International Journal of Engineering Research and Development
e-ISSN: 2278-067X, p-ISSN: 2278-800X, www.ijerd.com
Volume 9, Issue 10 (January 2014), PP. 08-16

Genomic DNA AnalysisUsing ANFIS and ANN

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Abstract:-Gene expression is governed by the promoter which frequently appears before its associated gene in DNA sequence. In order to locate a gene in a given sequence, researchers have to find the location of a promoter. Thus, the problem of promoter identification is of major significance within biology. So this issue maintains its importance. In this study, we employ ANN (Artificial Neural Network) and ANFIS(Adaptive Neuro-Fuzzy Inference System) classifiers to predict promoters of DNA sequences, and evaluate their performances. The obtained results show that the classifiers competethe existing techniques for identifying promoter regions.

Keywords:-Promoter prediction, ANN, ANFIS, data mining, bioinformatics, DNA

I. INTRODUCTION

In biology the cell is regarded as the basic unit of life in organisms, being the lowest level of structure that supports all life activities [1].Proteins are a major structural component of cells, having core responsibilities for the maintenance of shape and structure of the particular cell in addition to molecular recognition and catalysis. DNA, which forms the fundamental structural proponent for proteins, is the blueprint carrying all cell information and instructions responsible for protein synthesis and regulation. Molecular biology posits that the information is transmitted from the DNA strand through the RNA to proteins as illustrated by Fig.1.

This is the initial stage where RNA polymerase holoenzyme binds a gene onto mRNA i.e. messenger RNA sequence basing the DNA sequence as a template. The entire process of transcribing one gene characteristic on the other is referred to as an expression [2] and [3]:

This stage will occur in the specific cities considering the high specificity of the chromosome orientations. There exists a Blueprint that refers to a common name for genetic coding whichpossesses the instructions needed by cells in environmental adaptability. This is further collaborating with research that cites that in addition to the instructions carried by the blueprint, there exists a synthesis point for most of the molecule including the RNA and proteins. The instructions contained in the blueprint are designed in such a manner that they are only readable in transcription and translation.

In this sub sequential stage, the ribosomes synthesize the proteins with regard to the carried instructions on the mRNA. Such process through which the information on a single gene is transcribed onto another for facilitation of synthesis for another gene product is generally described as the gene expression. The new gene products, [2]and [5]are majorly comprised of protein structural aspects, though they exist as non-protein coding gene forms such as the rhino and the tRNA; having the minor non-coding RNAs such as mRNA and piRNA and the several diverse long non-coding RNAs that are later responsible for protein regulatory functions. Such specificity is as a result of the recognition by the RNA polymerase from the DNA sequence generally referred to as Promoter.

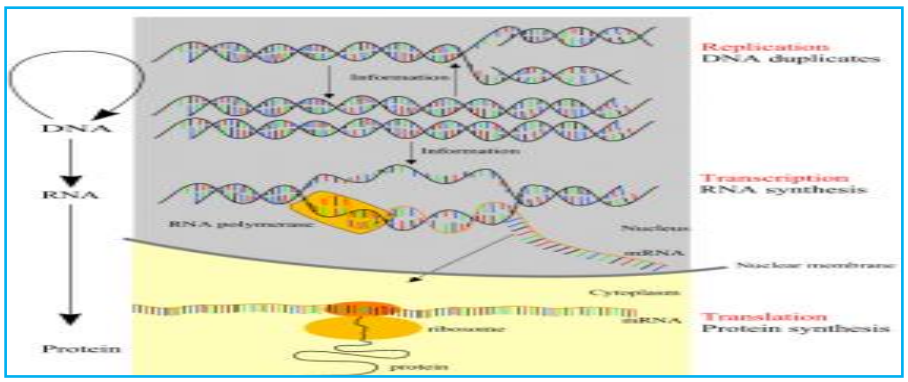

Fig. 1: The central dogma of molecular biology [3]

The promoter is a location within the DNA molecule where the transcription occurs. It is an indispensable location of the gene expression. Molecular biology cites that promoter prediction and identification is a major challenge in this field. More so, the gene data has over the past been observed to grow exemplary too fast to predict the promoter localities. This situation has compelled specialists to seek other intermediary measures in the prediction of the promoter in the DNA molecule. Such endeavor has integrated the use of computations.

It is of great significance to note that before the1990s' computer programs used for assembling coding arrays into translatable MRNA were not in existence, though various conventional techniques existed long since the 1980s and were used in the prediction of genomic DNA coding locations. Since the innovation and adoption of the digitalized techniques, prediction of the promoter has improved tremendously by each day. Such programs are GenViewer[8], GeneID[9], GenLang[10], GeneParser[11], FGENEH [12], SORFIND [13], Xpound[14], GRAIL[15], VEIL[16], GenScan[17]. This research endeavor, notes that the [18],GRAIL and GeneScan are the most used techniques in both learning institutions and commercially. These techniques are based their endeavor on the evaluation of whether the motifs in DFNA exist or not. Such motifs may be described as either promoter or no-promoter [19]. These researches are based on the manipulations of position weight matrices and the Markov models as indicated in [20][21] and[22]. The endeavor will also integrate artificial intelligence as opposed to a monopoly of statistical approaches.

Amongst them is the Neural Network shave that exhibit acceptable sensitive results. However, despite such efforts, the specificity of the results leaves much to be desired owing to a very high false positive occurrence. This is evidenced in [23]and [24]. In order to achieve a positive promoter prediction, the integration of computational approaches still poses great promise, though this has been subjected to hefty debating. In a bid to eliminate such discontent, specialists in molecular biology suggest that the integration of the ANN is a much proficient approach.

1.1. Promoter and Significance of promoter prediction

The Blueprint; a common name for genetic coding is believed to possess the instructions needed by cells in environmental adaptability. This is further collaborating with research that cites that in addition to the instructions carried by the blueprint, there exists a synthesis point for most of the molecule including the RNA and proteins. The instructions contained in the blueprint are designed in such a manner that they are only readable in two ways as mentioned earlier in this paper i.e. transcription and translation [25].

The messenger RNA; usually a single strand RiboNucleic Acid molecule, is amalgamated usually from one of the strands contained in DNA through a complementary of the origins. This strand does relate to a gene. Transcription will usually commence with the RNA polymerase being engulfed by a lone point in the DNA molecule known as the Promoter. [3]points out that, efforts to incorporate computerized biology have helped to easily locate the promoter regions.

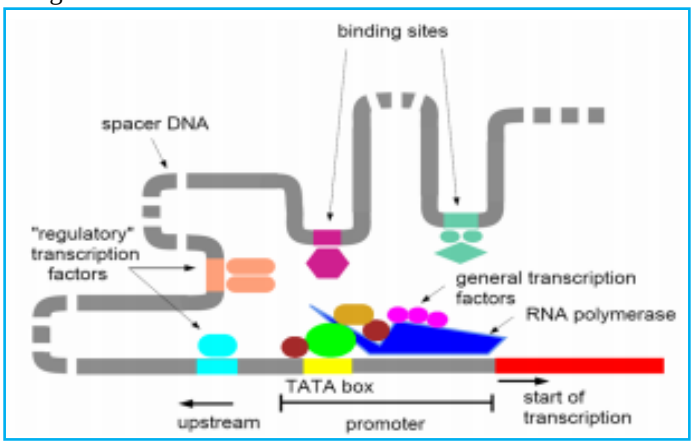

Fig. 2: Position of the promoter in a dna sequence.

This has had a very significant impact on transcription as these regions are numerous in the DNA molecule thus easing the gene expression [3].

This process is facilitated majorly by the Promoter having much consideration of the responsibility it has on the transcription from a DNA strand to an RNA strand. This is further identified as the sequential upstream from the Transcriptional Start Site (TSS). This is well illustrated in the Fig. 1 [6]. The entire process commences with the binding of the RNA polymerase to a promoter array in the DNA molecule up to a point where the coding is realized. Coding occurs during the upstream movement around the promoter usually starting at 3' end of the DNA molecule to the 5' point in a DNA molecule [26] [22].

In rare cases, then there may be the existence of the upstream of the TSS of DNA array that possess transcriptional characteristics, thus the presence of the promoter may not be a necessity. When promoter prediction is incorporated, a researcher is at ease to constrict down the entirely colossal DNA sequences. This paper acknowledges that through biological interventions, it is made easier to verify the DNA sequence that may either be transcribed or no. This though comes along with economic constraints.

In the recent past, the integration of computerization in the promoter identification and prediction has raised debate. And the results obtained by evaluating the classification model proposed in this paper confirm that applying ANN for promoter sequences recognition is promising

II. METARIAL andMETHODS

There are two core classes of the promoter prediction, namely '+' and '-'. These classes will denote the existence of promoter prediction in the DNA sequence, having the '+' denoting for a positive indication of promoter location in the DNA sequence and the '-' denoting the absence of promoter locations in the DNA sequence. This research paper proposes to deal with a supervised learning technique in the prediction of promoter regions in the DNA sequence.

2.1. Data Set

The research sought to incorporate the E. Cole promoter gene arrays of DNA in the testing the proficiency of ANN. Such data were collected from the UCI Repository[27]; this contains a set of 106 promoter and non-promoter instances. The research paper notes that such data is viable in the comparisons of ANN with the models existing in the literature; additionally such information involving the use of the data set is publicly available [4].

The 106 DNA arrays are composed of 57 nucleotides each. 53 of the DNA sequences in the data set had a '+' denoting, indicating the presence of promoter location in the DNA array. The research then sought to align the (+) parameter instances separately allowing for transcription. The following data characterize the (+) instances as observed from the experiment. One is that for every occurrence the (+) represents for the promoter positive presence, a name was also given in each instance and a classification of the DNA array was made composing of A, T, G and C stand for Adenine, Thymine, Guanine, Cytosine [27].

2.2. Adaptive Neuro-Fuzzy Inference System (ANFIS)

This is a Fuzzy Sugeno technique that is usually placed in a framework for adaptive systems to facilitate adaptation and learning [28].. It enhances the utilization of least-squares and a back propagation gradient descent technique. In addition, a hybrid learning algorithm is used in the identification of the membership function parameters and fuzzy IF- Then regulations that are usually considerate of single output or singleton [29]. The fuzzy inference is considered to bear two inputs and a single output. An equation is here below illustrated to affirm to the fuzzy if-then rules of Takagi and Sugeno rule[30].

Where if x=A and y=B then z is f (x, y)
Where A and B are the fuzzy sets in the antecedents and
Z = f (x, y) is a crisp function in the consequent.
F (x, y) is usually a polynomial for the input variables x and y.
Consider z= f (x, y) is a first-order Sugeno fuzzy inference system, which contains two rules.

Rule 1: If x is A1 and y is B1, Then: f1 =a1 x +b1 y +c1
Rule 2: If x is A2 and y is B2, Then: f2=a2 x +b2 y +c2

ANFIS structure **(Fig. 3.)**contains five layers excluding input layer.

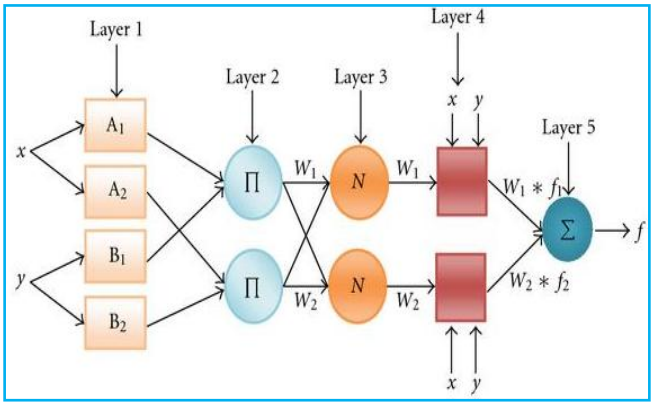

Fig.3: ANFIS structure [31]

Layer 0 is the input layer. It has no nodes where n is the number of inputs to the system.
The functionality of nodes in ANFIS can be summarized as follows [32].
Layer 1: Nodes are adaptive; membership functions (MFs) of input variables are used as node functions, and parameters in this layer are referred to as antecedent or premise parameters.
Layer 2: Outputs that indicate Nodes are the fixed using firing strengths
Layer 3: Outputs that indicate Nodes are the fixed using normalized and strong formality
Layer 4: The layer 1 gives the Nodes n adaptive feature for the first order technique and defuzzier parameters
Layer 5: An equal output in relation to the sum of the entire rules' output is fixed to the single node

2.3. Artificial Neural Network (ANN)

The artificial neuron is an enthused component in the body's natural neurons through computation modeling [33]. The artificial Neural Network works in an induced principle where in instances that the body's neurons do receive signals through the naturally induced synapses occurring in the dendrites of the neuron, with a much intense magnitude, the ANN is induced thus releasing signal messages via the axon. In other instances the signal may be sent to other synapses and probably induce other neurons as noted by [34]. Usually the human brain is capacitated with the ability to hold numerous and complex operations, thus hails from the possession of numerous and enabling elements such as the complex neurons that consist of a more than 10^3 to 10^4 more neuron affiliations. This compounds the neuron coverage in the brain to approximately 10^{14} interconnections [34]and [35].

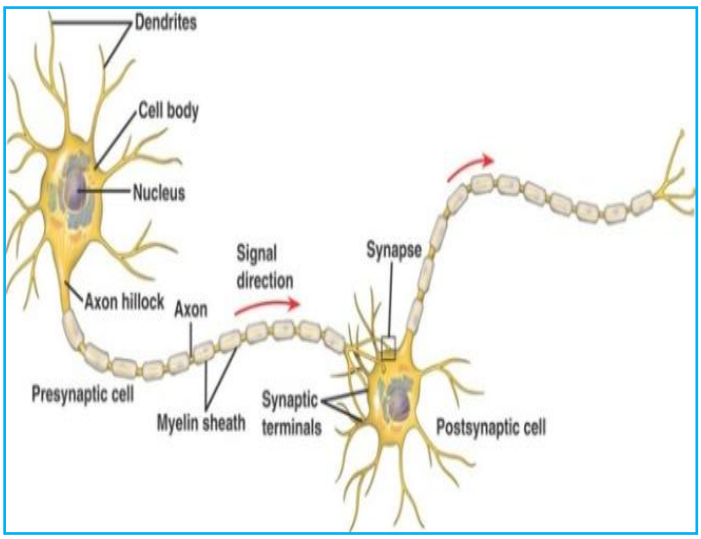

Fig. 4: Neural dendrites, axon, and synapse [37]

In modeling, the density of real neurons is highly exhibited, fundamentally comprising of synapses, which are compounded by the density of the respective signals, in addition this is taken under a mathematical simulation thus helping to evaluate the activation of the neuron. This moreover helps to compute the result of the artificial neuron. According to [26] this hails from the property of the ANN that they can integrate artificial neurons in the processing of information.

Usually, getting a precise definition of learning is a difficult task considering that the capability to learn is an essential characteristic of intelligence. From the experiment, it is posited that the ANN description is able to view from the efficient performance of a neuron task owing to updating of network systems. This is evidenced by the literature in [25] and [29].

One is able to obtain the desired output from the manipulation of the ANN; this is so by modifying the ANN weights. In such modifications, getting them by hand is a rather complicated and impossible task, giving supportive ground to the incorporation of ANN. In addition, [29] and [30], algorithms may be integrated in the modifications and alignments of ANN weights.

The paper acknowledges the back-propagation algorithm where ANN is aligned in layers and is simulated for a forward signal transmission, thus allowing for signal errors to be propagated on the reverse [30]. The input area is the location where the neurons impact the networks and therefore initiating the output. Fig. 5 illustrates a three layered neural network having inputs and output.

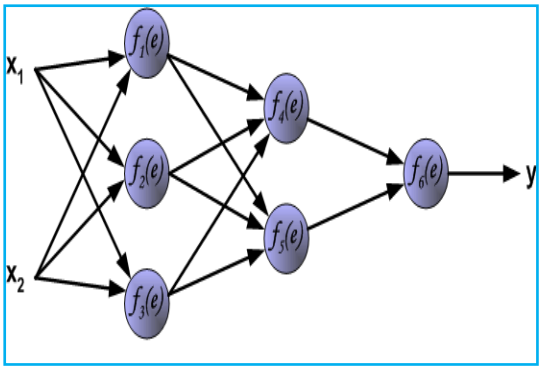

Fig. 5: Multi-layer neural network

A neuron possess two units that complement the products of weight coefficients and input signals with the other unit being responsible for the neuron activation function following its capability to decode non-linearity. The units are denoted as Signal e for adder output signal and Signal y for the output signal of non-linearity.

The experiment notes the necessity to obtain a training data set that will comprise of input signals of x1 and x2 with a desired output z. In the network training, modifications of ANN weights are evaluated using the algorithm that will seek to commence with manipulating for both input signals from the training data set. Consequently, the output signals' values are made easier to identify from each neuron in the network [33]. (See Fig. 5)

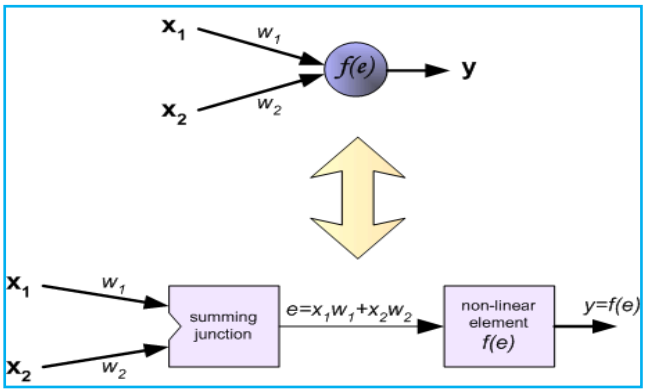

Fig. 6: Teaching Process of Multi-Layer NN

The 106 DNA sequences composing the E. coli will feature for having 4 values. These values will stand for the A, T, G and C i.e. Adenine, Thymine, Guanine and Cytosine. Training the ANN and the DNA array with the 57 nucleotides attached to each promoter instance is coupled as an ANN input. The DNA sequence instances present the network output usually a description of either (+) or (-) occurrence.

III. RESULTS AND DISCUSSION

The experiments aim at evaluating an approach for proper arrays in the prediction and identification of the Promoter using the ANN and ANFIS. It also integrates the comparison of existing approaches from past researches. Such endeavors are usually conducted in two phases that showcase a precise learning algorithm, training and testing. Training will involve establishing a classification model; testing entails the implementation of the classification model previously established.

A standard 5-fold cross-validation was integrated into the evaluation of the ANN performance by having the dataset being randomly portioned into 5 subsets. This classification ensures an equal ratio of (+) and (-) promoter locations in the DNA array.

The training occurred on the ANN for a series 5 times engaging only 4 subsets for each training while as retaining the remaining 5 for testing. As a result, 5 models were established during the cross-validation. Additionally, a final prediction performance was carried out on the subsets evaluating the average results from the experiment.

The performance of the promoter predictions was evaluated using the threshold parameters; accuracy (ACC), Mathew's Correlation Coefficient (MCC), sensitivity (SE) and specificity (SP). A couple of equations were integrated to affirm to the results. These were;

$$SE=TP/(TP+FN) \quad (1)$$
$$SP=TN/(TN+FP) \quad (2)$$
$$ACC= (TP+TN) / (TP+TN+FP+FN) \quad (3)$$
$$MCC=((TP*TN)-(FN*FP))/SQRT((TP+FN)*(TN+FP)*(TP+FP)*(TN+FN)) \quad (4)$$

TP is true positive (promoter predicted as promoter)
FN is false negative (promoter predicted as non- promoter)
TN is true negative (non- promoter predicted as non- promoter)
FP is false positive (non- promoter predicted promoter).

The detailed performance of modules in term of SE, SP, ACC and MCC is shown in the following tables.

This involved the testing of the several structures of the ANN with one layer, 'logsig' transfer function and 'trainrp', 'traincgp' learning algorithms and had the following results;

Table 1: The Performance of ANN-1

Hidden Layer / The number of neuron	Transfer Function	Learning Algorithms	MCC	SE	SP	ACC
40-1	logsig	trainrp	0.69	0.75	0.92	0.84
40-1	logsig	traincgp	0.70	0.71	0.97	0.84
40-1	logsig	trainscg	0.66	0.72	0.92	0.82

Table 2: The Performance of ANN-2

Hidden Layer / The number of neuron	Transfer Function	Learning Algorithms	MCC	SE	SP	ACC
75-1	logsig	trainrp	0.67	0.75	0.91	0.83
75-1	logsig	traincgp	0.67	0.75	0.91	0.83
75-1	logsig	trainscg	0.64	0.72	0.91	0.82

Table 3: The Performance of ANN-3

Hidden Layer / The number of neuron	Transfer Function	Learning Algorithms	MCC	SE	SP	ACC
100-1	logsig	trainrp	0.62	0.75	0.86	0.81
100-1	logsig	traincgp	0.69	0.69	0.97	0.83
100-1	logsig	trainscg	0.65	0.71	0.92	0.82

From the above experiment, this paper notes that there was a positive result, having a tremendous 0.84 (ACC) that is produced by the ANN with the one layer having 40 neurons, logsig transfer function and trainrp learning algorithm.

In the experiments with the ANFIS, the paper acknowledges with great attention that in preparation of FIS, an FCM (fuzzy c-means) was used. This also integrated the application of Genfis3 which its core role is the generation of Sugeno-type FIS structure (fismat) with a given coding for input data (Xin 57-element nucleotide sequence) and output data (Xout - two classes, promoter or non-promoter).

This information is illustrated as;ANFIS info:

Number of nodes: 9340
Number of linear parameters: 4640
Number of nonlinear parameters: 9120
Total number of parameters: 13760
Number of training data pairs: 80
Number of checking data pairs: 0
Number of fuzzy rules: 80

Table 4: The Performance of ANFIS						
	1. Model	**2. Model**	**3. Model**	**4. Model**	**5. Model**	**Average**
ACC	0.65	0.75	0.75	0.70	0.65	0.7008
SE	0.80	1.00	0.90	0.80	0.77	0.8538
SP	0.50	0.50	0.60	0.60	0.54	0.5477
MCC	0.31	0.58	0.52	0.41	0.32	0.4281

From the experiment on promoter prediction the best results were found to be at 0.70 (ACC) having been as a result of a non-satisfactory relationship as compared to ANN.

Doing a review on the literature affirms that the application of the leave-one-out cross-validation (LOOCV) in the promoter prediction and when evaluating the performances of the ANN and ANFIS. In these endeavors the entire data excluding the single observation that was engaged in training. Such techniques are a bigger integral part in Bioinformatics[43].

Table 5:The Errors of Some Machine Learning Algorithms on Promoter Data Set.		
System	Errors	**Classifier**
REX-1	0/106	**Inductive L.A**
ANN	**0/106**	**One hidden layer**
IREM	2/106	**Class-based entropy**
KBANN	4/106	**A hybrid ML system**
BP	8/106	**Standard**
ANFIS	**11/106**	**genfis3**
O'Neill	12/106	**Ad hoc tech. from the bio.**
NearNeigh	13/106	**A nearest neighbours**
ID3	**19/106**	**Quinlan's decision builder**

By comparison the classifiers already integrated in the experiments seeking to investigate on promoter prediction, as in Table 4. ANN as described there in the paper does perform better than classifier for promoter prediction, BP, ID3, KB, NN and O'Neil parameters bearing in mind the occurrence of errors.

IV. CONCLUSIONS

Usually, in Bioinformatics a challenge exists in endeavors seeking to predict and identify the location of promoter regions in the DNA molecule. In such quest to investigate on the same, this paper finds the ANN and ANFIS techniques as being potential eliminators of such challenge. Through the computational ANN, a model based on the structure and functions of biological neural networks is established. In this, information is expected to flow through the network structure of the ANN because a neural network changes - or learns, in a sense - based on that input and output. It will involve a hybrid learning procedure used to form an input-output mapping based on the training data pairs, in addition, employing a fuzzy inference system in the framework of adaptive networks. Thus, the writer finds it of significance that employing ANN for promoter prediction leads to promising results and leads to improvements, increasing the accuracy of the results obtained.

Employing Adaptive Neuro-Fuzzy Inference System is not an adequate method for prediction of promoter as exhibited by the results of the experiment. The dimensionality of this dataset should be reduced by means of the feature selection process, thereby in the future in a bid by increasing the accuracy of employing ANFIS.

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