Identification of Intrinsically Disordered Proteins and Regions by Length-Dependent Predictors Based on Conditional Random Fields

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Accurate identification of intrinsically disordered proteins/regions (IDPs/IDRs) is critical for predicting protein structure and function. Previous studies have shown that IDRs of different lengths have different characteristics, and several classification-based predictors have been proposed for predicting different types of IDRs. Compared with these classification-based predictors, the previously proposed predictor IDP-CRF exhibits state-of-the-art performance for predicting IDPs/IDRs, which is a sequence labeling model based on conditional random fields (CRFs). Motivated by these methods, we propose a predictor called IDP-FSP, which is an ensemble of three CRF-based predictors called IDP-FSP-L, IDP-FSP-S, and IDP-FSP-G. These three predictors are specially designed to predict long, short, and generic disordered regions, respectively, and they are constructed based on different features. To the best of our knowledge, IDP-FSP is the first predictor that combines a sequence labeling algorithm with IDRs of different lengths. Experimental results using two independent test datasets show that IDP-FSP achieves better or at least comparable predictive performance with 26 existing state-of-the-art methods in this field, proving the effectiveness of IDP-FSP.

INTRODUCTION

Proteins/regions whose native states are intrinsically disordered without a stable 3D structure are called intrinsically disordered proteins/regions (IDPs/IDRs).1–3 IDPs/IDRs are abundant in all species, especially in eukaryotes.1 IDPs/IDRs are associated with many biological functions,4–6 such as regulation of transcription and translation, storage of small molecules, cellular signal transduction, and protein phosphorylation. They execute functions mainly through a disordered state or induced folding when binding to a partner molecule.2 IDPs/IDRs are associated with many diseases,7 such as cardiovascular disease,8 cancer,9 and genetic diseases.10 Therefore, accurate identification of IDPs/IDRs is important for drug design and a better understanding of biological processes.

With the help of artificial intelligence and machine learning techniques,11 some computational predictors have been constructed,11–13 including physiochemically based predictors,14,15 machine learning-based predictors,16,17 template-based predictors, and meta-predictors.18 More information regarding these methods can be found in a recent review paper.1

Among these predictors, some predictors are constructed to identify IDRs of different lengths based on the assumption that IDRs with different lengths have different characteristics. In general, the intrinsically disordered regions are divided into long disordered regions (LDRs) and short disordered regions (SDRs). LDRs are defined as regions with more than 30 residues, and SDRs are defined as regions with 30 residues or less. These predictors can be divided into two categories: (1) predictors designed for LDRs or SDRs only, which do not work well for predicting LDRs and SDRs, such as POODLE-L,19 POODLE-S,20 and Spritz,21 and (2) predictors designed for both LDRs and SDRs. Compared with the first-category predictor, these predictors can achieve better performance when predicting both LDRs and SDRs, such as VSL1,22 VSL2,23 and SPINE-D.24 The superior performance of these predictors indicates that length-dependent predictors can capture the different characteristics of IDRs with vary lengths. Furthermore, the better performance of the second-category predictors shows that these length-dependent predictors are complementary. According to the comparison results presented in a recent review paper,1 the sequence labeling methods outperform the classification methods, and the latest proposed IDP-conditional random field (CRF) predictor25 based on CRFs achieves state-of-the-art performance.

Inspired by these methods, we propose a predictor called IDP-FSP based on CRFs. IDP-FSP is a fusion of three CRF-based predictors—IDP-FSP-L, IDP-FSP-S, and IDP-FSP-G—that are specifically...
designed to predict long, short, and generic disordered regions, respectively. To the best of our knowledge, IDP-FSP is the first predictor that combines a sequence labeling algorithm with IDRs of different lengths. Experimental results using two independent test datasets show that IDP-FSP achieves better or at least comparable predictive performance with 26 highly related state-of-the-art predictors in this field.

RESULTS AND DISCUSSION
The Influence of Different Ratios of Positive and Negative Samples on Three Length-Dependent Predictors
In this study, a series of training datasets with different ratios of positive and negative samples is generated by randomly removing negative samples from the origin training datasets. Different ratios would affect the performance of the computational predictors, and both accuracy (ACC) and Matthew’s correlation coefficient (MCC) are two important metrics in this field. The ACC, MCC, and the sum of ACC and MCC changing curves of the proposed three specialized predictors with different ratios are shown in Figure 1. We can see that different ratios have significant effects on the performance of the predictors IDP-FSP-S and IDP-FSP-G compared with IDP-FSP-L because the positive and negative ratios of the training datasets of IDP-FSP-S and IDP-FSP-G are extremely imbalanced. In particular, IDP-FSP-S and IDP-FSP-G achieve the best performance when the training datasets are imbalanced, which helps CRFs to capture the imbalanced information between positive and negative samples. In Figure 1D, we can see that IDP-FSP-L, IDP-FSP-S, and IDP-FSP-G achieve the best performance with window sizes of 13, 11, and 13, respectively.

Fusion of Length-Dependent Predictors Can Improve Predictive Performance
IDP-FSP is an ensemble of three length-dependent predictors, including IDP-FSP-L, IDP-FSP-S, and IDP-FSP-G. This fusion approach has been successfully applied to solve many important tasks in bioinformatics. These three specialized predictors are trained on their respective types of training datasets, and their parameters are adjusted separately by using their corresponding benchmark test datasets. The performance of IDP-FSP-L, IDP-FSP-S, IDP-FSP-G, and IDP-FSP on different types of test datasets is shown in Table 1 and Figure 3, from which the following conclusions can be drawn. (1) IDP-FSP-L and IDP-FSP-S have better predictive performance on their corresponding datasets than on other datasets, which fully illustrates that LDRs and SDRs have different characteristics. (2) For a certain type of dataset, the corresponding predictor obtains better or comparable performance in terms of ACC. IDP-FSP-L, IDP-FSP-S, and IDP-FSP-G are constructed based on different types of datasets and use different positive and negative ratios of training datasets, which are 1:1, 1:5, and 1:2, respectively. The more negative samples are in the training dataset, the more negative sample information is included, leading to higher predictive performance for negative samples. Therefore, IDP-FSP-S and IDP-FSP-G outperform IDP-FSP-L for predicting the negative samples. For test datasets \( S_{\text{long}} \) and \( S_{\text{short}} \), the proportion of negative samples is much higher than that of \( S_{\text{long}} \), and, therefore, the MCC is more dependent on the predictive performance of negative samples. As a result, the MCC values obtained by IDP-FSP-S and IDP-FSP-G are higher than that
of IDP- FSP- L. (3) IDP- FSP outperforms IDP- FSP- G on every dataset, indicating that fusing these specialized predictors can effectively improve predictive performance.

IDP- FSP achieves good performance mainly because the following two reasons: (1) IDP- FSP is a fusion of three specializes predictors constructed based on the LDR dataset, SDR dataset, and generic dataset, respectively. Therefore, IDP- FSP can capture the characteristics of different IDRs. (4) IDP- FSP is able to capture the complementarity of the three specialized predictors.

Visualization of Predicted Proteins

In this section, the true structure and the predicted structure of three proteins are visualized to show the advantages of our proposed method. These proteins are PDB: 1MSVA, 3KC2B, and 1O0BA. For these proteins, the PyMOL (https://pymol.org/2/) software is used to generate the 3D structure of their ordered regions, and the 3D structure of their disordered regions is drawn manually.

The schematic diagrams of PDB: 1MSVA, 3KC2B, and 1O0BA are shown in Figures 4, 5, and 6, respectively. According to these figures, we can observe the following. (1) IDP- FSP- L and IDP- FSP- S can correctly identify some IDRs incorrectly predicted by IDP- FSP- G. For example, for the IDR [22, 27] of protein PDB: 1MSVA in Figure 4 and the IDR [268, 288] of protein PDB: 3KC2B in Figure 5, IDP- FSP- G fails to identify them. However, IDP- FSP is able to identify them. (2) IDP- FSP- L and IDP- FSP- S can correct some erroneous IDRs predicted by IDP- FSP- G. For example, for the ordered region [134, 171] of protein PDB: 1O0BA in Figure 6, IDP- FSP- G predicts it as an IDR. However, both IDP- FSP- L and IDP- FSP- S predict it as an ordered region, correcting the predictive results of IDP- FSP- G. (3) For some regions, IDP- FSP is more accurate than IDP- FSP- G. For example, for the IDR [443, 453] of protein PDB: 1O0BA in Figure 6, IDP- FSP- G predicts [438, 454] as an IDR, and IDP- FSP predicts [443, 453] as an IDR. For the IDR [329, 354] of protein PDB: 1MSVA in Figure 4, IDP- FSP- G predicts [342, 345] as an IDR, and IDP- FSP predicts [328, 354] as an IDR, which corrects 13 false negatives predicted by IDP- FSP- G. These observations indicate that IDP- FSP- L and IDP- FSP- S can capture the characteristics of LDRs and SDRs, respectively, and can predict some IDRs that IDP- FSP- G fails to predict. Besides, it is further proven that IDP- FSP can capture the complementarity of these three length-dependent predictors.

Comparison with the Existing Methods

The proposed method is compared with 26 highly related methods using two widely used independent test datasets (MxD494 and SL329). As shown in Tables 2 and 3, IDP- FSP achieves a predictive performance comparable with two state-of-the-art predictors and outperforms 24 other highly related predictors. In particular,
IDP-FSP outperforms IDP-CRF in predicting MxD494 and SL329. IDP-CRF is also a CRF-based model. Different from IDP-CRF, IDP-FSP is a fusion of three CRF-based predictors that are constructed based on different types of IDRs. This fully demonstrates the effectiveness of constructing predictors for LDRs, SDRs, and generic disordered regions. In addition to IDP-CRF, IDP-FSP achieves performance comparable with MFDp18 on dataset MxD494 and SPOT-disorder17 on dataset SL329 and outperforms all other related methods using these two datasets.

Conclusions
In this study, an ensemble predictor, IDP-FSP, is proposed that fuses three length-dependent predictors specially designed for the prediction of long, short, and generic disordered regions. The experimental results using different types of test datasets show that LDRs and SDRs have different characteristics, and there is complementarity between these three proposed specialized predictors. The experimental results using two independent test datasets show that IDP-FSP achieves better or at least comparable predictive performance with 26 currently existing state-of-the-art methods. IDP-FSP achieves good performance mainly for the following reasons. The proposed three length-dependent predictors can capture the different characteristics of different types of IDRs. Therefore, IDP-FSP fusing these specialized predictors can capture the characteristics of different types of IDRs and the complementarity among the three specialized predictors.

MATERIALS AND METHODS

Benchmark Datasets
The benchmark dataset used in this study was constructed by Zhang et al.24 and contains 4,229 proteins, and the similarity between sequences is less than 25%. The benchmark dataset is divided into 3,000 proteins for training and 1,229 proteins for testing. In this study, according to different types of IDRs, the training dataset and test dataset are divided into two datasets. One is the LDR dataset, in which each protein contains at least one LDR, and the other is the SDR dataset, in which each protein contains only SDRs. Therefore, the benchmark dataset can be formatted as

\[
S_{\text{Train}}^{\text{all}} = S_{\text{Train}}^{\text{long}} \cup S_{\text{Train}}^{\text{short}} \\
S_{\text{Test}}^{\text{all}} = S_{\text{Test}}^{\text{long}} \cup S_{\text{Test}}^{\text{short}}
\]

(Equation 1)

where \(S_{\text{Train}}^{\text{all}}\) represents the LDR dataset in the training dataset containing 3,428 proteins, which is used to train IDP-FSP-L; \(S_{\text{Train}}^{\text{short}}\) represents the SDR dataset in the training dataset containing 2,658 proteins, which is used to train IDP-FSP-S; and \(S_{\text{all}}^{\text{Train}}\) is the union of...
Train long and Train short, which is used to train IDP-FSP-G. Similarly, Test long represents the LDR dataset in the test dataset containing 144 proteins, which is used to test IDP-FSP-L, and Test short represents the SDR dataset in the test dataset containing 1,085 proteins, which is used to test IDP-FSP-S. Test all is the union of Test long and Test short, which is used to test IDP-FSP-G. These different types of datasets are given in Data S1.

MxD494 and SL329 are two widely used independent test datasets adopted for this study to test different methods. To test our method fairly, sequences with a similarity of more than 25% between the benchmark dataset and the two test datasets were removed from the benchmark dataset.

Figure 5. A Schematic Diagram of Protein PDB: 3KC2B with IDRs Predicted by IDP-FSP-L, IDP-FSP-S, IDP-FSP-G, and IDP-FSP
Yellow residues represent ordered residues, and red residues represent disordered residues. (A) IDRs predicted by IDP-FSP-L: \{1, 12\} and \{268, 288\}. (B) IDRs predicted by IDP-FSP-S: \{1, 12\}, \{268, 291\}, and \{348, 352\}. (C) IDRs predicted by IDP-FSP-G: \{1, 13\} and \{347, 352\}. (D) IDRs predicted by IDP-FSP: \{1, 13\}, \{268, 291\}, and \{348, 352\}. (E) True IDRs: \{1, 12\} and \{268, 288\}. The curly braces represent the position intervals of IDRs in the protein sequence.

Figure 6. A Schematic Diagram of Protein PDB: 1O0BA with IDRs Predicted by IDP-FSP-L, IDP-FSP-S, IDP-FSP-G, and IDP-FSP
Yellow residues represent ordered residues, and red residues represent disordered residues. (A) IDR predicted by IDP-FSP-L: \{1, 24\}. (B) IDRs predicted by IDP-FSP-S: \{1, 9\}, \{443, 453\}, and \{550, 554\}. (C) IDRs predicted by IDP-FSP-G: \{1, 26\}, \{134, 171\}, \{438, 454\}, and \{548, 554\}. (D) IDRs predicted by IDP-FSP: \{1, 26\}, \{443, 453\}, and \{550, 554\}. (E) True IDRs: \{1, 24\}, \{443, 453\}, and \{548, 554\}. The curly braces represent the position intervals of IDRs in the protein sequence.
The previously proposed predictor IDP-CRF has been proven that CRFs combined with PSSMs, kmer, secondary structure (SS), and relative solvent accessibility (RSA) are effective for predicting IDPs/IDRs. Therefore, these four state features were adopted for IDP-FSP-L, IDP-FSP-S and IDP-FSP-G we used in this study. The features of IDP-FSP-L, IDP-FSP-S and IDP-FSP-G we used are described in The Framework of IDP-FSP.

### State Features

The PSSMs are generated by running PSI-BLAST searching against the nrdb90 database. For PSI-BLAST, the parameters E-value and iteration time are set to 0.001 and 3, respectively, and other parameters are set to default. The final features are obtained by using the formula:

\[
\text{norm}(x) = \begin{cases} 
0.0 & \text{if } x \leq -5 \\
0.5 + 0.1x & \text{if } -5 < x < 5 \\
1.0 & \text{if } x \geq 5
\end{cases}
\]  

(Equation 3)

where \(x\) is the value of PSSMs. kmer defines the occurrence frequencies of \(k\) neighboring residues. The PSSM and kmer (k set to 1) features of target residue are constructed based on the subsequence centered on the target residue.

The SS features are obtained by using the profile-based PSIPRED v.4.01 package. If the profile of a protein is not generated by
searching against the nrdb90 database, then sequence-based PSIPRED is used instead of profile-based PSIPRED. The RSA information is generated by using the Sable v.2 package. For the Sable package, two parameters, SA_ACTION and SA_OUT, are set to SVR and RELATIVE, respectively, and other parameters are set to default. For each target residue, both SS and RSA are one-dimensional features.

**CRFs and Implementation**

Being widely used in the field of bioinformatics, CRFs are a probabilistic model proposed by Lafferty et al. for labeling sequence data. In this study, protein sequences and their corresponding label sequences are used to train the CRF model, which is a conditional probability model to annotate unlabeled protein sequences. In particular, CRFs have been adopted and proven to be effective for predicting IDPs/IDRs. FlexCRFs are a widely used tool of CRFs. In this study, the modified FlexCRFs as described in a previous paper are adopted, which can handle real value features. For FlexCRFs, the first-order Markov CRFs are used, and two parameters, num_iterations and init_lambda_val, are set to 50 and 0.05, respectively.

**The Framework of IDP-FSP**

Previous studies have shown that LDRs and SDRs have different characteristics, so constructing specialized predictors for LDRs and SDRs can effectively improve the predictive performance of IDPs/IDRs. Therefore, we construct three specialized predictors—IDP-FSP-L, IDP-FSP-S, and IDP-FSP-G—for predicting long, short, and generic disordered regions, respectively. These three specialized predictors are built based on CRFs, and the parameters of CRFs are described in CRFs and Implementation. The features and parameters adopted in these three predictors are optimized separately by using their corresponding test datasets. IDP-FSP-L is constructed based on PSSMs and kmer. IDP-FSP-S and IDP-FSP-G are constructed based on all of the features described in Features. Furthermore, the window sizes and ratios of the three predictors were optimized separately and are discussed in The Influence of Different Ratios of Positive and Negative Samples on Three Length-Dependent Predictors and The Influence of Different Window Sizes on Three Length-Dependent Predictors, respectively. However, for unlabeled proteins, it is unknown whether they contain LDRs or SDRs or both types of IDRs. A predictor designed for one type of IDRs cannot achieve good performance for other types. To solve this problem, these three specialized predictors are combined into IDP-FSP via voting. To illustrate this more intuitively, a flowchart of IDP-FSP is shown in Figure 7.

**Criteria for Performance Evaluation**

Two commonly used metrics, sensitivity (Sn) and specificity (Sp), are used in this study. Because of the imbalance of positive samples (disordered residues) and negative samples (ordered residues) in the IDP/IDR datasets, balanced ACC and MCC are also adopted. They are defined as

\[
Sn = \frac{TP}{TP + FN},
\]

\[
Sp = \frac{TN}{TN + FP},
\]

\[
ACC = \frac{1}{2} \left( \frac{TP}{TP + FN} + \frac{TN}{TN + FP} \right),
\]

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

(Equation 4)

where TP, TN, FP, and FN represent the number of true positive, true negative, false positive, and false negative samples, respectively.

**SUPPLEMENTAL INFORMATION**

Supplemental Information can be found online at https://doi.org/10.1016/j.omtn.2019.06.004.

**AUTHOR CONTRIBUTIONS**

B.L. and Y.L. designed the experiments and participated in drafting the manuscript and performing the statistical analysis. Y.L. performed the experiments. X.W. and S.C. participated in revising the manuscript.
CONFLICTS OF INTEREST
The authors declare no competing interests.

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