Solenoid and non-solenoid protein recognition using stationary wavelet packet transform

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ABSTRACT

Motivation: Solenoid proteins are emerging as a protein class with properties intermediate between structured and intrinsically unstructured proteins. Containing repeating structural units, solenoid proteins are expected to share sequence similarities. However, in many cases, the sequence similarities are weak and non-detectable. Moreover, solenoids can be degenerated and widely vary in the number of units. So that it is difficult to detect them. Recently, several solenoid repeats detection methods have been proposed, such as self-alignment of the sequence, spectral analysis and discrete Fourier transform of sequence. Although these methods have shown good performance on certain data sets, they often fail to detect repeats with weak similarities. In this article, we propose a new approach to recognize solenoid repeats and non-solenoid proteins using stationary wavelet packet transform (SWPT). Our method associates with three advantages: (i) naturally representing five main factors of protein structure and properties by wavelet analysis technique; (ii) extracting novel wavelet features that can capture hidden components from solenoid sequence similarities and distinguish them from global proteins; (iii) obtaining statistics features that capture repeating motifs of solenoid proteins.

Results: Our method analyzes the characteristics of amino acid sequence in both spectral and temporal domains using SWPT. Both global and local information of proteins are captured by SWPT coefficients. We obtain and integrate wavelet-based features and statistics-based features of amino acid sequence to improve the classification task. Our proposed method is evaluated by comparing to state-of-the-art methods such as HHrepID and REPETITA. The experimental results show that our algorithm consistently outperforms them in areas under ROC curve. At the same false positive rate, the sensitivity of our WAVELET method is higher than the others used sequence–sequence comparison to find suboptimal self-alignments. Repeating parts of the sequence appear as off-diagonal regions of similarity. They allow the detection of basic repeating units and locations of units along the sequence. HHrepID has been reported to be the most sensitive self-alignment approach to detect repeats (Biegert et al., 2008). However, HHrepID often cannot detect repeats with weak similarities.

Other approaches to recognize solenoid repeats use periodic patterns in proteins such as (Coward et al., 1998), (Murray et al., 2002), (Murray et al., 2004), REPPER (Gruber et al., 2005) and REPETITA (Marsella et al., 2009). Repeating protein motifs, TIM barrels, propeller blades, coiled coils and leucine-rich repeating structures have been analyzed (Murray et al., 2002) and used to detect repeats in known protein structure. The data utilized in Murray et al. (2002) are relative accessible surface area and simple hydrophobicity that provide information of the protein structure and the length of their repeats, which can provide information about a possible 3D structure of the repetitive protein (Kajava, 2001). There are four main structural classes (Kajava, 2001): Class I, crystalline structures (1- to 2-residue repeats); Class II, fibrous proteins (3- to 4-residue repeats); Class III, solenoid proteins (5- to 42-residue repeats); and Class IV, domain-forming repeats (30 or more residues). Solenoid proteins contain a superhelical arrangement of repeating structure units (Kobe et al., 2000). This arrangement contrasts the structure of most Class-IV proteins that fold into globular domains in more complex manners.

Repeats in Class I and Class II have only 1–4 residues, hence they have low sequence complexity and can be easily detected. Globular repeats in Class IV have their sufficient length to be detected by database search tools like PSI-BLAST (Altschul et al., 1997). Solenoid proteins are built of repeated structural units. The repeating units of the solenoids consist of one to several segments of secondary structure, among which are α-helices (Kajava et al., 2002), β-strands (Hennetin et al., 2006) and 31 helices. The solenoid proteins have purely α-helices or β-strands or a mixture of the secondary structures (Kobe et al., 2000). They are expected to share sequence similarities. However, in some cases, the sequence similarities are weak such as protein farnesyltransferase (FTase; Boguski et al., 1992) and insulin-like growth factor-1 receptor (IGF-1R; Bajaja et al., 1987), so that they are non-detectable (Kobe et al., 2000). Therefore, database search tools like PSI-BLAST relying on clear conservation pattern are not good tools to detect solenoid repeats.

In recent years, several methods have been proposed to identify solenoid repeats. Some of them are based on self-alignment of the sequence such as REPRO (George et al., 2000), RADAR (Heger et al., 2000), TRUST (Sklarzycz et al., 2004), HHrep (Soding et al., 2006) and HHrepID (Biegert et al., 2008). HHrep and HHrepID utilized hidden Markov model comparison (HMM–HMM), while the others used sequence–sequence comparison to find suboptimal self-alignments. Repeating parts of the sequence appear as off-diagonal regions of similarity. They allow the detection of basic repeating units and locations of units along the sequence. HHrepID has been reported to be the most sensitive self-alignment approach to detect repeats (Biegert et al., 2008). However, HHrepID often cannot detect repeats with weak similarities.

1 INTRODUCTION

With several interesting features of repeating sequences, significant progress has been made in the identification of the DNA and protein repeats, understanding the duplication mechanism and special features of the repeat evolution (Kajava, 2001). Repeats are usually found in non-coding genomic regions. However, repeating sequences are also found in about 14% of all proteins coded by all known genes with about 25% of all eukaryotic proteins (Marcotte et al., 1999). The known protein structures can be classified by...
sequence. REPPER (Gruber et al., 2005) searches for periodicities of particular, user-defined types (hydrophobic, polar, positively charged) using the Fourier transform of sequence. However, it primarily aims at the analysis of fibrous proteins and does not allow insertions between repeating units. REPETITA (Mansella et al., 2009) utilizes sequence profile with the discrete Fourier transform to detect degenerated repeats (Lupas et al., 1997). It includes the five numeric scales proposed by Atchley (Atchley et al., 2005) to characterize the amino acid sequence. Compared to TRUST and RADAR, REPETITA has been reported to be more sensitive. However, similar to IHRepID, REPETITA also cannot detect some repeats with weak similarities.

Wavelet analysis has been widely applied to process biomedical signals (Unser et al., 1996). Some applications of wavelet transforms in genome sequence analysis and gene expression data analysis have been proposed (Li, 2003). A key advantage of wavelet transforms over the Fourier transform is their ability to simultaneously capture both spectral and temporal information within the signal (Daubechies, 1992; Mallat et al., 1989). In contrast, the Fourier transform does not give local information of proteins, because the Fourier coefficients only contain globally averaged information. Wavelet analysis has an improved ability to capture hidden components from biological data and is a good link between biological systems and the mathematics objects (Li, 2003). The wavelet transforms can be categorized as: continuous wavelet transform (CWT) and discrete wavelet transform (DWT). The CWT was used to detect and characterize repeating motifs in protein sequence and structure data (Murray et al., 2002). It maps a signal to a time-scale joint representation calculated by continuously shifting a continuously scalable function over a signal and calculating the correlation between them. The resulting wavelet coefficients are highly redundant. In molecular biology and genetics, we are more interested in discretely sampled rather than continuous functions. The DWT was used to classify protein subcellular location images (Chebira et al., 2007). Stationary wavelet packet transform (SWPT) is one of discrete wavelet analysis techniques. A main advantage of the stationary wavelets over the DWT is its shift invariant property (Coifman et al., 1995). The SWPT is suitable for many bioinformatics applications, such as DNA copy numbers smoothing and detection (Huang et al., 2008; Nguyen et al., 2010).

In this article, the SWPT technique is proposed to characterize proteins by five representation factors: polarity, secondary structure, molecular volume, codon diversity and electrostatic charge. We propose to extract new features from the SWPT of five factors and from statistics of amino acid sequence, and employ them to classify solenoid and non-solenoid proteins. Empirical studies on solenoid protein detection have been performed to compare proposed method to other related methods. Experimental results demonstrate the promising performance of our proposed approach.

2 METHODS

A flow diagram with all steps of our algorithm is given in Figure 1. The individual steps including wavelet analysis technique, feature extraction, feature selection, and classification will be described in following subsections.

2.1 The proposed method

The framework of proposed method is shown in Figure 1. At first, a protein sequence is translated into five numerical signals derived by Atchley (Atchley et al., 2005). These five signals represent polarity, secondary structure, molecular volume, codon diversity and electrostatic charge. All signals are normalized to zero mean, since the averages are not significant to detect repeats. Next, each signal is decomposed into 16 subbands by SWPT wavelet transform (see Section 2.2). Eighty subbands obtained from five signals are used to extract eighty wavelet features as in Equation (5). In addition to wavelet features, probability features of 20 amino acids are also computed for each protein sequence. Seventeen features are selected from total 100 features using the forward feature selection method. Finally, the quadratic discriminant classifier described in Section 2.5 is applied to classify protein sequences.

Inspired by wavelet analysis for the protein structure and sequence (Murray et al., 2002), we propose to use the SWPT to analyze characteristics of amino acid sequence. However, there are two main differences between Murray’s method and ours. The first difference is that the data utilized in Murray et al. (2002) is relative accessible surface area and simple hydrophobicity, while the data utilized in our method is five patterns that summarize a large portion of the physio-chemical and biological properties of amino acids (Atchley et al., 2005; Mansella et al., 2009). To obtain these five factors, 495 amino acid indices which include general attributes, such as molecular volume or size, hydrophobicity and charge, as well as more specific measures, such as the amount of nonbonded energy per atom or side chain orientation angle are analyzed. This analysis simplifies high-dimensional data by generating a smaller number of factors that would summarize the entire constellation of amino acid physiochemical properties. The resultant factors are linear functions of the original data, are fewer in number than the original, and are useful for clusters of covarying traits that describe the underlying or latent structure of the variables. The first resultant factor is a polarity index which is bipolar, large positive and negative factor coefficients and also reflects simultaneous covariance in portion of polarity versus nonpolarity, and hydrophobicity versus hydrophilicity. Therefore, the hydrophobicity feature used in the previous study is also involved in the first factor. The second difference is that Murray (Murray et al., 2002) used the continuous wavelets which are highly redundant, but we are more concerned with discrete sampling rather than continuous functions for protein sequence representation. Moreover, since some amino acids play important roles in structure of solenoids, we propose statistics features to capture repeating motifs of solenoids.

2.2 Stationary wavelet packet transform

The SWPT is based on filters $H_1$ and $G_1$ and on an up-sampling operator. The filter $H_1$ is a low-pass filter defined by a sequence $h_1(n)$ and the high-pass filter $G_1$ defined by a sequence $g_1(n)$. Given a signal $x(n)$ of length $N$, the first level of the SWPT produces two subbands: approximation subband $a_1(n)$
The high-pass filter of \( h(n) \) is given by \( h(n) = -0.1294, 0.2241, 0.8365, 0.4830 \) and \( g(n) = \{-0.4830, 0.8365, -0.2241, -0.1294\} \) when 42 filters are used. Values of \( k \) in the above summation are from 1 to \( N_s \), where \( N_s \) is the length of \( n \). Two new subbands \( s_{12} \) and \( s_{13} \) have the same length as the original signal \( s(n) \). The low-pass filter \( H_l \) is assumed to satisfy the internal orthogonal relation as

\[
\sum_{i} h_k(n)h_k(n+i+2) = 0, \quad \text{for all integers } i \neq 0 \quad \text{and} \quad \sum_{i} h_k(n)g_k(n+i+2) = 0, \quad \text{for all integers } i.
\]

The high-pass filter \( G_l \) satisfies the same internal orthogonal relation as \( H_l \) and the mutual orthogonal relation as

\[
\sum_{i} h_k(n)h_k(n+i) = 0, \quad \text{for all integers } i.
\]

Each signal (factor) is decomposed into 16 subbands by SWPT. The energy \( E_k(\ell) = \frac{1}{N_s} \sum_{i=1}^{N_s} |s_k(\ell)|^2 \) of the \( k \)-th subband coefficients and \( N_s \) is the number of coefficients.

Solenoid proteins contain a superhelical arrangement of repeating structural units. The most common arrangement of the solenoid proteins is a single-stranded superhelix which is formed by one or several elements of secondary structure (such as \( \alpha \)-helices, \( \beta \)-strands and 3\text{\(\alpha\)}\helices) winding along the superhelical axis. Each repeat contains at least one turn with an irregular conformation introduced between the secondary structures. The minimal structural unit corresponding to one repeat has one \( \alpha \)-helix and one \( \beta \)-strand. Several representative structural repeating motifs are summarized below, where the asterisk denotes a polar residue, \( \rho \) denotes nonpolar residues, and \( s \) is any residue.

- **A-(N,D)-L*-x-a: the pentapeptide repeat protein (Bietman et al., 1998);**
- **S-x-(N,V)-x-G: the pentapeptide repeat of anti-freeze protein (Greathar et al., 2000) contains one \( \beta \)-strand and one turn.**
- **Pentapeptide repeat proteins (PRPs) are found primarily in bacteria, especially cyanobacteria.**
- **SAxGxx: the hexapeptide repeat of LxxA (Raete et al., 1995) contains one \( \beta \)-strand and one turn.**
- **SAxGxx: the hexapeptide repeat of SAxxA (Kajava et al., 1998) is shown in Figure 2a.**
- **RHR: the repeat motif of RHR proteins.**

The newly uncovered structural features may help scientists discover the biological role of pentapeptide repeat proteins within the cell. Several representative structural repeating motifs are summarized below, where the asterisk denotes a polar residue, \( \rho \) denotes nonpolar residues, and \( s \) is any residue.
Two groups of data are studied: (i) 105 solenoid repeats proteins; (ii) 247 globular proteins (non-solenoid) without structural repeat. These data are downloaded from the website (http://protein.bio.unipd.it/repetita/) of the previous study (Marsella et al., 2009). Marsella took an initial set of 32 proteins with solenoid repeats and used the TESE server (Sirocco, 2008) to find more protein domains belonging to the same solenoid folds as the initial set. By limiting the maximal residual structural similarity according to the CATH classification (Pearl et al., 2003), TESE allows the user to generate ad hoc non-redundant sets of proteins with known structure. The final set of 105 solenoid domains was yielded by choosing representatives with at most 35% pairwise sequence identity (i.e. CATH 'S' level). Marsella also generated the set of 247 non-solenoid protein domains with TESE by randomly choosing X-ray structures with different topologies and no detectable sequence similarity (i.e. CATH 'T' level). A training set of 50 solenoid proteins and 119 non-solenoid, and a testing set

Table 1. Selected wavelet features from a total of 100 features using the forward feature selection method

| Feature | 35 | 49 | 27 | 41 | 10 | 88 | 68 | 46 | 51 |
|---------|----|----|----|----|----|----|----|----|----|
| Factor  | V  | IV | II | 1  | V  | III| I  | 1  | 1  |
| Subband | 7  | 9  | 6  | 9  | 2  | 14 | 10 | 11 |  |

All five factors from I to IV at different subbands corresponding to solenoid properties and structure are selected.

Table 2. Selected statistics features from a total of 100 features using the forward feature selection method

| Feature | 90 | 92 | 99 | 94 | 82 | 89 | 93 | 97 | 88 |
|---------|----|----|----|----|----|----|----|----|----|
| Amino acid | L | N | W | Q | C | K | P | T |

The occurrence frequency of amino acid L in sequences is the first choice to capture structural repeating motifs.
of 55 solenoid proteins and 128 non-solenoid ones are selected as in Marsella et al. (2009). The solenoid proteins contain the main repeat classes such as all α, all β, and α/β with available structure information or they have their structures and evolutions related to these major folds.

Sequences are composed of long strings of alphabetic letters rather than arrays of numerical values. A metric for comparing such alphabetic data is sophisticated. Therefore, a method proposed by Atchley (Atchley et al., 2005) to quantify alphabetic information inherent to biological sequences was applied. Five patterns that summarize a large portion of the physio-chemical and biological properties of amino acids were obtained. These five factors represent polarity, secondary structure, molecular volume, codon diversity and electrostatic charge.

### 3.2 Comparisons to existing methods

We compare the classification performance of our WA VELET method against four exiting methods in protein repeats detection: RADAR (Heger et al., 2000), TRUST (Sklarzyczk et al., 2004), HHrepID (Biegert et al., 2008) and REPETITA (Marsella et al., 2009). Sensitivity, specificity and accuracy of all methods are computed for training set, testing set and overall data.

RADAR and TRUST detect internal sequence symmetries by comparing the protein sequence itself and utilize sequence–sequence comparison to find suboptimal. RADAR builds a repeat profile to determine exact borders and extract a multiple alignment of repeats self-alignments, and TRUST explicitly makes use of consistency that has led to improvements in multiple sequence alignment. In TRUST and RADAR methods, predictions are considered when at least two repeat units are detected.

HHrepID utilizes hidden Markov model comparison. The maximum expected accuracy algorithm that maximizes the sum of posterior probabilities in the alignment and a probabilistic approach to consistency through a merging procedure based on posterior probabilities are also applied. HHrepID has been reported to be most sensitive to date (Biegert et al., 2008). We use default settings for HHrepID method. The MAC threshold is set to 0.5 and the P-value threshold for suboptimal alignment is set to 0.1.

REPETITA detects solenoid repeats and discriminates them from globular proteins using information from sequence profiles together with the discrete Fourier transform, based on the assumption that few characteristics of sequence repeats uniquely identify structural repeats.

### 3.3 Results and discussions

We summarize experimental results including sensitivity, specificity and accuracy in Table 3. Data sets used for evaluations are the training set, testing set and overall data. We evaluate both training set and testing set to verify that our predictive model does not overfit the training data. Bold values represent the proposed method.

| Method     | Training (%) | Test (%) | Overall (%) |
|------------|--------------|----------|-------------|
| Sensitivity| HHrepID 70.0 | 63.6     | 66.7        |
|            | REPETITA 70.0| 69.0     | 70.0        |
|            | WA VELET 96.0| 90.9     | 93.3        |
| Specificity| HHrepID 93.3 | 89.8     | 91.5        |
|            | REPETITA 85.0| 83.0     | 84.0        |
|            | WA VELET 93.3| 91.4     | 92.3        |
| Accuracy   | HHrepID 86.4 | 82.0     | 84.1        |
|            | REPETITA 80.5| 78.7     | 79.6        |
|            | WA VELET 94.1| 91.3     | 92.6        |

Fig. 3. Comparisons of RADAR, TRUST, HHrepID, REPETITA and WA VELET methods for solenoid detection: the number of true positive solenoid proteins against the number of false positive proteins detected above a threshold significance when overall data are used.

We evaluate all methods using ROC curve as shown in Figure 3. The number of true positive solenoid proteins against the number of false positive proteins detected above a threshold significance is computed. In the case of HHrepID method, we used the total repeat P-value for threshold significance. The signed distance from the optimal line is used for significance measure in REPETITA method. For RADAR and TRUST methods, the number of repeat units is used. Predictions are considered where at least two repeat units have been detected. In our method, we use the posterior probabilities obtained from the QDA classifier for threshold significance. The performances of all methods in terms of areas under the ROC curve are shown in Table 4 when the false positive ranges from 0 to 20. The performance of WA VELET is better than other methods from 21% to 46% in areas under the ROC curve.

At a false positive rate (FPR) of 8% (20/247), WA VELET method is able to detect about 60% more solenoid proteins than RADAR and about 50% more than REPETITA. TRUST and HHrepID can detect better than RADAR and REPETITA. However, WA VELET method performs about 37% better than TRUST and 29% better than HHrepID in sensitivity at FPR of 8%. When the FPR is from
Table 4. Performance of all methods in terms of areas under ROC curve in overall data when false positives are from 0 to 20

| Method      | RADAR | TRUST | REPETITA | HHrepID | WAVELET |
|-------------|-------|-------|----------|---------|---------|
| Area        | 798   | 1009  | 1057     | 1168    | 1475    |

Bold values represent the proposed method.

Fig. 4. Sensitivity, specificity and accuracy of WAVELET method for solenoid and non-solenoid classification against the number of selected features. Overall data are used.

3% to 8%, WAVELET also outperforms the others. The solenoid proteins detected using WAVELET is close to using HHrepID, when FPR is 1–3%. But they are much more than RADAR, TRUST and REPETITA. Compared to RADAR and TRUST in detecting solenoids, HHrepID is an identifier with higher sensitivity. This agrees with results reported in Biegert et al. (2008) that HHrepID is most sensitive to date. When FPR is <1%, the sensitivity of HHrepID method is higher than the others. However, the highest sensitivity of HHrepID in this simulation is about 67% for overall data, while that of WAVELET method can reach 93% at the same FDR of 8%. Because the structure information using wavelet feature is combined with statistical information in our WAVELET method, a higher classification accuracy was achieved.

Figure 4 shows the overall performances of WAVELET when the number of features changes from 1 to 17. The WAVELET's performance almost increases when the number of features increases. The accuracy of the WAVELET ranges from 77% to 93% corresponding to 1 to 17 features. In REPETITA method, only two features are used. A small number of features often cannot capture enough biological information for detection. Therefore, there are only 70% solenoid data detected by REPETITA method, while WAVELET method with 17 features can detect 93% solenoid data.

We also show some examples of RADAR, TRUST, REPETITA, HHrepID and WAVELET methods for solenoid protein detection in Table 5. These solenoid proteins are plotted in Figure 5. Three of six sample solenoids are non-detectable by RADAR and TRUST methods. REPETITA can detect four solenoids, WAVELET can detect all of six solenoids, while HHrepID cannot find any repeats in these solenoid sequences. All above simulation results illustrate that WAVELET method outperforms the others.

Table 5. Examples of solenoid detection using RADAR, TRUST, REPETITA, HHrepID and WAVELET methods

| CATH Domain | RADAR | TRUST | REPETITA | HHrepID | WAVELET |
|-------------|-------|-------|----------|---------|---------|
| 1p5qA02     | True  | False | True     | False   | True    |
| 1xt0A00     | False | True  | False    | False   | True    |
| 1o8A00      | False | False | False    | False   | True    |
| 1ho8A01     | True  | False | True     | False   | True    |
| 2a4zA03     | False | True  | True     | False   | True    |
| 1tdtA02     | True  | False | True     | False   | True    |

All sequences shown in this table are solenoids. ‘True’ is a correct detection and ‘False’ is a wrong detection.

Fig. 5. Examples of solenoid proteins: (a) 1p5qA02, (b) 1xt0A00, (c) 1o8A00, (d) 1ho8A01, (e) 2a4zA03 and (f) 1tdtA02. Detection results of these solenoids using RADAR, TRUST, REPETITA, HHrepID and WAVELET methods are shown in Table 5. Rainbow coloring from blue to red shows the topology from N to C terminus. Cartoon representations of these sample solenoid proteins are available in previous study (Marsella et al., 2009).

4 CONCLUSION

In this article, we proposed a new WAVELET method to recognize solenoid proteins and global proteins using SWPT and statistical features of amino acid sequences. In order to detect solenoid repeats with weak similarities, we took advantages of the integration of wavelet-statistics features and the SWPT analysis of five factors representing protein structure and properties. Our new features can capture structure, properties of solenoid proteins and hidden components from sequence similarities, to distinguish them from global proteins. The proposed approach was validated by comparing to other state-of-the-art methods in solenoid proteins detection experiments. In all results, our new scheme improved the solenoid protein recognition in all statistical metrics, including sensitivity, specificity and accuracy. The WAVELET method is a promising approach for solenoid protein classification. Based on different types of training data, the WAVELET method can be applied to classify different kinds of solenoids or different kinds of protein structures in future work.

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