraints. For instance, during the development process, developers distinct the number and the type of fuzzy system membership functions while designing of ANFIS model. In addition, it is very essential that the number of training epochs, the number of membership functions and the number of fuzzy rules should be regulated precisely. As shown in (fig-4), for the training stage we have adjusted for the ANFIS with two inputs and each input has three membership function (Low, Medium, High) respectively and one output also the number of with epochs equal 10.

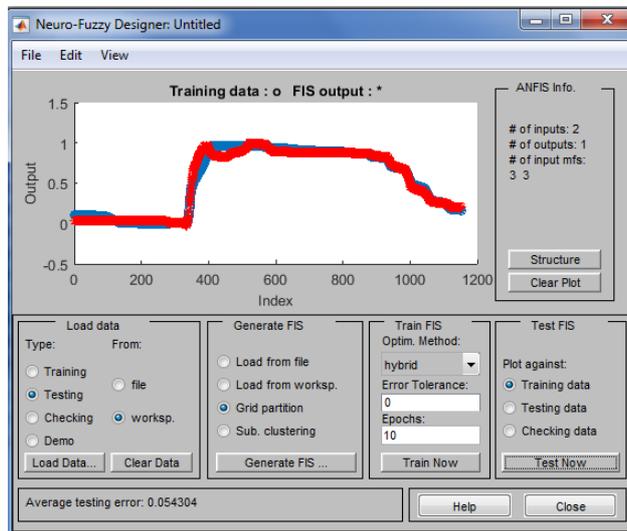


**Figure 4: ANFIS training error.**

Furthermore, Mapping of those parameters is highly important for the system since it possibly force the system either to over fit the data or will not be capable to fit the data. This modifying can be acquired by utilizing a hybrid algorithm. This algorithm combine several techniques such as the least-squares method besides the gradient descent method with a mean square error method. The smaller difference between ANFIS output and the wanted objective means a better (more accurate) ANFIS system. Therefore, we tend to decrease the training error in the training process as shown in (fig-4



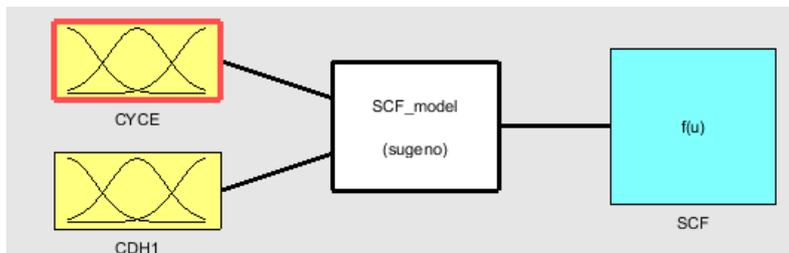
**Figure 5: ANFIS Testing Data.**



**Figure 6: ANFIS Training Data and FIS output.**

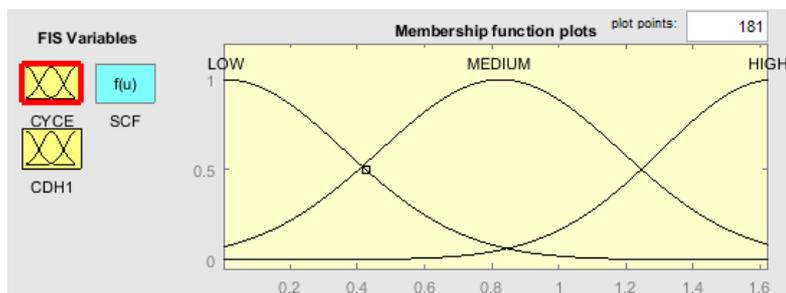
### 3. RESULTS AND DISCUSSION

Consequently, the results obtained by simulation are in good agreement with experimental measurements. For instance, the extracted Sugeno fuzzy inference mimicked the behavior of SCF. This fuzzy inference system has two inputs and one output inputs such as CYCE and CDH1 as shown in (fig-7).



**Figure 7: The constructed SCF fuzzy inference system by ANFIS.**

The SCF (FIS) reflects the same functionality as that of the ODE model Equation 1, but the fuzzy system can work without the need for kinetic parameters. In this way, the SCF fuzzy system can cover the limitations of the SCF ODE model. Both rely on the protein concentration levels to activate or degrade SCF protein level. The SCF fuzzy inference model should interpret the relations between SCF activator and degrader. The two inputs variables are both measured as Low, Medium and High protein concentrations measurements levels. These levels represent the fuzzy set format. As shown in (fig-8) and Table-1. For CYCE and (fig-9) and Table-2 for CDH1. Each table encloses the membership functions and range of input variables named as CYCE and CDH1.



**Figure 8: CYCE membership functions**

**Table 1: Membership function and range of input Variable (CYCE).**

CYCE fuzzy set parameters values	
LOW	[0.0006131 1.624]
MEDIUM	[0.0006131 1.624]
HIGH	[0.0006131 1.624]

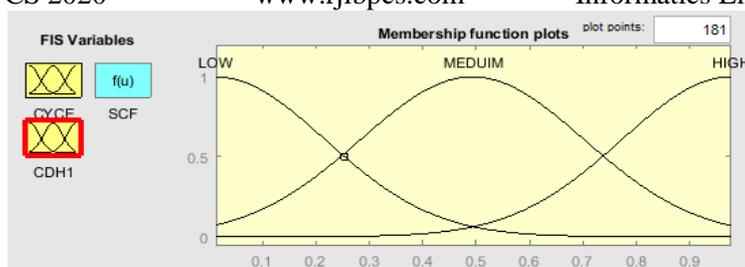


Figure 9: CDH1 membership functions.

Table 2: Membership function and range of input Variable (CDH1).

CDH1 fuzzy set parameters values	
LOW	[0.01247 0.9774]
MEDIUM	[0.01247 0.9774]
HIGH	[0.01247 0.9774]

While the output variable is measured as PRESENT, VERY LOW, LOW, LESS THAN MEDIUM, MEDIUM, ABOVE MEDIUM, AROUND HIGH, HIGH and SATURATED protein concentrations measurements levels. These levels represent the fuzzy set format. As shown in Table-3 and (fig-10); it encloses membership function and range of output variable.



Figure 10: SCF membership functions

Table 3: Membership function and range of output Variable (SCF).

SCF fuzzy set parameters values	
PRESENT	[0.0006926 0.9659]
VERY_LOW	[0.0006926 0.9659]
LOW	[0.0006926 0.9659]
LESS_THAN_MEDIUM	[0.0006926 0.9659]
MEDIUM	[0.0006926 0.9659]
ABOVE_MEDIUM	[0.0006926 0.9659]
AROUND_HIGH	[0.0006926 0.9659]
HIGH	[0.0006926 0.9659]
SATURATED	[0.0006926 0.9659]

Also, the recommended skills is a congregation of linguistic fuzzy rules which designate the relationship between distinct input variables (CYCE and CDH1) and output (SCF). These fuzzy rules are substantially utilized for inspect the best valuation for protein measurements levels. The fuzzy rules which interpret the behavior of these species as shown in in Table-4. These rules are used for compute and predict the crisp value using centroid defuzzification method of Sugeno type inference in Matlab that implies the SCF level. The linguistic fuzzy reasoning is expected to provide accurate results using these linguistic knowledge descriptions for the SCF Model as an alternative to using mathematical descriptions in ODE equations.

**Table 4: Fuzzy rules for the SCF fuzzy model, it encloses the fuzzy rules which are built on IF THEN statement. The first column represents the rule number; and the second and third columns represent system inputs while the last column represents SCF status. Each row represents a rule that describes the impact of inputs on the SCF value. For instance, in Rule 1, when CycE concentration is low (low availability) and CDH1 concentration is low (low availability) then SCF level also goes to less than very low level, this is small amount of availability and can be presented by (present) level, and so on for the rest of the rules.**

1. If (CYCE is LOW) and (CDH1 is LOW) then (SCF is PRESENT) (1)
2. If (CYCE is LOW) and (CDH1 is MEDUIM) then (SCF is VERY_LOW) (1)
3. If (CYCE is LOW) and (CDH1 is HIGH) then (SCF is LOW) (1)
4. If (CYCE is MEDIUM) and (CDH1 is LOW) then (SCF is LESS_THAN_MEDIUM) (1)
5. If (CYCE is MEDIUM) and (CDH1 is MEDUIM) then (SCF is MEDIUM) (1)
6. If (CYCE is MEDIUM) and (CDH1 is HIGH) then (SCF is ABOVE_MEDIUM) (1)
7. If (CYCE is HIGH) and (CDH1 is LOW) then (SCF is AROUND_HIGH) (1)
8. If (CYCE is HIGH) and (CDH1 is MEDUIM) then (SCF is HIGH) (1)
9. If (CYCE is HIGH) and (CDH1 is HIGH) then (SCF is SATURATED) (1)

Correspondingly, Table-5 shows the protein concentration measurements that are used as input data for the ODE model to calculate SCF values as outputs; this provided the SCF value. Also, these same input values would be used as inputs for our fuzzy experiments, and the results from the SCF fuzzy inference system will be compared with the SCF value from the ODE model as shown in (fig-11). This is the validation process for the developed fuzzy model. The results from the SCF fuzzy inference model closest to the ODE results.

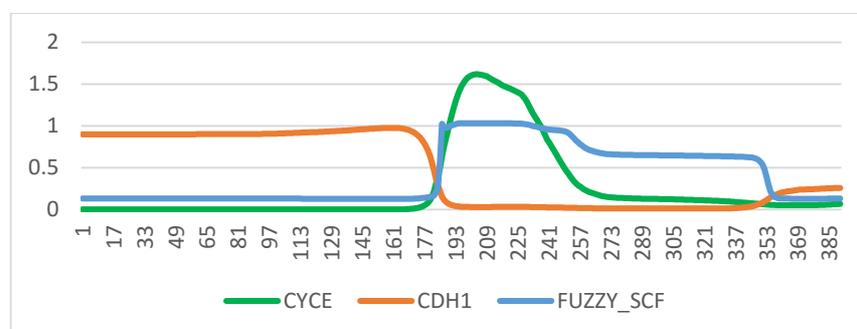
**Table 5: ODE model input and output protein concentration measurements. The protein concentration measurements that are used as input data for the ODE model to calculate SCF values as outputs.**

ODE model- result		
CycE	Cdh1	SCF
0.001	0.9	0.1



**Figure 11: Compute and predict SCf value via SCF fuzzy inference system depending on CYCE and CDH1 portions values without need for kinetic parameters. We utilized the suitable linguistic variables as input and output for estimate a crisp value for protein concentration amount. This work deals with some neuro fuzzy rules and these rules are relied on CYCE and CDH1 as inputs and the SCF protein as inputs**

Furthermore, the developed fuzzy inference system elucidated the relations between the SCF activator and inhibitor. For instance, over cell organism progression, CycE is activator of SCF, so when has a low level, CDH1 protein level decreases gradually while CycE increases dramatically. These changes in activator and degrader cause SCF levels to go up for a period. The SCF protein level as shown in (fig-12) goes up from being low to medium and then a high level; this is considered the maximum for that protein level. However, when CDH1 becomes active again, its concentration increases leading to reduction of SCF concentration gradually to zero as shown in (fig-12).



**Figure 12: Predicting SCF activity via Fuzzy inference system using a very large inputs data set. The proposed model calculates and predicts the protein concentration Level for SCF by employing extracted Takagi Sugeno type inference.**

However, there is some variation between the two in terms of exact values. Our aim is to provide a simpler and easier model than the ODE model and is a close approximation of it. This SCF FIS could be enhanced to provide better results. Therefore, in the next work, we attempt to optimize this model using one of the most popular autonomous optimization methods such as genetic algorithm or particle swarm optimization.

#### **4. CONCLUSION**

This paper estimated an adaptive neural fuzzy inference system for predicting protein concentration measurements values to explore proteins activities in organism. The proposed system is useful to predict and compute protein level for biological species in a simple manner. The proposed model can simply compute the crisp values best based on ambiguous and missing biological knowledge and without need for kinetic parameters which face scarcity limited in some organism. Essentially, the ANFIS extract an adaptive fuzzy inference system (Sugeno- type fuzzy systems) through the proficiency of learning fuzzy rules from data. Subsequently, in this research we relied on available biological data that represent protein concentration. These expression data, combined with half-life durations of mRNA and protein components that can be found in the literature. After succeeding the new fuzzy inference system from the ANFIS, we validate the outcome form the new extracted and developed model by comparing the result form the fuzzy inference model with the result from the ODE model. Herein, in the selected case study the developed model operates with two inputs variables (CYCE and CDH1) based on neuro fuzzy rules to compute the crisp value for the output variable (SCF). The developed Takagi Sugeno type inference model should be an alternative option to predict proteins activities magnitude instead of most popular and complex method such as ODE models. We inserted two proteins concentrations samples for (CYCE and CDH1) as input to the fuzzy inference system and make sure the outcome for the SCF is compatible for the protein concentration value form the ODE model.

#### **ETHICS APPROVAL AND CONSENT TO PARTICIPATE**

Not applicable.

#### **HUMAN AND ANIMAL RIGHTS**

No Animals/Humans were used for studies that are base of this research.

#### **CONSENT FOR PUBLICATION**

Not applicable.

#### **AVAILABILITY OF DATA AND MATERIALS**

The authors confirm that the data supporting the findings of this research are available within the article.

#### **FUNDING**

None

#### **CONFLICT OF INTEREST**

Authors have no conflict of interest.

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