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Protein Structural Classes Prediction Based On Convolutional Neural Network Classifier with Feature Selection of Hybrid PSO-FA Optimization Approach

Sarneet Kaur[1], Ashok Sharma[2], Parveen Singh[3]

[12]Department, [12]Lovely Professional University, [3]University of Jammu
E-mail: [1]sarneetkaur@live.com,[2]ashok.23877@lpu.co.in, [3]imparveen@gmail.com

Abstract: Protein can be classified in different classes like A (All α), B (All β), C (α+β), and D (α/β). A lot of work has been performed for analyzing the Sub-cellular localization of protein structure. The visualization of protein folding into compact conformation is evaluated. In the present work different algorithms like particle swarm optimization (PSO), Firefly algorithm (FFA) and K-Mean clustering algorithms are used to classify different structures of protein. A Conventional neural network (CNN) classifier is utilized for analyzing and comparing different protein classes in terms of SVM classifier available conventionally in terms of various performance parameters. Near 100 % accuracy, sensitivity, specificity, and MCC values are obtained for class A & class B protein structures. However, somewhat lower values of these parameters are obtained for class C and class D protein structures. CNN classifier proved better than SVM classifier and can be helpful in predicting the protein structures. A hybrid PSO-FFA algorithm is used to extract the features for different classes of protein. Structures of four classes of protein are evaluated in terms of scoring spaces and fitnessvalues.

Keywords:Convolutional Neural Networks, Firefly Algorithm, Particle Swarm Optimization, Protein Folding.

1. INTRODUCTION:

Sub-cellular localization of protein structure is attempted by numerous researchers by using several techniques of deep learning and machine learning. Most of these researchers have classified the handcrafted image features of protein using CNN techniques like Resnet, Inception, and Vgg16. A lot of time is taken by these networks for training and considerable memory is used to store such networks. In most of the previous attempts Sub-cellular localization of protein, chiefly machine learning approaches areutilized.

Fivedifferentcategories(Hoechst,Giantin,NOP4,LAMP2,andTubulin)ofproteinareclassifiedby Bolandetal. [1] using several features like Haralick texture and Zernike moments provided to neural network (88%) and classification tree (66%). Boland and Murphy [2] localized the protein structure in ten distinct cell organelles utilizing HeLa dataset and utilizing different features like Haralick grain, SLF (Sub-cellular location feature), and Zernike moments fed to the neural networks (83%). Multi-resolution (MR) decomposition is carried out by Chebira et al. [3] which arefollowed by the processes of feature extraction and then classification of images are done for every MR space. Accuracy of 95% was achieved with 2-D Hela dataset utilizing NN classifier for extracting 26 different features. Hung and Murphy [4] performed a

comparison offivedifferent techniques ofML and observed that Ada boost technique of optimization of neural networksfor 2D Hela images provides 88.2% accuracy. Nanni andLumini[5] obtained 85% accuracy with Hela dataset utilizing SVM technique on Invariant digital patterns. Although the problem of protein localization wastackled successfully usingmachine learning methods for extracting discriminate features from different images. Litjens et al. [6] emphasized that the tendency of relating CNN for classifying microscopic descriptions is growing by the years. Different steps of feature extraction are reduced using deep learning and system is allowed to learn features of image by itself. Kraus et al. [7] utilized elevenlayers CNN model (DeepLoc) to classify budding yeast cell images of proteome into fifteen different categories and achieved 84% accuracy. Parnamaa and Leopold [8] trained neural network (DeepYeast) for classifying fluorescent protein with sub-cellular localization and achieved 91% accuracy. Liimatainen et al. [9] trained a Full Convolutional Network (FCN)to detect protein in thirteendifferent cell organelles for Human Protein. Xiao et al. [10] utilized transfer learning to classify deep yeast protein images for depicting ten different classes. Eleven layers of Vgg and Resnet were trained and accuracy of 87% and 88% was obtained for these two datasets respectively. Pre-trained networks such as InceptionV3, ResNet50, and InceptionResnetV2 by were applied by Kensert et al. [11] for classifying mechanism of action datasets with 95-97% accuracy. Thus organelle proteome was efficiently classified by CNN. Training of CNN can be performed using fine-tuned or scratch as per database size. Human protein can be easily classified into major cell compartments. There are limited cell organelles and classified for obtaining single cellimages.Machinelearningandfeatureextractiontechniquesareusedtoobtaintheexcellentresults .Results can be be further improved using image resizing and cropping. But for protein structure learning, only a few CNN models are used till date.

Native Conformations of Proteins:

Proteins are considered as molecular instruments that are used to express genetic information. Protein iscreated by human body using datareceived from human Deoxyribonucleic Acid (DNA) that is composed of linear chain of deoxyribo nucleotides. DNA codes are used for producing a protein with respective linear chain of amino acid. This resulted into folding of protein into a meticulous 3D shape which is called as native conformation. 3D structure of protein also called as conformation is accountable directly for its operation [12]. Basically, proteins are created from naturally-occurring similar sets of twenty amino acids. From these different combinations, a cell can be used to produce proteins with remarkably different activities and properties [13]. On the basis of their side chain properties there are five main classes of amino acids: (1) hydrophobic (water-hating or non-polar); (2) hydrophilic (water-liking or polar); (3) aromatic; (4) negatively charged; (5) and positively charged [13]. Protein’s shape is specified by sequence of its amino acid. To obtain an accurate protein foldan important role is played by cellular environment. The shape of protein can be determined by the hydrophobic force of clusters. Alberts et al. [14] described that hydrophobic molecules of protein are liable to be enforced together in aliquid environment so as to minimize the effect of hydrogen-bonded networks ondifferent molecules of water. So, non-polar side sequences in proteins tend to bunch in the inside of molecule, whereas the polar groups are likely to be arranged outside of molecule. Therefore, hydrogen bonds can be formed with combination of water and polar molecules of protein. Figure 1 provides an illustration of how protein is folded into its compact conformation.It is noted that hydrophobic core regions are established in the inside of protein whereas hydrophilic amino acidiswrapping the interiorhydrophobicacid.

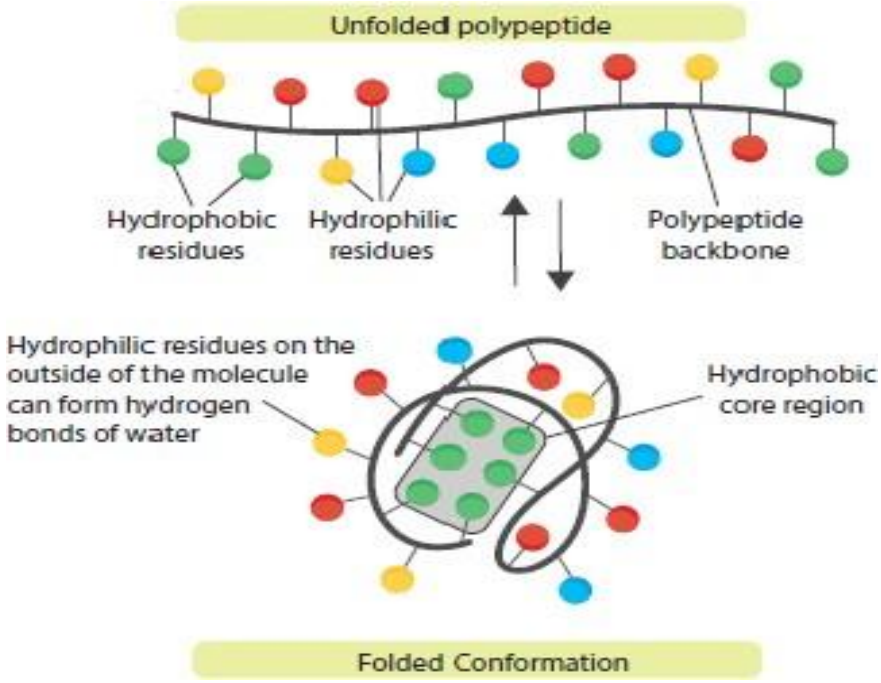


Fig. 1 Visual Representation of Protein Folding into a Compact Conformation

Currently, there are two main methods for predicting the neighboring 3D structures for protein, i.e. using an X-Ray Crystallographer (XRC) and a Nuclear Magnetic Resonance (NMR). Although, XRC is a costly technique with respect to time and economy, yet during the crystallization process of protein, problem can occur, and there is a possibility that the final conformation obtained may not be the native one. NMR is a most recent method to predict the protein structure and is not restricted to the number of molecules to be crystallized. However as with the case of XRC, NMR also presents a small amount of uncertainty in predicting the 3D protein structure. Furthermore, significant human efforts as well as vastly equipped laboratories are required in both the processes. In the current scenario, studies are involved in silico methods for predicting the native protein structure withan aim for reducing the gap between sequence and structure, the economic cost and time efforts. The PSP is a problem to find the protein's native structure, with a knownsequence of several amino acids [13, 15]. Computational methods are approaching the PSP are divided into three major categories: (1) comparative modeling or homology, (2) ab-initio, and (3) fold recognition or threading.

2. METHODOLOGY:

1. In first step dataset information is extracted from excel of 25PDB dataset. After this pre-processing of data is performed where dataset is refined and then training and testing modules areseparated.
2. In the second step sequence alignment is applied to a secondary proteinstructure.
3. Next feature selection technique is applied to a secondary protein structure.A hybrid model using PSO and Firefly optimization is utilized for feature selection. It helps in selecting the best attribute of secondary structure of protein and improving the system accuracy and reducing the timecomplexity
4. In the fourth step the CNN layer is initialized for training of CNNmodel.
5. After initialization of CNN, itis trained with different classes of proteins and

secondary structure of protein ispredicted.

6. In the last step parameter performance of projected CNN model isassessed.

Different training options for CNN models are highlighted in Table 1. Matrices like Max Epochs, Learn Rate Drop Factor, Initial Learn Rate, Learn Rate Drop time, , and Mini Batch Size are used to train the currently utilized CNN model.

Table 1: Hypermeters for Model Tuning

Sr.No.	Training Option	Parameter Value
1	Max Epochs	100
2	Learn Rate Drop cause	0.1
3	Learn Rate Drop Time	20
4	Initial Learn Rate	0.001
5	Mini Batch Size	8

FLOWCHART

In this section, the flowchart of present study is shown in Figure 2 and its various components explained below.

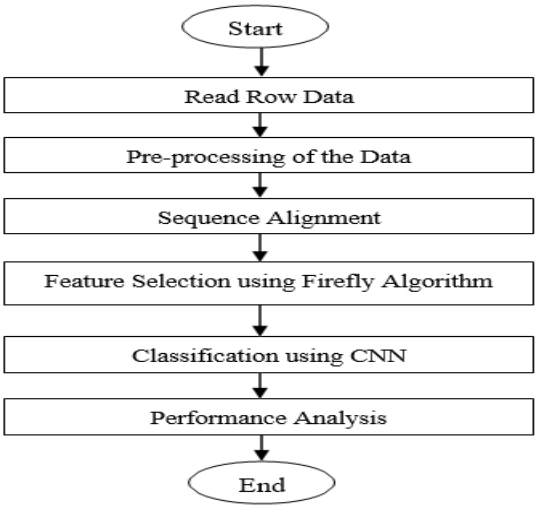


Fig. 2 Flowchart of the Present Study

- Firefly algorithm(FFA)

A Firefly algorithm is proposed by X-S Yang is inspired by nature, multimodal metaheuristic algorithm and is based on blinking performance of fireflies [16]. Unique tiny rhythmic flashes are produced by every species of fireflies and the process of producing flashes is called as bioluminescence. Firefly algorithm is designed on the basis of three ideal principles: (i) as all fireflies are having the unisex nature, so a firefly can be attracted toward another firefly in spite of their sex factor. (ii) Attractiveness is directly related to the luminance level of the fireflies, therefore the less bright firefly is always attracted by a bright firefly. (iii) An objective function is used to calculate the brightness level in a firefly [17]. Brightness and attractiveness are directly proportional to distance, so if the distance is increased then both these properties are decreased [18]. If any firefly does not find another firefly in its surrounding space,thenitsmovementwillberandominanydirection.Flashinglight isthemainpropertyinafireflyalgorithm [19] that is accountable for attracting the neighboring fireflies. Firefly can charge and discharge its light at regular interval, thus they are having an oscillatory behavior. Generally, fireflies stay mostly active for the period of the night times of

summer season [20]. When any firefly comes in contact witha neighboring firefly, mutual coupling is occurred between both the fireflies. Any male firefly tries to attract the neighboring female firefly through its signals [21].In response to these signals by male firefly, the female firefly discharges its flashing lights. Consequently, distinct illuminating patterns of male as well as female fireflies are produced to encode the information like sex and identity of the species [22]. Generally, a female firefly can be more attracted towards any male firefly with brighter illuminating light. Blinking intensity is inversely proportional to source distance of fireflies. In some unique cases, a female firefly is unable to differentiate between the weakest and strongest flash, which are generated by a distant or neighboring male firefliesrespectively.

Table 2 Firefly Algorithm

```
Step-1: Generate initial population of fireflies X randomly.
        X = {w1,w2,...wn}
Step-2: Compute the brightness of each firefly by using objective function f(wi) as
        B = {B1,B2....Bn} = {f(w1),f(w2),...f(wn)}.
Step-3 : Set light absorption coefficient γ.
Step-4 : While (t ≤ max iteration )
                For i=1 to n
                        For j=1 to i
                                If (Ij> Ii)
                                        Move firefly i to firefly j by using eq. (6).
                                End if
                                Attractiveness varies with distance r via exp(– γr²).
                                Evaluate new fireflies and update brightness.
                        End for
                End for
                t = t+1
        End while
Step-5: Rank fireflies according to their fitness and find the best one.
Step-6: If Stopping criteria is reached, then go to step-7.
        Else go to step-4.
Setp-7 : Stop.
```

A firefly's brightness can be established by an objective function. Firefly attractiveness directly depends on light intensity perceived by neighboring fireflies; variation in attractiveness (β) can be defined with respect to distance (r), and is provided by relationships in equation 1 as

$$=\beta e^{-\gamma r}2 \qquad (1)$$

Here $\beta 0$is the attractiveness value at distance r = 0. A particular firefly's movement towards a brighter firefly 'j' can be determined by equation 2 as:

$$x^{t+1} = x^t + \beta e^{-\gamma r}2\, i(x^t - x^t) + \propto \qquad (2)$$

In equation 2, second term is because of attraction. Last term is because of randomizationand $\propto t$is the parameter of randomization, also $\in^t$is a vector with all the numbers as random which is drawn using Gaussian distribution function at any time(t).The case with $\beta 0$= 0 is considered as a random walk. Additionally, randomization parameter $\propto t$can be expanded to other distribution functions like L´evy flight function.

- **Particle Swarm Optimization (PSO) Algorithm**

PSO is based on a meta-heuristic principle of swarm optimization. A set of prospective solutions are used by PSO which are called as particle swarm for solving optimization

problems. Firstly, PSO is applied for solving continuous optimization problem and later on it is adapted for solving binary as well as discrete optimization domains. Particles normally fly in the setback area, where they search the high valuesolutions. These particles commune with oneanother in a mutual searchattempt. Combined swarm intelligence is the main driving force in PSO, which prove its success in handling numerous difficult problems.

The process of searchingis started when a swarm of particles are scattered randomly in thesearch area. After every iteration, particle adjustsits position (*p*)andvelocity (*v*)utilizing information collected by it or received byits neighbors. Theequation for velocity and positionof particle swarms with present particle states (*v'*and *p'*):

$$v = \omega v' + R_1(p_{\mathrm{p}} - p') + R_2(p_{\mathrm{g}} - p') \quad (1)$$

Here 'ω'controls the particle's inertia. The $p_{\mathrm{p}}$is best position obtained by particle, and$p_{\mathrm{g}}$is the best positionobtained by its neighbors. The R_1 and R_2 are homogeneously distributed randomvariables that load the learning resources.

- **CNN CLASSIFIER**

CNNarchitecture used to map the protein chains into folds and is provided in 3. It consists of totalfifteen layers including one input layer, ten convolution layers, one pooling layer, one hidden layer, and one flattening layer. Softmax function is utilized and applied to the output layer nodes for predicting the fold probability of proteins. Positional information of protein sequences is represented by $L \times 45$ input numbers of a protein sequence having variable length L. CNN network accepts variable sequence protein features as input, that are changed into hidden features using ten hidden layers of CNN. Two windows of size 6and size 10 are used. CNN can alternate between the pooling and convolution layers and the output can be available at fully connected layers which include nonlinear classifiers, like Softmax classifier, used to estimate the condition probability for each class. Nonlinearity is introduced in CNNs by using rectified linear units (ReLU) which is an activation function with nonlinear transformations resulting into 10 x L hidden features.

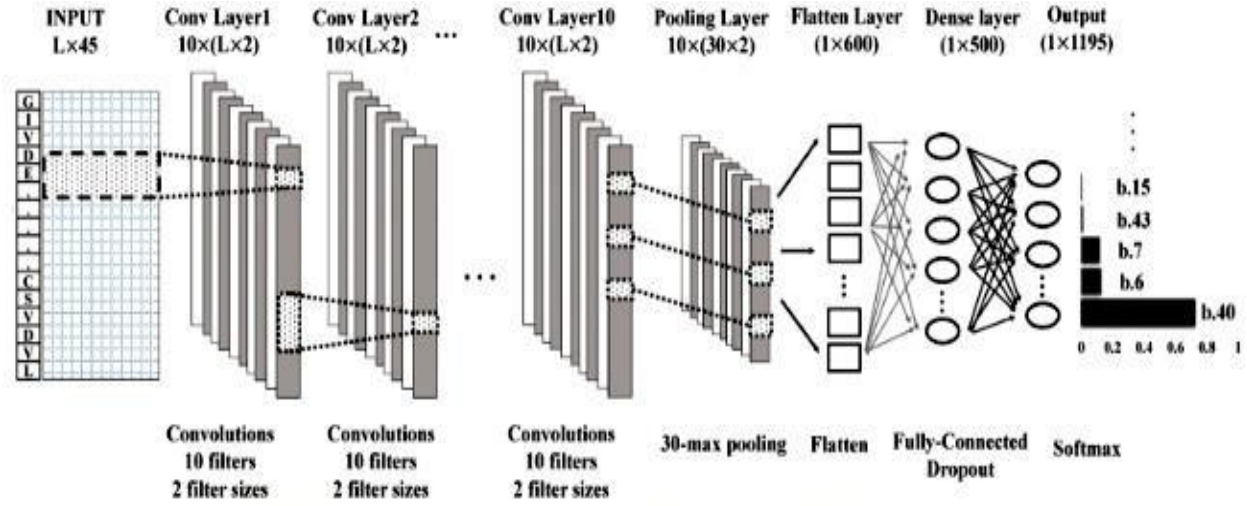


Fig. 3The Architecture of Convolutional Neural Network (CNN) for Fold Classification

PERFORMANCEEVALUATION

For evaluating the quality of classification, four different parameters are used frequently, which include individual sensitivity (denoted as 'Sens'), specificity (denoted as 'Spec'), Matthew's correlation coefficient (denoted as 'MCC'), and overall accuracy (denoted as

OA)for each structural class over entire dataset. Equations (3-6) are used to represent theseparameters.

$$sens_j = \frac{TP_j}{TP_j+FN_j} = \frac{TP_j}{|C_j|} \quad (3)$$

$$Spec_j = \frac{TN_j}{FP_j+TN_j} \quad (4)$$

$$MCC_j = \frac{(TP_j*TN_j)-(FP_j*FN_j)}{\sqrt{(FP_j+TP_j)(TP_j+FN_j)(FP_j+TN_j)(TN_j+FN_j)}} \quad (5)$$

$$OA = \frac{\sum_j TP_j}{\sum_i |C_j|} \quad (6)$$

Where Cj is the structural class, TPj is true positives, TNj is true negatives, FPj is false positives, and FNj is false negatives.

3. RESULTS &DISCUSSIONS

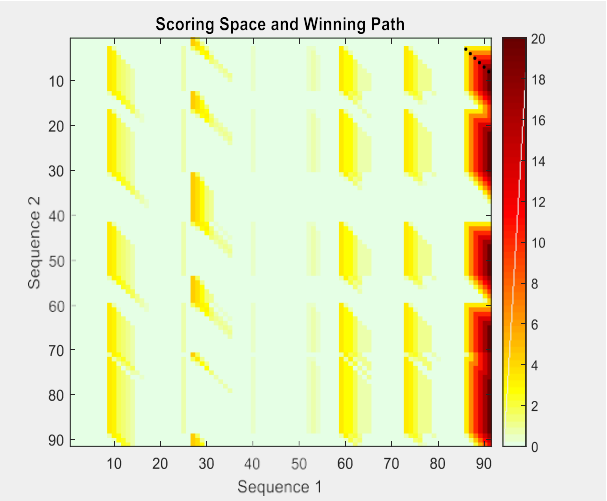


Fig. 4(a): Scoring space for ClassAProtein

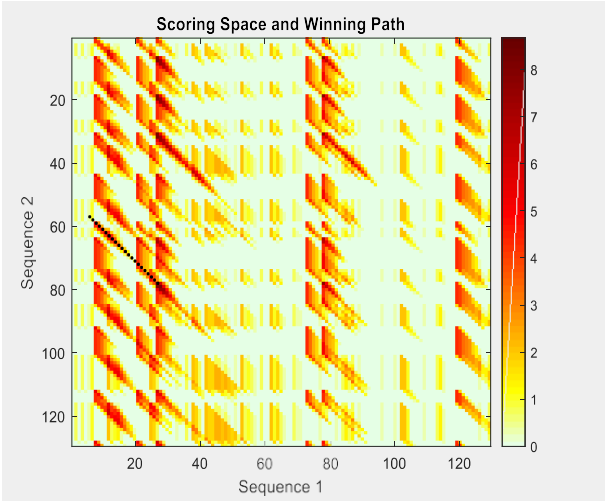


Fig. 4(b): Scoring space for Class BProtein

Figures 4(a-d) provides the scoring spaces for protein structures of Class A, B, C, and D. Scoring spaces are heat maps used to displaying the best score for the entire the fractional alignments of both sequences. Best score is represented by a pair of two subsequences i.e. Seq1 (s1:n1) and a Seq2 (s2:n2). Here n1 is the position of Seq1, n2 is a position of Seq2, s1 is a Seq1 position ranging between 1:n1, and s2 is a Seq2 position which is ranging between

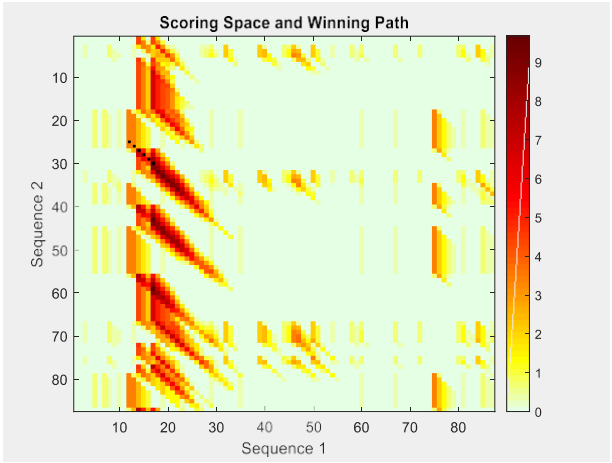


Fig. 4(c): Scoring space for ClassCProtein

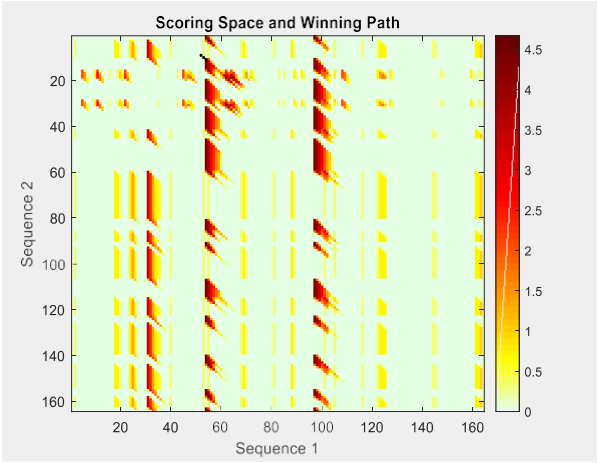


Fig. 4(d): Scoring space for Class DProtein

1:n2. The best score fora pair of definite sub-sequence is calculated by scoring the entire possible alignments for given sub-sequences by accumulating gap and matchpenalties. Black dots in scoring space represent the winning path. Positions pairing are illustrated as best possible local alignment. Also, color of last point in the lower right portion of winning path signifies the alignment score of best local for these two sequences.

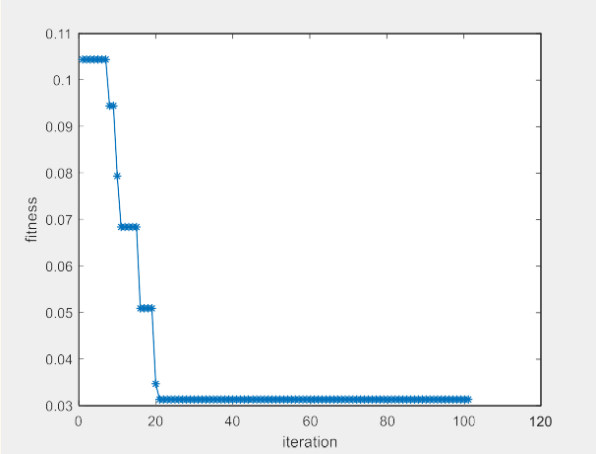


Fig. 5(a): Fitness value for ClassA Protein

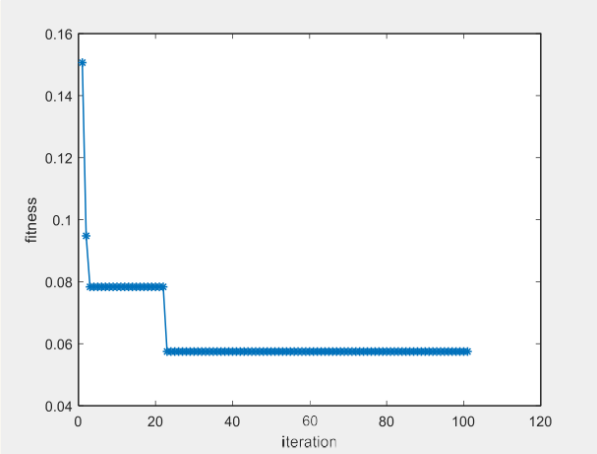


Fig. 5(b): Fitness value for Class BProtein

Figures5 (a-d) provides fitness values of selected protein feature from dataset with respect to different iterations for protein class A,B,C and D structures. Fitness curve is used to graphically represent the optimization evaluation with respect to number of individuals assessed for different protein classes.

Fig. 5(c): Fitness value for ClassC Protein

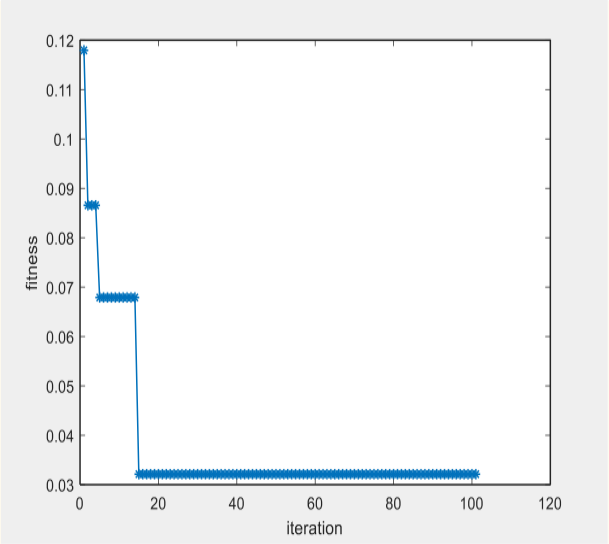
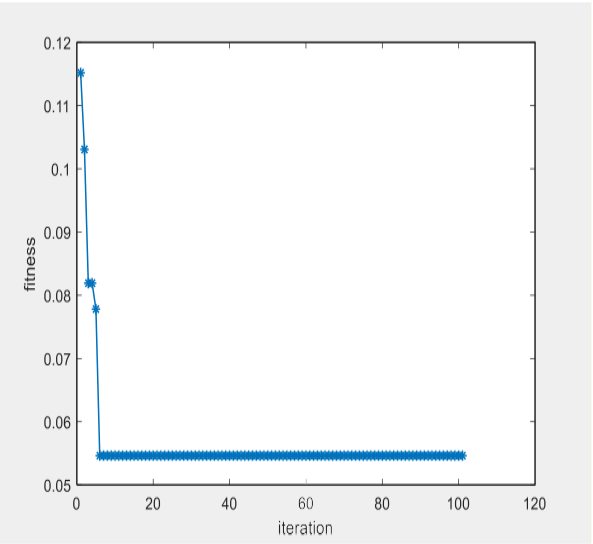


Fig. 5(d): Fitness value for Class BProtein



The results of all the parameters are predicted by the CNN technique with Firefly and PSO based feature selection and sequence alignment method. Table 3 shows comparison of CNN and SVM techniques in term of accuracy values. The table suggested that the accuracies of class A and B are nearly 100%. The results indicated that currently utilized CNN method provides greater accuracy values for all classes ofprotein.

Table 3 Comparison of Accuracy for SVM and CNN Techniques for Various Protein Classes

		Accuracy (%)	
Sr. No.	Classes	SVM	CNN
1	All α (A)	99.77	99.96
2	All β (B)	99.77	99.81
3	α+β (C)	85.09	98.59
4	α/β (D)	78.64	99.32

Table 4 provides a comparison of CNN and SVM techniques in term of sensitivity values. The table suggested that the sensitivity of class A and B are nearly 100%. The results indicated that currently utilized CNN method provides greater sensitivity values for all classes of protein.

Table 4 Comparison of Sensitivity for SVM and CNN Techniques for Various Protein Classes

		Sensitivity (%)	
Sr. No.	Classes	SVM	CNN
1	All α (A)	99.77	100
2	All β (B)	99.77	99.81
3	α+β (C)	85.09	97.22
4	α/β (D)	78.64	98.41

Table 5 provides a comparison of CNN and SVM techniques in term of specificity values. The table suggested that the specificity of class A and B, and C are 100% for CNN technique. The results indicated that currently utilized CNN method provides greater specificity values for all classes of protein

Table 5 Comparison of Specificity for SVM and CNN Techniques for Various Protein Classes

		Specificity (%)	
Sr. No.	Classes	SVM	CNN
1	All α (A)	99.51	100
2	All β (B)	99.42	100
3	α+β (C)	94.59	100
4	α/β (D)	95.45	95.65

Table 6 provides a comparison of CNN and SVM techniques in term of MCC values. The table suggested that the MCC values for class A and Bare nearly 100% for CNN technique. The results indicated that currently utilized CNN method provides greater MCC values for all classes of protein.

Table 6 Comparison of MCC Values for SVM and CNN Techniques for Various Protein Classes

Sr. No.	Classes	MCC%	
		SVM	CNN
1	All α (A)	98.93	99.12
2	All β (B)	98.77	99.05
3	α+β (C)	79.63	97.22
4	α/β (D)	75.10	98.62

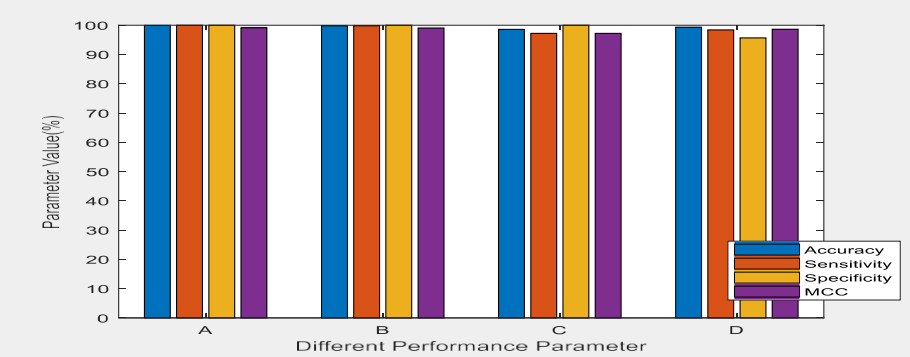


Fig. 6 Comparison of Difference performance Parameters for Various Protein Classes

Figure 6 combines all the results of tables 2-5 and provides the values of different performance parameters like accuracy, sensitivity, specificity and MCC calculated using CNN technique on 25PDB dataset for different protein structural classes A, B, C, and D.

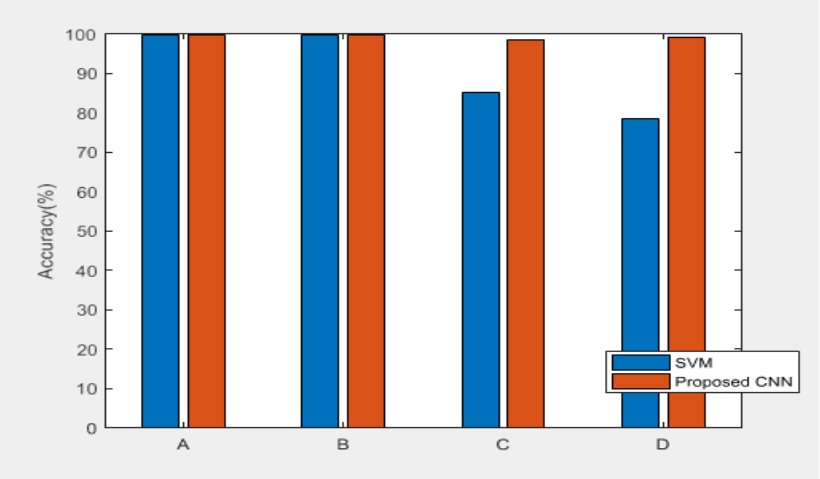


Fig. 7 Comparison of Accuracy Parameters for SVM and CNN Techniques

Figure 7 provides a comparison of accuracy values using SVM and CNN techniques for protein structure classes A, B, C, and D. The results indicate that currently utilized CNN technique provides better results in terms of accuracy.

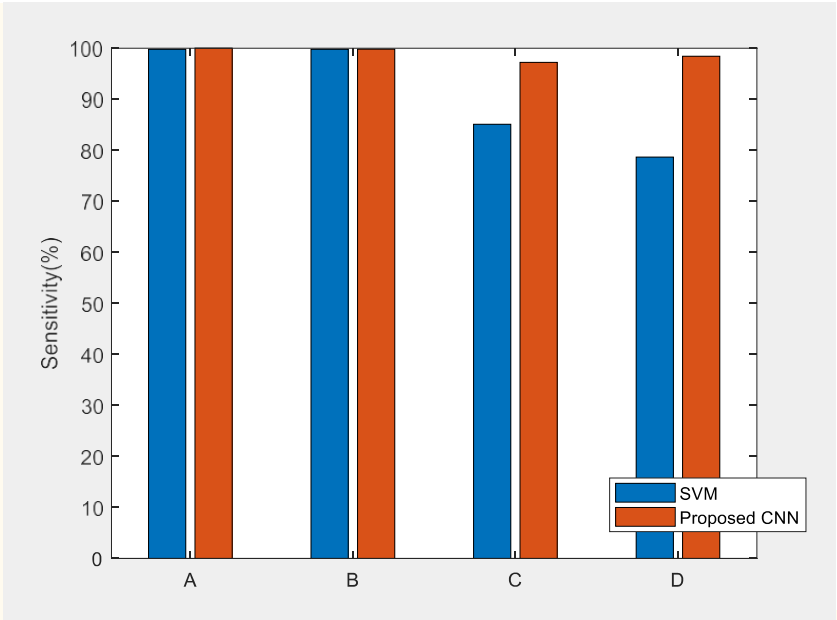


Fig. 8: Comparison of Sensitivity with SVM and CNN methods for various protein classes

Figure 8 provides a comparison of sensitivity values using SVM and CNN techniques for protein structure classes A, B, C, and D. The results indicate currently utilized CNN technique provides better results in terms ofsensitivity.

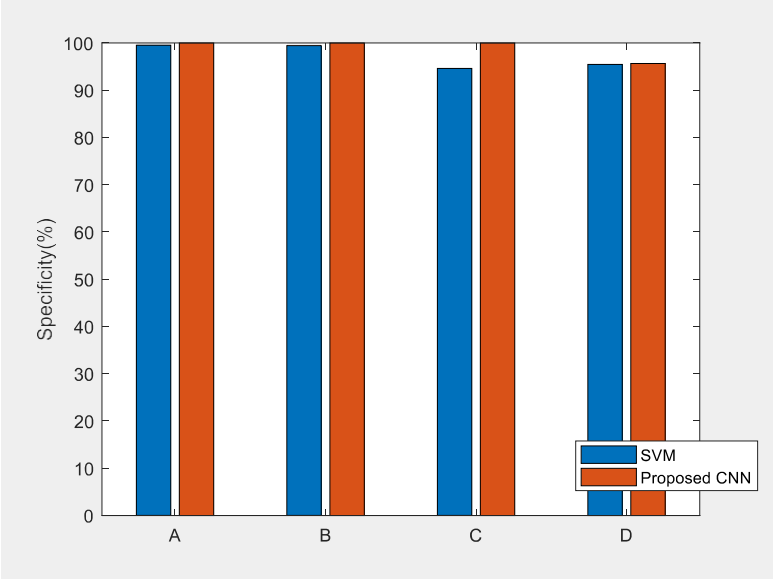


Fig. 9: Comparison of Specificity with SVM and CNN methods for various protein classes

Figure 9 provides a comparison of specificity values using SVM and CNN techniques for protein structure classes A, B, C, and D. The results indicate that currently utilized CNN technique provides better results in terms of specificity.

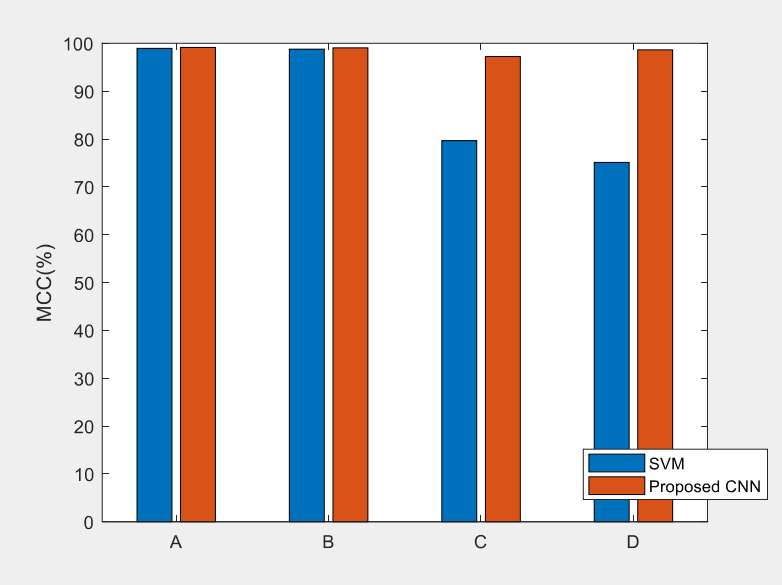


Fig. 10: Comparison of MCC with SVM and CNN methods for various protein classes

Figure 10 provides a comparison of MCC values using SVM and CNN techniques for protein structure classes A, B, C, and D. The results indicate that CNN technique provides better results in terms of MCC values.

Table 6 Performance comparison of different methods on 25 PDB dataset

	Accuracy (%)			
Techniques	all-α	all-β	α+β	α/β
Normalized Lempel-Ziv-SVM	94.4	83.3	83.5	73.2
SVM classifier and the Jackknife	93.7	81.7	74.3	70.7
Wrapper-SVM	95.03	81.26	83.24	77.55
Double Layer SVM	99.77	99.77	85.09	78.64
Presently utilized CNN technique	99.96	99.96	99.96	99.96

4. CONCLUSION

Sub-cellular localization of protein structure is attempted by numerous researchers by using several techniques of deep learning and machine learning. In present study deep learning technique of CNN is utilized as a classifier which is compared with SVM with respect to accuracy, specificity, sensitivity, and MCC values for all four classes of protein. The accuracy of CNN classifier is much higher than SVM classifier. Clustering is performed using K- mean algorithm. A Hybrid PSO-Firefly algorithm is used for feature extraction of various classes of protein. 25 PDB dataset is used to analyze the protein structure in terms of various performance parameters. Also, scoring spaces and fitness values are evaluated for different classes ofprotein.

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