Research Article

Predicting β-Turns in Protein Using Kernel Logistic Regression

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Received 15 September 2012; Accepted 22 December 2012

1. Introduction

The number of known protein sequence is increasing rapidly as a result of genome and other sequencing projects. Consequently, this increase widens sequence-structure gap rapidly [1, 2]. Thus computational tools for predicting protein structure and function are highly needed to narrow the widening gap [3]. There are four distinct levels of protein structures. These levels are primary structure which refers to amino acid linear sequence of the polypeptide, secondary structure, which is defined by the patterns of hydrogen bonds between backbone amide and carboxyl groups, tertiary structure, which is the three-dimensional structure of a single protein molecule, and quaternary structure, which is a larger assembly of several protein molecules or polypeptide chains.

The basic elements of the secondary structure of proteins are α-helices, β-sheets, coils, and turns. A turn is a structural motif where the α-atoms of two residues are separated by few (usually from 1 to 5) peptide bonds, and the distance between them is less than 7Å, while the corresponding residues do not form a regular secondary structure element such as an α-helix or β-sheet. Different turns are classified according to the separation between the two end residues. The end residues are separated by four peptide bonds in α-turns, three peptide bonds in β-turns, two peptide bonds in γ-turns, one bond in δ-turns, and five bonds in π-turns. β-turns are the most common found type of turns that constitute approximately 25% of the residues in protein. They play a significant role in protein configuration and function, and their formation is a vital stage during the protein folding. They were found to be more helpful in the context of molecular recognition and in modeling interactions between peptide substrates receptors, because they tend to be more solvent exposed than buried [4]. In the recent years it has been found that β-turns are important in the design of various peptidomimetics for many diseases [5]. Therefore, development of effective and efficient prediction methods for β-turns identification in protein is useful in fold recognition and drug design [6].

β-turns are further classified into different types according to the dihedral angles (φ, ψ) of the central two residues. The classification scheme proposed by Hutchinson and Thornton [7] recognizes nine distinct types of β-turn: I, I', II, II', Vla1, Vla2, Vlb, VIII, and IV. In this classification, the most frequently occurring type is type IV, which constitutes...
approximately (35%) of the $\beta$-turns. Types VIa1, VIa2, and VIb are rare types.

Most of the successful $\beta$-turns prediction methods are based on either support vector machines (SVMs) or neural networks (NNs). Zheng and Kurgan [6] applied SVM-based ensemble to predict $\beta$-turns. They used position-specific scoring matrices (PSSMs) and secondary structure information as features in their prediction model. Kountouris and Hirst [8] developed a method based on SVM; their method uses PSSMs, predicted secondary structures, and predicted dihedral angles as input features to the SVM. Shepherd et al. [9] used a neural network to predict both the location and types of $\beta$-turn in protein; they incorporated secondary structure information on the features used as input to the NN. Kaur and Raghava [10] used two feedforward backpropagation networks with a single hidden layer, where the first sequence-structure network is trained with the PSSMs. The initial prediction from the first network and the predicted secondary structure using PSIPRED [11, 12] are used as input to the second structure-structure network to refine the prediction obtained from the first network. Petersen et al. [13] presented a neural network method called NetTurnP, for predicting $\beta$-turns and $\beta$-turn types. Their method consists of two artificial neural network layers; they used PSSMs, secondary structure, and surface accessibility as input to their model.

There is another method that can perform well as SVMs and NNs, which is the Kernel Logistic Regression (KLR). KLR is a kernel version of logistic regression (LR). It is often not found in predicting protein secondary structures and $\beta$-turns due to its computational demand. However, unlike SVMs and NNs, KLR yields a posteriori probabilities based on a maximum likelihood argument, which is, besides predicting class labels, KLR provides interpretation about this labeling. When it comes to $\beta$-turn type prediction, KLR has an additional advantage that its extension to multiclass classification is well described. Karsmakers [14, 15] proposed a fast and accurate approximate implementation of KLR for Automatic Speech Recognition (ASR). He described a different practical technique suited for large datasets, based on fixed-size least squares support vector machines (FS-LSSVMs), of which he named fixed-size kernel logistic regression (FS-KLR). Karsmakers used trust region Newton’s method for large-scale LR [16] as a basis to solve the approximate problem and Nyström method to approximate the features’ matrix. In this paper, we show that FS-KLR can be used in predicting $\beta$-turns in an efficient and effective way, and it yields results that are comparable to the state-of-the-art methods.

2. Methods

2.1. Data Sets. The uniform dataset of 426 nonhomologous proteins (BT426) [17], the dataset of 547 protein sequence (BT547), and the dataset of 823 protein sequence (BT823) are used to evaluate the performance of our KLR method. Several researchers used BT426 as a golden set of sequences upon which performance values are reported and compared. This dataset consists of protein chains whose structure has been determined by X-ray crystallography at a resolution of $< 2.0\AA^*$ or better. Each chain contains at least one $\beta$-turn region. In total 23,580 amino acids, corresponding to 24.9% of all amino acids, have been assigned to be located in $\beta$-turns. None of the sequences in the dataset shares more than 25% sequence identity. BT426 has been used by various recent $\beta$-turns prediction methods; therefore, we can use it to make direct comparisons with these methods. The other two datasets: BT547 and BT823 are constructed for training and testing COUDES [18].

2.2. Features Vector. The features that are used in this study include PSSMs and secondary structure information.

2.2.1. PSSMs. Several studies show that PSSMs contributed significantly to the accuracy of $\beta$-turns prediction [6, 13]. The PSSMs are in the form of $20 \times M$, where $M$ represents the sequence length. The PSSMs were generated using the iterative PSI-BLAST program [19] against National Center for Biotechnology Information (NCBI) nonredundant (nr) sequence database using the default parameters. The PSSMs values are scaled to values between 0 and 1. A window size of seven residues is used for the PSSMs. This is in accordance with Shepherd et al. [9] who found that the optimal prediction for $\beta$-turns is achieved using window size of seven or nine. The total number of the features that are based on PSSMs is $(20 \times 7 = 140)$.

2.2.2. Secondary Structure Information. For the secondary structure information features, four secondary structure prediction methods are utilized for all protein chains. These four prediction methods are PSIPRED [12, 20], JNET [21], TRANSEC [22], and PROTEUS [22]. The secondary structures were predicted as three structure states: helix ($H$), strand ($E$), and coils ($C$). These three structure states are encoded as $100$ for helix, $010$ for strand, and $001$ for coils. The secondary structure information features are organized as follows: (1) a binary value denoting the prediction of a given secondary structure method from the aforementioned used prediction methods for the central residue; that is, if PSIPRED predicted the central amino acid to be helix, JNET predicted it to be coil, TRANSEC predicted it to be helix, and PROTEUS predicted it to be helix, then this binary value will be $10000011$ $010000$, so the total number of features using this organization is 12; (2) the confidence value obtained from the central residue using the four prediction methods. The confidence score is divided by 10 to normalize it to a unit interval, and the total number of features using this organization is 4. (3) A binary value denoting a specific configuration of the secondary structure is predicted using the four prediction methods for the central and the two adjacent residues. Here we have four patterns 1, 2, 3, and 4. If the predicted secondary structure using specific method is coils 001, the secondary structure for the pattern 1 will be CCC and for pattern 2, 3, and 4 will be CCX, XCC, and XCX, respectively, where $X = E$, $H$. The total number of features based on this organization is $(4 \times 3 \times 2 \times 4 = 48 \text{ features})$. (4) The ratio between the number of residues
in a given secondary structures and the window size for the four prediction methods, the number of features based on this organization will be (3 secondary structure * 4 prediction methods = 12). The total number of features based on secondary structure information is 76. The motivation to use this organization comes from [6].

The predicted secondary structure information is added to the PSSMs features. The total number of the features that are based on PSSMs and secondary structure information is 216. Similarly as in [6], feature’s selection methods based on information gain and CHI squared are employed to reduce the number of features to 90 features. Figure 1 shows the overall architecture of our KLR method.

2.3. Prediction Method. The fixed-size kernel logistic regression (FS-KLR) was applied to predict β-turns. KLR is the kernel version of LR, which is a well-known statistical model for classification. Unlike LR, KLR enables the classification of linearly nonseparable problems by transferring the input features to a higher-dimensional space, via the kernel trick. The kernel is a transformation function that must satisfy Mercer’s necessary and sufficient conditions, which state that a kernel function must be expressed as an inner product and must be positive semidefinite. Similar to LR, KLR can be fitted using the maximum likelihood estimate (MLE).

Iteratively reweighted least square (IRLS) algorithm is one of the most popular techniques used to find the MLE of the LR models. IRLS is a nonlinear optimization algorithm that uses a series of weighted least squares (WLS) sub-problems to search for the MLE. It is a special case of Fisher’s scoring method, a quasi-Newton algorithm that replaces the objective function’s Hessian with the Fisher information. For LR, IRLS is a special form of Newton’s method in which each iteration finds the WLS estimates for a given set of weights, which are used to construct a new set of weights. KLR also can be fitted effectively using IRLS [15].

Unlike SVMs, KLR does not use risk minimization principle, but it is based on conditional maximum likelihood inference, which results in estimates of a posteriori class probabilities via logit stochastic models:

\[ P(Y = -1 | X = x; f) = \frac{\exp(f(x))}{1 + \exp(f(x))}, \]
\[ P(Y = 1 | X = x; f) = \frac{1}{1 + \exp(f(x))}, \]

where \( f(x) = w^T \phi(x) + b \). \( w \) is the vector of the KLR parameters, and \( b \) is the intercept. The penalized negative log likelihood (PNLL) is normally used to infer the parameters of the KLR model. In the primal weight space, the objective function for the PNLL is as follows:

\[ \min_{w,b} \frac{1}{2w} \sum_{i=1}^{N} \log(1 + \exp(-y_i f(x_i))) + \frac{\lambda}{2} w^T w, \]

where \( \lambda \) is the regularization parameter. The solution \( w \) can be expressed in terms of \( \alpha \) and computed using IRLS iteration as

\[ w = \sum_{i=1}^{N} \alpha_i \phi(x_i). \]

In the dual representation, the function values \( f(x) \) in the KLR logit models can be computed as follows:

\[ f(x) = \sum_{i=1}^{N} \alpha_i K(x, x_i) + b, \]

where \( K(x, x_i) = \phi(x)^T \phi(x_i) \).

The IRLS method is suitable for small size problems, but for large-scale problems this method becomes computationally expensive. Based on fixed-size least squares support vector machines (FS-LSSVMs) Karsmakers [14, 15] implemented a fixed-size variant of the standard KLR formulation (FS-KLR) which does easily scale to very large datasets. In his method, he adopted Nyström approximation method.

In Nyström approximation, the kernel matrix will be decomposed into eigenvalues/eigenvectors matrices in the form:

\[ K_{n \times n} = U_n \Lambda_n U_n^T, \]

where \( \Lambda_n = \text{diag}(\lambda_1, \lambda_2, \ldots, \lambda_n) \geq 0 \) are the eigenvalues of the matrix \( K \), \( U_n \) is the matrix of the eigenvectors that correspond to the eigenvalues, and \( n \) is the number of the data points. We can select the first \( p \) eigenvectors and eigenvalues from the matrices \( U \) and \( \Lambda \), respectively, where \( p \ll n \), to approximate the kernel matrix. This approximation is motivated by its widely usage, for example, principal component analysis. Using this approximation reduces the computational cost drastically. However, computing the eigendecomposition is also computationally expensive. To reduce the computational cost of computing the eigendecomposition we selected a small sample of size

![Figure 1: The architecture of the KLR method.](image-url)
m from the features’ matrix to construct the following eigen-

\[ K_{n,m} = U_m \Lambda_m U_m^T. \]  

(6)

We can extend the eigenvalues/eigenvectors of the \( K_{n,m} \) 
to all the points using the following Nystrom approximation:

\[ \tilde{\lambda}_i^{(m)} = \frac{n}{m} \lambda_i^{(m)}, \]

\[ \tilde{u}_i^{(m)} = \frac{1}{m} \lambda_i^{(m)} K_{n,m} u_i^{(m)}, \]  

(7)

where \( \lambda_i^{(m)} \) and \( u_i^{(m)} \) are the \( i \)th eigenvalue/eigenvector of 
the \( m \times m \) eigenproblem and \( K_{n,m} \) is the appropriate \( n \times m \)
submatrix of \( K \).

The selected sample of size \( m \) from the features’ matrix 
can be called prototype vectors (PVs). These PVs can be 
selected using k-center clustering. The use of k-center 
clustering is justified in [23], which observed that the Nystrom 
low-
rank approximation depends crucially on the quantization error induced by encoding the sample set with landmark 
points. This suggests that one can simply use the clusters 
obtained with a k-center (such as k-means) algorithm, which 
finds a local minimum of the quantization error. The PVs 
selection methods using k-center clustering suffer from the 
fact that they will select outliers as prototypes. In cases where 
the number of PVs is relatively small, the fraction of pro-
totypes chosen to represent the nonoutlier and outlier data 
is unbalanced, and, therefore, the classification performance 
will not be optimal. When the number of PVs is increased, the 
performance will also increase to that of KLR. Hence taking 
to account outliers removal can result in a sparser model. 
The sparse kernel logistic regression problem is solved in the 
primal space using Newton’s trust region algorithm, which 
is given in [16]. This algorithm yielded the best performance 
compared to the state-of-the-art alternatives. Convergence 
speed and cost per iteration will be balanced in that low-
cost approximate because Newton’s steps will be taken in the 
beginning of the algorithm and full Newton directions at the 
end for fast convergence. In this paper, the following radial 
basis function (RBF) is used as a kernel function:

\[ K(x_i, x_j) = e^{-\gamma|x_i - x_j|^2}, \]  

(8)

where \( \gamma \) is the kernel parameter.

2.4. Model Selection. Model selection is the process of deter-
mining the optimal regularization parameter \( \lambda \) and the kernel 
parameter \( \gamma \). It is a very important step in fitting kernel 
models to maximize generalization performance. The cross-
validation-based method is used to determine the optimal 
parameters for \( \beta \)-turns prediction.

2.5. Training and Testing. In order to evaluate a prediction 
method it is necessary to have different datasets for training 
and testing. The jackknife test is the most objective and 
rigorous cross-validation method compared with independent 
dataset test and subdataset test [24]. In a full jackknife test of 
\( N \) proteins, one protein is removed from the set; the training 
is done on the remaining \( N - 1 \) proteins, and the test is 
done on the removed protein. This process is repeated \( N \) 
times by removing one protein in turn. Since this training 
technique is very time consuming most of the recent \( \beta \)-
turns prediction methods use sevenfold cross-validation to 
assess their performances. We also used sevenfold cross-
validation to assess the accuracy of FS-KLR. In sevenfold 
cross-validation, the datasets will be divided into seven 
subsets, each containing equal number of proteins. Each set 
is an unbalanced set that retains the naturally occurring 
proportion of \( \beta \)-turns. Six of the seven subsets were merged 
together to form a training set that was used to train the FS-
KLR methods, and the seventh was used for validation. This 
process was repeated seven times in order to have a different 
set for validation each time. The final prediction results are 
taken as the average of the results from the seven testing sets.

2.6. Performance Measures. The quality of prediction is eval-
uated using five measures: MCC, \( Q_{\text{total}} \), \( Q_{\text{predicted}} \), \( Q_{\text{observed}} \), 
and Specificity. These measures are consistent with the test 
procedures and measures applied to evaluate competing 
methods. Let (true positives) TP be the number of cor-
rectly classified \( \beta \)-turns residues, (true negatives) TN be 
the number of correctly classified non-\( \beta \)-turns residues, (false 
positives) FP be the number of non-\( \beta \)-turns incorrectly 
classified as \( \beta \)-turns residues, and (false negatives) FN be 
the number of \( \beta \)-turns incorrectly classified as non-\( \beta \)-turns 
residues. The Matthews correlation coefficient (MCC) can be 
calculated as [25]

\[ \text{MCC} = \frac{(TP \times TN - FP \times FN)}{\sqrt{(TP + FN) \times (TN + FP) \times (TP + FP) \times (TN + FN)}}. \]  

(9)

The result of MCC is in the range of \(-1 \) and 1, where a 
value of 1 indicates a perfect positive correlation, a value of 
\(-1 \) indicates a perfect negative correlation, and a value of 0 
indicates no correlation.

\( Q_{\text{total}} \) (prediction accuracy), which is defined as the 
percentage of correctly classified residues, is calculated as 
follows:

\[ Q_{\text{total}} = \frac{TP + TN}{TP + TN + FP + FN} \times 100. \]  

(10)

Probability of correct prediction or \( Q_{\text{predicted}} \) is the per-
centage of correctly predicted \( \beta \)-turns among the predicted 
\( \beta \)-turns. It is also called predicted positive value (PPV), and 
it is given as follows:

\[ Q_{\text{predicted}} = \frac{TP}{TP + FP} \times 100. \]  

(11)

Sensitivity or coverage (also known as \( Q_{\text{observed}} \)) is the 
percentage of correctly predicted \( \beta \)-turns among the 
observed \( \beta \)-turns, or it is the fraction of the total positive 
samples that are correctly predicted, and it is given as follows:

\[ Q_{\text{observed}} = \frac{TP}{TP + FN} \times 100. \]  

(12)
Table 1: $Q_{total}$ and MCC for different values of selected vectors $m$.

| Number of selected vectors $l$ | $Q_{total}$ | MCC   |
|-------------------------------|-------------|-------|
| 70                            | 79.96       | 0.46  |
| 80                            | 80.32       | 0.47  |
| 90                            | 80.25       | 0.47  |
| 100                           | 80.38       | 0.47  |
| 110                           | 80.41       | 0.47  |
| 120                           | 80.54       | 0.48  |
| 130                           | 80.51       | 0.48  |

Specificity is the fraction of total negative samples that are correctly predicted

$$\text{Specificity} = \frac{TN}{TN + FP} \times 100. \quad (13)$$

3. Results

The selected number of Pvs ($m$) where $m \ll n$ from the feature matrix affects the accuracy and the MCC of the prediction. A relatively small or big $m$ will yield low performance. To select the optimal number of vectors a cross-validation is used starting with relatively small $m$ and adding more vectors to $m$ until a point where adding more vectors does not improve the classification performance reached. Table 1 shows the prediction accuracy and MCC using different values of $m$. In Figure 2, we see that the highest MCC is achieved for $m$ equal 120, while Figure 3 shows that the highest accuracy is achieved using $m$ equal to 115 or 120. The dataset used for the two figures is BT426.

After a short analysis of various values of threshold, we set its value to 0.45 to obtain the results in Table 1. The $Q_{total}$ has improved slightly when the threshold value is set to 0.50, while the MCC dropped to less than 0.46. Similarly, the MCC has increased when the threshold value is set to 0.40, but at the cost of $Q_{total}$, which has dropped to less than 79%. The number of selected vectors $m$ in this research is set to 120 for BT426 dataset. Using this value for $m$ we obtained a $Q_{total}$ of 80.54%, MCC of 0.48, $Q_{predicted}$ of 59%, $Q_{observed}$ of 62%, and Specificity of 86%. The MCC is a robust and reliable performance measure that accounts for both overpredictions and underpredictions. A high MCC value indicates a high prediction performance.

To increase the performance of our KLR model further we used state changing rules. In these rules we put in our consideration that $\beta$-turns occur in a group of at least four adjacent residues. After analyzing the results obtained by the KLR prediction, the state changing rules, which will make the prediction to be more $\beta$-turn like, are derived as follows.

1. Change isolated nonturn predictions to turn (i.e., tnt $\rightarrow$ ttt).
2. Change isolated turn prediction to non-turn prediction (i.e., ntn $\rightarrow$ nnn).
3. Change the residues that are neighboring two isolated turn predictions to turn (i.e., ntnn $\rightarrow$ tttt).
4. If there is isolated triplet of turns predictions, then change the adjacent nonturn prediction with the highest KLR probability output to turn (i.e., ntttn $\rightarrow$ ttttn or ntttt).

The above rules should be executed in orders. After applying these rules, we obtained a better performance, where the MCC has increased from 0.48 to 0.50.

Table 2 shows the comparison between our KLR method and other best existing $\beta$-turns prediction methods. Our KLR method achieves prediction accuracy $Q_{total} = 80.7\%$, $Q_{predicted} = 58.98\%$, $Q_{observed} = 65.25\%$, sensitivity = 85.34\%, and MCC = 0.50. We note that the $Q_{total}$ of our method is 0.2% lower than the $Q_{total}$ of BTNpred and E-SSpred, but because $\beta$-turns account for approximately 25% of the globular protein residues, $Q_{total}$ is a poor measure by itself, as it is possible to achieve $Q_{total}$ of 75% by predicting all residues to be non-$\beta$-turns. Instead, our method shows high MCC 0.50 compared to BTNpred 0.47 and E-SSpred 0.44. The NetturnP and our method have the highest MCC 0.50 among the other $\beta$-turns prediction methods. Other than BTNpred and E-SSpred our KLR shows the highest $Q_{total}$. When combining $Q_{total}$ and MCC our method has the highest performance among the other prediction methods. Considering the baseline accuracy which equals 75%, our method provides 5.7/25 = 0.23% error rate reduction, while BTNpred and E-SSpred provide 5.9/25 = 0.24% error rate reduction, and the second best method (SVM) provides 4.8/25 = 0.19% error rate reduction. The $Q_{observed}$ of our method is higher by 9.65% than the $Q_{observed}$ of BTNpred,
Table 2: Comparison of KLR with other recent β-turns prediction methods on BT426 dataset.

| Method       | Dataset | Q_total | Q_pred | Q_obs | Specificity | MCC  |
|--------------|---------|---------|--------|-------|-------------|------|
| KLR          | BT426   | 80.7    | 58.98  | 65.25 | 85.34       | 0.50 |
| BTNpred [6]  | BT426   | 80.9    | 62.7   | 55.6  | N/A         | 0.47 |
| NetTurnP [13]| BT426   | 78.2    | 54.4   | 75.6  | 79.1        | 0.50 |
| BetaTPred2   | BT426   | 75.5    | 49.8   | 72.3  | N/A         | 0.43 |
| BTPRED [9]   | BT426   | 74.9    | 55.3   | 48.0  | N/A         | 0.35 |
| DEBT [8]     | BT426   | 79.2    | 54.8   | 70.1  | N/A         | 0.48 |
| SVM [26]     | BT426   | 79.8    | 55.6   | 68.9  | N/A         | 0.47 |
| BTSVM [27]   | BT426   | 78.7    | 56.0   | 62.0  | N/A         | 0.45 |
| E-SSpred [28]| BT426   | 80.9    | 63.6   | 49.2  | N/A         | 0.44 |
| 1–4 & 2-3 correlation model [29] | BT426 | 59.1 | 32.4 | 61.9 | N/A | 0.17 |

Table 3: Comparison of KLR with other recent β-turns prediction methods on BT547 and BT823 datasets.

| Method      | Dataset | Q_total | Q_pred | Q_obs | Specificity | MCC  |
|-------------|---------|---------|--------|-------|-------------|------|
| KLR         | BT547   | 80.46   | 59.04  | 65.36 | 85.34       | 0.50 |
| BTNpred [6] | BT547   | 80.5    | 61.6   | 54.2  | 54.2        | 0.45 |
| COUDES [18] | BT547   | 76.6    | 47.6   | 70.4  | 70.2        | 0.43 |
| SVM [26]    | BT547   | 76.6    | 47.6   | 70.4  | 70.2        | 0.43 |
| KLR         | BT823   | 80.66   | 58.42  | 64.64 | 64.64       | 0.49 |
| BTNpred [6] | BT823   | 80.6    | 60.8   | 54.6  | 54.6        | 0.45 |
| COUDES [18] | BT823   | 74.2    | 47.5   | 69.6  | 69.6        | 0.41 |
| SVM [26]    | BT823   | 76.8    | 53.0   | 72.3  | 72.3        | 0.45 |

The ROC curve, which is a plot of the sensitivity against the false-positive rate for the evaluation of the KLR, is shown in Figure 5. From the ROC curve, we calculated the area under the curve (AUC), which is a threshold-independent measure. An AUC value above 0.7 is an indication of a handle large-scale datasets.
environment since and by their side-chain packing interactions and local environment 
both by their intrinsic preference to sample favorable space. 

interactions in forming the native states of different proteins 
are frequent sites of posttranslational modifications such as phosphorylation and glycosylation, which are used to tune interactions [4].

β-turns are also involved in the biological activity of peptides as the bioactive structures that interact with other molecules such as receptors, enzymes, or antibodies. Recent years have seen interest in mimicking β-turns for the synthesis of medicines. Thus, β-turn is an important component of protein structure whose prediction can provide enormous information to the researchers working in the field of drug design. So the prediction of β-turns would not only aid in overall tertiary structure prediction but also assists in fold recognition studies.

Throughout the previous research on β-turns prediction, predictors based on machine-learning method emphasize selecting proper features to improve prediction performance. Secondary structures and PSSMs are widely used in the predictions and have been proven to be the most helpful features. Using these features the proposed KLR method achieves comparable results to the SVMs methods. To design a method that can be applied in β-turn prediction, there are four main concerns. These concerns are (1) the size of the dataset, (2) the need for dealing with input examples of variable length, (3) the need to have probabilistic outcomes, and (4) the need to perform multiclass classification. When the dataset is very large such as the β-turns data, people neglect the last two concerns and concentrate on selecting a classifier that deals with large datasets effectively. Since SVMs methods are designed in a way that can handle large-scale datasets, they become the choice for most of the β-turns classification methods. However, SVMs do not address the last two concerns directly. KLR is not used in large-scale datasets such as β-turns data classification although it provides elegant solution to the last two concerns, simply because it is inapplicable in such datasets. The last two concerns are very important for β-turns classification, since there is a need for multiclass classification for the β-turns type. FS-KLR extends the applicability of KLR for large-scale datasets. This way it can address all of the aforementioned concerns.

4. Discussion

Prediction of β-turns has attracted researchers interest because it plays the following important roles.

β-turns have been proposed to be important in folding because they are capable of initiating productive structure formation without a large loss in chain entropy since the interactions involved in turn formation are largely local [32]. They can play two different roles in the folding reaction of a protein. They can be either folding-active elements and function as initiation sites or folding-passive elements that form only after other regions develop. These different roles are likely to arise from the relative importance of the various interactions in forming the native states of different proteins [33].

Turns can influence the stability of a protein’s native state both by their intrinsic preference to sample favorable space and by their side-chain packing interactions and local environment [34]. Since β-turns usually occur on the exposed surface of a protein, they are well suited to participate in ligand binding, molecular recognition, protein-protein, or protein-nucleic acid interactions, thus modulating protein functions and intermolecular interactions. Additionally, they are frequent sites of posttranslational modifications such as phosphorylation and glycosylation, which are used to tune interactions [4].

β-turns are also involved in the biological activity of peptides as the bioactive structures that interact with other molecules such as receptors, enzymes, or antibodies. Recent years have seen interest in mimicking β-turns for the synthesis of medicines. Thus, β-turn is an important component of protein structure whose prediction can provide enormous information to the researchers working in the field of drug design. So the prediction of β-turns would not only aid in overall tertiary structure prediction but also assists in fold recognition studies.

Throughout the previous research on β-turns prediction, predictors based on machine-learning method emphasize selecting proper features to improve prediction performance. Secondary structures and PSSMs are widely used in the predictions and have been proven to be the most helpful features. Using these features the proposed KLR method achieves comparable results to the SVMs methods. To design a method that can be applied in β-turn prediction, there are four main concerns. These concerns are (1) the size of the dataset, (2) the need for dealing with input examples of variable length, (3) the need to have probabilistic outcomes, and (4) the need to perform multiclass classification. When the dataset is very large such as the β-turns data, people neglect the last two concerns and concentrate on selecting a classifier that deals with large datasets effectively. Since SVMs methods are designed in a way that can handle large-scale datasets, they become the choice for most of the β-turns classification methods. However, SVMs do not address the last two concerns directly. KLR is not used in large-scale datasets such as β-turns data classification although it provides elegant solution to the last two concerns, simply because it is inapplicable in such datasets. The last two concerns are very important for β-turns classification, since there is a need for multiclass classification for the β-turns type. FS-KLR extends the applicability of KLR for large-scale datasets. This way it can address all of the aforementioned concerns.

5. Conclusion

In this paper, we presented sparse KLR method for β-turns prediction. Our method is based on FS-KLR in which trust region Newton’s method for large-scale LR is used as a basis to solve the approximate problem, while Nyström method is used to approximate the features’ matrix. Our method uses secondary structure information and PSSMs as input features. Empirical evaluations using three nonredundant datasets show that our predictions provide favorable $Q_{\text{total}}$, $Q_{\text{observed}}$, and MCC when compared with the state-of-the-art methods that used secondary structure information and PSSMs as features. Using our method we achieved $Q_{\text{total}}$ and MCC of 80.7% and 0.50, respectively, on BT426 dataset. In addition, KLR yields probabilistic outputs and its extension to the multiclass case is well defined, which will be appropriate for β-turns types prediction. The computational complexity...
of our method is $O(nm^2)$ and its computation time is by far less than that of SVMs methods.

**Conflict of Interests**

The authors declare that there is no conflict of interests.

**Acknowledgments**

This work is supported in part by the National Natural Science Foundation of China under Grant nos. 61232001, 61073036, and 61128006, the Ph.D. Programs Foundation of Ministry of Education of China no. 20090162120073, and the Freedom Explore Program of Central South University no. 201012200124.

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