SeqFea-Learn: A Python pipeline tool for feature extraction, feature selection, machine learning and deep learning based on DNA, RNA and protein sequence data

Name Surname[1,*], Name Surname[2] and Name Surname[2]

[1] Department, Institution, Town, State, Postcode, Country

[2] Department, Institution, Town, State, Postcode, Country

Methods Description

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Introduction

SeqFea-Learn is a Python pipeline tool for analyzing DNA, RNA, and protein sequencing data that integrated 19 feature extraction methods for DNA, 15 feature extraction methods for RNA, 32 feature extraction methods for Protein sequencing data, 21 feature selection methods, 15 dimensionality reduction methods, 7 clustering methods, 5 sampling methods, 10 classification methods, and 3 deep learning methods. This document will provide user detailed descriptions for each method.

DNA feature extraction method

SeqFea-Learn contains 19 DNA feature extraction methods.

Feature Extraction Method	Method Number
Kmer	1
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1. Kmer

For Kmer descriptor, the DNA sequences are represented as the occurrence frequencies of k neighboring nucleic acids. The Kmer (k=3) descriptor can be calculated as:

$$f(t) = \frac{N(t)}{N}, \quad t \in \{AAA, AAC, AAG, \ldots, TTT\}$$

where $N(t)$ is the number of kmer type t, while N is the length of a nucleotide sequence.

2. Reverse compliment kmer (RCKmer)

The reverse compliment kmer is a variant of kmer descriptor, in which the kmers are not expected to be strand specific. For instance, for a DNA sequence, there are 16 types of 2-mers (i.e. 'AA', 'AC', 'AG', 'AT', 'CA', 'CC', 'CG', 'CT', 'GA', 'GC', 'GG', 'GT', 'TA', 'TC', 'TG', 'TT'), ‘TT’ is reverse compliment with ‘AA’. After removing the reverse compliment kmers, there are only 10 distinct kmers in the reverse compliment kmer approach ('AA', 'AC', 'AG', 'AT', 'CA', 'CC', 'CG', 'GA', 'GC', 'TA').

3. Pseudo dinucleotide composition (PseDNC)

PseDNC is an approach incorporating the contiguous local sequence-order information and the global sequence-order information into the feature vector of the DNA sequence. Given a DNA sequence D, the PseDNC feature vector of D is defined:

$$D = [d_1, d_2, d_3, \cdots, d_{16}, d_{16+1}, \cdots, d_{16+\lambda}]$$

$$d_k = \begin{cases} \dfrac{f_k}{\sum_{i=1}^{16} f_i + \omega \sum_{j=1}^{\lambda} \theta_j} & (1 \le k \le 16) \\ \dfrac{\omega \theta_{k-16}}{\sum_{i=1}^{16} f_i + \omega \sum_{j=1}^{\lambda} \theta_j} & (17 \le k \le 16 + \lambda) \end{cases}$$

where f_k is the normalized occurrence frequency of dinucleotides in the RNA sequence, the parameter λ is an integer, representing the highest counted rank (or tier) of the correlation along a RNA sequence, w is the weight factor ranged from 0 to 1, θ_j is called the correlation factor that reflects the sequence-order correlation between all the most contiguous dinucleotides along a RNA sequence, which is defined:

$$\begin{cases} \theta_1 = \dfrac{1}{L-2} \sum_{i=1}^{L-2} \Theta(R_i R_{i+1}, R_{i+1} R_{i+2}) \\ \theta_2 = \dfrac{1}{L-2} \sum_{i=1}^{L-2} \Theta(R_i R_{i+1}, R_{i+2} R_{i+3}) \\ \theta_3 = \dfrac{1}{L-2} \sum_{i=1}^{L-2} \Theta(R_i R_{i+1}, R_{i+3} R_{i+4}) \\ \qquad \cdots\cdots \\ \qquad \cdots\cdots\cdot \\ \theta_\lambda = \dfrac{1}{L-1-\lambda} \sum_{i=1}^{L-1-\lambda} \Theta(R_i R_{i+1}, R_{i+\lambda} R_{i+\lambda+1}) \end{cases}$$

where the correlation function is given by

$$\Theta(R_iR_{i+1},R_jR_{j+1})=\frac{1}{\mu}\sum_{u=1}^{\mu}[P_u(R_iR_{i+1})-P_u(R_jR_{j+1})]^2$$

where μ is the number of physicochemical indices, in this approach, 6 indices reflecting the local RNA structural properties are employed to generate the PseDNC feature vector, $P_u(R_iR_{i+1}),P_u(R_jR_{j+1})$ represents the numerical value of the u-th physicochemical index of the dinucleotide R_iR_{i+1},R_jR_{j+1}.

4. Pseudo k-tuple nucleotide composition (PseKNC)

PseKNC extends the PseDNC approach by incorporating *k*-tuple nucleotide composition. Given a DNA sequence D, the feature vector of D is defined:

$$D=[d_1,d_2,d_3,\cdots,d_{4^k},d_{4^k+1},\cdots,d_{4^k+\lambda}]$$

$$d_k=\begin{cases}\dfrac{f_k}{\sum_{i=1}^{4^k}f_i+\omega\sum_{j=1}^{\lambda}\theta_j} & (1\le k\le 4^k)\\[2ex] \dfrac{\omega\theta_{k-4^k}}{\sum_{i=1}^{4^k}f_i+\omega\sum_{j=1}^{\lambda}\theta_j} & (4^k\le k\le 4^k+\lambda)\end{cases}$$

where λ is the number of the total counted ranks (or tiers) of the correlations along a DNA sequence; f_u is the frequency of oligonucleotide that is normalized to ; ω is a weight factor; $\sum_{i=1}^{4^k}f_i=1$ is given by

$$\theta_j=\frac{1}{L-j-1}\sum_{i=1}^{L-j-1}\Theta(R_iR_{i+1},R_{i+j}R_{i+j+1})\ (j=1,2,\cdots,\lambda;\lambda<L)$$

which represents the j-tier structural correlation factor between all the j-th most contiguous dinucleotides. The correlation function $\Theta(R_iR_{i+1},R_{i+j}R_{i+j+1})$ is defined by

$$\Theta(R_iR_{i+1},R_{i+j}R_{i+j+1})=\frac{1}{\mu}\sum_{v=1}^{\mu}[P_v(R_iR_{i+1})-P_v(R_{i+j}R_{i+j+1})]^2$$

where μ is the number of physicochemical indices, in this study, 6 indices reflecting the local DNA structural properties are employed to generate the PseKNC feature vector; $P_v(R_iR_{i+1}), P_v(R_{i+j}R_{i+j+1})$ represents the numerical value of the *v-th* physicochemical index for the dinucleotide $R_iR_{i+1}, R_{i+j}R_{i+j+1}$.

5. Dinucleotide-based auto covariance (DAC)

The DAC measures the correlation of the same physicochemical index between two dinucleotides separated by a distance of lag along the sequence, which can be calculated as:

$$DAC(u,l) = \sum_{i=1}^{L-l-1} (P_u(R_iR_{i+1}) - \bar{P}_u)(P_u(R_{i+l} + R_{i+l+1}) - \bar{P}_u) / (L-l-1)$$

where u is a physicochemical index, L is the length of the RNA sequence $P_u(R_iR_{i+1})$ means the numerical value of the physicochemical index u for the dinucleotide R_iR_{i+1} at position i, $\bar{P}_u$ is the average value for physicochemical index u along the whole sequence:

In such a way, the length of DAC feature vector is $N \times lag$, where N is the number of physicochemical indices, and lag is the maximum of sequence.

6. Dinucleotide-based cross covariance (DCC)

Given a DNA sequence, the DCC approach measures the correlation of two different physicochemical indices between two dinucleotides separated by lag nucleic acids along the sequence, which can be calculated by:

$$\mathrm{DCC}(u_1,u_2,l) = \sum_{i=1}^{L-l-1} \left(P_{u_1}(R_iR_{i+1}) - \bar{P}_{u_1}\right)\left(P_{u_2}(R_{i+l}R_{i+l+1}) - \bar{P}_{u_2}\right) / (L-l-1)$$

where u_1,u_2 are two different physicochemical indices, L is the length of the DNA sequence, $P_{u_1}(R_iR_{i+1}), P_{u_2}(R_iR_{i+1})$ is the numerical value of the physicochemical index u_1,u_2 for the dinucleotide R_iR_{i+1}. $\bar{P}_{u_1}$ is the average value for physicochemical index value u_1 along the whole sequence:

$$\overline{P_u} = \sum_{j=1}^{L-1} P_u\left(\mathrm{R}_j \mathrm{R}_{j+1}\right) / (L-1)$$

In such a way, the length of the DCC feature vector is $N \times (N-1) \times lag$, lag is the maximum of sequence; N is the number of physicochemical indices.

7. Dinucleotide-based auto-cross covariance (DACC)

DACC is a combination of DAC and DCC. Therefore, the length of the DACC feature vector is $N \times N \times lag$, where N is the number of physicochemical indices and lag is the maximum of sequence.

8. Trinucleotide-based auto covariance (TAC)

The Trinucleotide-based auto covariance (TAC) encoding measures the correlation of the same physicochemical index between trinucleotides separated by lag nucleic acids along the sequence, and can be calculated as:

$$TAC(u,l) = \sum_{i=1}^{L-l-2} (P_u(R_i R_{i+1} R_{i+2}) - \bar{P}_u)(P_u(R_{i+l} R_{i+l+1} R_{i+l+2}) - \bar{P}_u) / (L-l-2)$$

where u is a physicochemical index, L is the length of the DNA sequence $P_u(R_i R_{i+1} R_{i+2})$ means the numerical value of the physicochemical index u for the dinucleotide $R_i R_{i+1} R_{i+2}$ at position i , $\bar{P}_u$ is the average value for physicochemical index u along the whole sequence. The dimension of TAC feature vector is $N \times lag$, where N is the number of physicochemical indices, and lag is the maximum of sequence.

9. Trinucleotide-based cross covariance (TCC)

The trinucleotide-based cross covariance (TCC) encoding measures the correlation of two different physicochemical indices between two trinucleotides separated by lag nucleic acids along the sequence. The TCC encoding can be calculated as:

$$TCC\left(u_1, u_2, l\right) = \sum_{i=1}^{L-l-2} \left(P_{u_1}\left(R_i R_{i+1} R_{i+2}\right) - \bar{P}_{u_1}\right)\left(P_{u_2}\left(R_{i+l} R_{i+l+1} R_{i+l+2}\right) - \bar{P}_{u_2}\right) / (L-l-2)$$

where u_1, u_2 are two different physicochemical indices, L is the length of the DNA sequence, $P_{u_1}\left(R_i R_{i+1} R_{i+2}\right), P_{u_2}\left(R_i R_{i+1} R_{i+2}\right)$ is the numerical value of the physicochemical index

u_1, u_2 for the dinucleotide $R_i R_{i+1} R_{i+2}$. $\bar{P}_{u_1}$ is the average value for physicochemical index value u_1 along the whole sequence:

$$\overline{P_u} = \sum_{j=1}^{L-1} P_u \left(R_j R_{j+1} R_{j+2} \right) / (L-1)$$

In such a way, the length of the TCC feature vector is $N \times (N-2) \times lag$, lag is the maximum of sequence; N is the number of physicochemical indices.

10. Trinucleotide-based auto-cross covariance (TACC)

The trinucleotide-based auto-cross covariance (TACC) encoding is a combination of TAC and TACC encoding. Thus, the dimension of the TACC encoding is $N \times N \times lag$, where N is the number of physicochemical indices and lag is the maximum of DNA sequence.

11. Nucleic acid composition (NAC)

The nucleic acid composition (NAC) encoding calculates the frequency of each nucleic acid type in a nucleotide sequence. The frequencies of all 4 natural nucleic acids (i.e. “ACGT or U”) can be calculated as:

$$f(t) = \frac{N(t)}{N}, \ t \in \{A, C, G, T(U)\}$$

where *N*(*t*) is the number of nucleic acid type *t*, while *N* is the length of a nucleotide sequence.

12. Di-nucleotide composition (DNC)

The Di-Nucleotide Composition gives 16 descriptors. It is defined as:

$$D(r,s) = \frac{N_{rs}}{N-1}, \ r,s \in \{A, C, G, T(U)\}$$

where N_{rs} is the number of di-nucleotide represented by nucleic acid types *r* and *s*.

13. Tri-nucleotide composition (TNC)

The Tri-Nucleotide Composition gives 64 descriptors. It is defined as:

$$D(r,s,t) = \frac{N_{rst}}{N-2}, \ r,s,t \in \{A,C,G,T(U)\}$$

where N_{rst} is the number of tri-nucleotide represented by nucleic acid types *r, s* and *t*.

14. zCurve mathematical formula (zCurve)

Z-curve theory is often used in genomic sequence analysis. It has got three components in three axis. They are defined as following.

$$\begin{cases} x\ axis = (\sum A + \sum G) - (\sum C + \sum T) \\ y\ axis = (\sum A + \sum C) - (\sum G + \sum T) \\ z\ axis = (\sum A + \sum T) - (\sum G + \sum C) \end{cases}$$

Three features will generate using the zCurve method.

15. Monokgap theoretical description (MonoKGap)

When -kgap=n then the $(4)\times(4)\times n$ features will exist for DNA and RNA but $(20)\times(20)\times n$ features will exist for protein. When -kgap=1, feature structure will be X_X.

When -kgap=2, feature structure will be X_X, and X__X. When -kgap=3, feature structure will be X_X. X__X, and X___X. Described with appropriate examples: When -kgap=1 then only sixteen features will exist for DNA and RNA but four hundred (400) features will exist for protein. Features will be numbers of A_A, A_C, A_G, A_T, C_A, C_C, C_G, C_T, G_A, G_C, G_G, G_T, T_A, T_C, T_G, and T_T of the whole sequence of DNA respectively. When -kgap=2 then only thirty-two features will exist for DNA and RNA but eight hundred (800) features will exist for protein. Features will be numbers of A_A, A_C, A_G, A_T, C_A,C_C, C_G, C_T, G_A, G_C, G_G, G_T, T_A, T_C, T_G,T_T, A__A, A__C, A__G, A__T, C__A, C__C, C__G, C__T, G__A, G__C, G__G, G__T, T__A, T__C, T__G, and T__T of the whole sequence of DNA respectively.

When -kgap=3 then only forty-eight features will exist for DNA and RNA, but one thousand and two hundred (1,200) features will exist for protein. Features will be numbers of A_A, A_C, A_G, A_T, C_A,C_C, C_G, C_T, G_A, G_C, G_G, G_T, T_A, T_C, T_G,T_T, A__A, A__C, A__G,A__T, C__A, C__C, C__G, C__T, G__A, G__C, G__G, G__T, T__A, T__C, T__G, T__T, A___A, A___C, A___G, A___T, C___A, C___C, C___G, C___T, G___A, G___C, G___G,G___T, T___A, T___C, T___G, and T___T of the whole sequence of DNA respectively.

16. MonoDiKGap Theoretical Description (MonoDiKGap)

When kgap=n then the $(4)\times(4\times 4)\times n$ features will exist for DNA and RNA, but $(20)\times(20\times 20)\times n$ features will exist for protein.

When -kgap=1, feature structure will be X_XX.

When -kgap=2, feature structure will be X_XX, and X__XX.

When -kgap=3, feature structure will be X_XX, X__XX, and X___XX. Described with appropriate examples:

When -kgap=1 then only sixty-four (64) features will exist for DNA and RNA, but eight thousand (8,000) features will exist for protein. Features will be numbers of A_AA, A_AC,A_AG, A_AT, A_CA, A_CC, A_CG, A_CT, A_GA, A_GC, A_GG, A_GT, A_TA, A_TC, A_TG,A_TT, C_AA, C_AC, C_AG, C_AT, C_CA, C_CC, C_CG, C_CT, C_GA, C_GC, C_GG, C_GT,C_TA, C_TC, C_TG, C_TT, G_AA, G_AC, G_AG, G_AT, G_CA, G_CC, G_CG, G_CT, G_GA,G_GC, G_GG, G_GT, G_TA, G_TC, G_TG, G_TT, T_AA, T_AC, T_AG, T_AT, T_CA, T_CC,T_CG, T_CT, T_GA, T_GC, T_GG, T_GT, T_TA, T_TC, T_TG, and T_TT of the whole sequence of DNA respectively.

When -kgap=2 then only hundred and twenty-eight (128) features will exist for DNA and RNA, but sixteen thousand (16,000) features will exist for protein. Features will be numbers of A_AA, A_AC,A_AG, A_AT, A_CA, A_CC, A_CG, A_CT, A_GA, A_GC, A_GG, A_GT, A_TA, A_TC, A_TG,A_TT, C_AA, C_AC, C_AG, C_AT, C_CA, C_CC, C_CG, C_CT, C_GA, C_GC, C_GG, C_GT,C_TA, C_TC, C_TG, C_TT, G_AA, G_AC, G_AG, G_AT, G_CA, G_CC, G_CG, G_CT, G_GA,G_GC, G_GG, G_GT, G_TA, G_TC, G_TG, G_TT, T_AA, T_AC, T_AG, T_AT, T_CA, T_CC,T_CG, T_CT, T_GA, T_GC, T_GG, T_GT, T_TA, T_TC, T_TG,T_TT, A__AA, A__AC, A__AG, A__AT, A__CA, A__CC, A__CG, A__CT, A__GA, A__GC,A__GG, A__GT, A__TA, A__TC, A__TG, A__TT, C__AA, C__AC, C__AG, C__AT, C__CA,C__CC, C__CG, C__CT, C__GA, C__GC, C__GG, C__GT, C__TA, C__TC, C__TG, C__TT,G__AA, G__AC, G__AG, G__AT, G__CA, G__CC, G__CG, G__CT, G__GA, G__GC, G__GG,G__GT, G__TA, G__TC, G__TG, G__TT, T__AA, T__AC, T__AG, T__AT, T__CA, T__CC,T__CG, T__CT, T__GA, T__GC, T__GG, T__GT, T__TA, T__TC, T__TG, and T__TT of the whole sequence of DNA respectively.

RNA feature extraction method

SeqFea-Learn contains 15 RNA feature extraction methods.

Feature Extraction Method	Method Number
Kmer	1
Reverse compliment Kmer (RCKmer)	2
Nucleic acid composition (NAC)	3
Di-nucleotide composition (DNC)	4
Tri-Nucleotide Composition (TNC)	5
Binary encoding (BE)	6
zCurve Mathematical Formula (zCurve)	7
Dinucleotide based auto covariance (DAC)	8
Dinucleotide based cross covariance (DCC)	9
Di-nucleotide based auto-cross covariance (DACC)	10
Position-specific dinucleotide propensity (PSDNP)	11
Position-specific trinucleotide propensity (PSTNP)	12
MonoKGap theoretical description (MonoKGap)	13
MonoDiKGap theoretical description (MonodiKGap)	14
Pseudo di-nucleotide composition (PseDNC)	15

1. Kmer

For kmer descriptor [1, 2], the RNA sequences are represented as the occurrence frequencies of k neighboring nucleic acids. The Kmer (k=3) descriptor can be calculated as:

$$f(t) = \frac{N(t)}{N}, \quad t \in \{AAA, AAC, AAG, \ldots, TTT\}$$

where $N(t)$ is the number of kmer type t, while N is the length of a nucleotide sequence.

2. Reverse compliment kmer (RCKmer)

The reverse compliment kmer [1, 3] is a variant of kmer descriptor, in which the kmers are not

expected to be strand-specific. For instance, for a DNA sequence, there are 16 types of 2-

mers (i.e. 'AA', 'AC', 'AG', 'AT', 'CA', 'CC', 'CG', 'CT', 'GA', 'GC', 'GG', 'GT', 'TA', 'TC', 'TG', 'TT'), ‘TT’ is reverse compliment with ‘AA’. After removing the reverse compliment kmers, there are only 10 distinct kmers in the reverse compliment kmer approach ('AA', 'AC', 'AG', 'AT', 'CA', 'CC', 'CG', 'GA', 'GC', 'TA').

3. Pseudo dinucleotide composition (PseDNC)

PseDNC [4] is an approach incorporating the contiguous local sequence-order information and the global sequence-order information into the feature vector of the RNA sequence. Given a RNA sequence D, the PseDNC feature vector of D is defined:

$$D=[d_1,d_2,d_3,\cdots,d_{16},d_{16+1},\cdots,d_{16+\lambda}]$$

$$d_k=\begin{cases}\dfrac{f_k}{\sum_{i=1}^{16}f_i+\omega\sum_{j=1}^{\lambda}\theta_j} & (1\le k\le 16)\\[2ex] \dfrac{\omega\theta_{k-16}}{\sum_{i=1}^{16}f_i+\omega\sum_{j=1}^{\lambda}\theta_j} & (17\le k\le 16+\lambda)\end{cases}$$

where f_k is the normalized occurrence frequency of dinucleotides in the RNA sequence, the parameter λ is an integer, representing the highest counted rank (or tier) of the correlation along a RNA sequence, w is the weight factor ranged from 0 to 1, θ_j is called the correlation factor that reflects the sequence-order correlation between all the most contiguous dinucleotides along a RNA sequence, which is defined:

$$\begin{cases}\theta_1=\dfrac{1}{L-2}\sum_{i=1}^{L-2}\Theta(R_iR_{i+1},R_{i+1}R_{i+2})\\ \theta_2=\dfrac{1}{L-2}\sum_{i=1}^{L-2}\Theta(R_iR_{i+1},R_{i+2}R_{i+3})\\ \theta_3=\dfrac{1}{L-2}\sum_{i=1}^{L-2}\Theta(R_iR_{i+1},R_{i+3}R_{i+4})\\ \qquad\cdots\cdots\\ \qquad\cdots\cdots\cdot\\ \theta_\lambda=\dfrac{1}{L-1-\lambda}\sum_{i=1}^{L-1-\lambda}\Theta(R_iR_{i+1},R_{i+\lambda}R_{i+\lambda+1})\end{cases}$$

where the correlation function is given by

$$\Theta(R_iR_{i+1},R_jR_{j+1})=\frac{1}{\mu}\sum_{u=1}^{\mu}[P_u(R_iR_{i+1})-P_u(R_jR_{j+1})]^2$$

where μ is the number of physicochemical indices, in this approach, 6 indices reflecting the local RNA structural properties are employed to generate the PseDNC feature vector,

$P_u(R_iR_{i+1}), P_u(R_jR_{j+1})$ represents the numerical value of the u-th physicochemical index of the dinucleotide R_iR_{i+1}, R_jR_{j+1}.

4. Dinucleotide-based auto covariance (DAC)

The DAC [5, 6] measures the correlation of the same physicochemical index between two dinucleotides separated by a distance of lag along the sequence, which can be calculated as:

$$DAC(u,l) = \sum_{i=1}^{L-l-1} (P_u(R_iR_{i+1}) - \bar{P}_u)(P_u(R_{i+l} + R_{i+l+1}) - \bar{P}_u) / (L-l-1)$$

where u is a physicochemical index, L is the length of the RNA sequence $P_u(R_iR_{i+1})$ means the numerical value of the physicochemical index u for the dinucleotide R_iR_{i+1} at position i, $\bar{P}_u$ is the average value for physicochemical index u along the whole sequence:

In such a way, the length of DAC feature vector is $N \times lag$, where N is the number of physicochemical indices, and lag is the maximum of sequence.

5. Dinucleotide-based cross covariance (DCC)

Given a RNA sequence, the DCC approach [5, 6] measures the correlation of two different physicochemical indices between two dinucleotides separated by lag nucleic acids along the sequence, which can be calculated by:

$$\mathrm{DCC}(u_1, u_2, l) = \sum_{i=1}^{L-l-1} \left(P_{u_1}(R_iR_{i+1}) - \bar{P}_{u_1}\right)\left(P_{u_2}(R_{i+l}R_{i+l+1}) - \bar{P}_{u_2}\right) / (L-l-1)$$

Where u_1, u_2 are two different physicochemical indices, L is the length of the RNA sequence, $P_{u_1}(R_iR_{i+1}), P_{u_2}(R_iR_{i+1})$ is the numerical value of the physicochemical index u_1, u_2 for the dinucleotide R_iR_{i+1}. $\bar{P}_{u_1}$ is the average value for physicochemical index value u_1 along the whole sequence:

$$\overline{P_u} = \sum_{j=1}^{L-1} P_u\left(\mathrm{R}_j\mathrm{R}_{j+1}\right) / (L-1)$$

In such a way, the length of the DCC feature vector is $N \times (N-1) \times lag$, lag is the maximum of sequence; N is the number of physicochemical indices.

6. Dinucleotide-based auto-cross covariance (DACC)

DACC is a combination of DAC and DCC [5, 6]. Therefore, the length of the DACC feature vector is $N \times N \times lag$, where N is the number of physicochemical indices and lag is the maximum of sequence.

7. Nucleic acid composition (NAC)

The Nucleic acid composition (NAC) [7] encoding calculates the frequency of each nucleic acid type in a nucleotide sequence. The frequencies of all 4 natural nucleic acids (i.e. “ACGT or U”) can be calculated as:

$$f(t) = \frac{N(t)}{N},\ t \in \{A, C, G, T(U)\}$$

where $N(t)$ is the number of nucleic acid type t, while N is the length of a nucleotide sequence.

8. Di-nucleotide composition (DNC)

The Di-Nucleotide Composition [7] gives 16 descriptors. It is defined as:

$$D(r,s) = \frac{N_{rs}}{N-1},\ r,s \in \{A, C, G, T(U)\}$$

where N_{rs} is the number of di-nucleotide represented by nucleic acid types r and s.

9. Tri-nucleotide composition (TNC)

The Tri-Nucleotide Composition [7] gives 64 descriptors. It is defined as:

$$D(r,s,t) = \frac{N_{rst}}{N-2},\ r,s,t \in \{A, C, G, T(U)\}$$

where N_{rst} is the number of tri-nucleotide represented by nucleic acid types r, s and t.

10. zCurve mathematical formula (zCurve)

Z-curve theory [8] is often used in genomic sequence analysis. It has got three components in three axis. They are de_ned as following.

$$\begin{cases} x\ axis = (\sum A + \sum G) - (\sum C + \sum T) \\ y\ axis = (\sum A + \sum C) - (\sum G + \sum T) \\ z\ axis = (\sum A + \sum T) - (\sum G + \sum C) \end{cases}$$

Three features will generate using the zCurve method.

11. MonoKGap Theoretical Description (MonoKGap)

When kgap=n then the $(4)\times(4)\times n$ features will exist for RNA [8].

When -kgap=1, feature structure will be X_X.

When -kgap=2, feature structure will be X_X, and X__X.

When -kgap=3, feature structure will be X_X. X__X, and X___X.

Described with appropriate examples:

When -kgap=1 then only sixteen (16) features will exist for DNA and RNA but four hundred (400) features will exist for protein. Features will be numbers of A_A, A_C, A_G, A_T, C_A,C_C, C_G, C_T, G_A, G_C, G_G, G_T, T_A, T_C, T_G, and T_T of the whole sequence of DNA respectively.

When -kgap=2 then only thirty two (32) features will exist for DNA and RNA but eight hundred (800) features will exist for protein. Features will be numbers of A_A, A_C, A_G, A_T, C_A,C_C, C_G, C_T, G_A, G_C, G_G, G_T, T_A, T_C, T_G,T_T, A__A, A__C, A__G,A__T, C__A, C__C, C__G, C__T, G__A, G__C, G__G, G__T, T__A, T__C, T__G, and T__T of the whole sequence of DNA respectively.

When -kgap=3 then only forty eight (48) features will exist for DNA and RNA, but one thousand and two hundred (1,200) features will exist for protein. Features will be numbers of A_A, A_C, A_G, A_T, C_A,C_C, C_G, C_T, G_A, G_C, G_G, G_T, T_A, T_C, T_G,T_T, A__A, A__C, A__G,A__T, C__A, C__C, C__G, C__T, G__A, G__C, G__G, G__T, T__A, T__C, T__G, T__T, A___A, A___C, A___G, A___T, C___A, C___C, C___G, C___T, G___A, G___C, G___G,G___T, T___A, T___C, T___G, and T___T of the whole sequence of DNA respectively.

12. MonoDiKGap Theoretical Description (MonoDiKGap)

When -kgap=n then the $(4)\times(4\times4)\times n$ features will exist for RNA [8].

When -kgap=1, feature structure will be X_XX.

When -kgap=2, feature structure will be X_XX, and X__XX.

When -kgap=3, feature structure will be X_XX, X__XX, and X___XX.

Described with appropriate examples:

When -kgap=1 then only sixty four (64) features will exist for DNA and RNA, but eight thousand (8,000) features will exist for protein. Features will be numbers of A_AA, A_AC,A_AG, A_AT, A_CA, A_CC, A_CG, A_CT, A_GA, A_GC, A_GG, A_GT, A_TA, A_TC, A_TG,A_TT, C_AA, C_AC, C_AG, C_AT, C_CA, C_CC, C_CG, C_CT, C_GA, C_GC, C_GG, C_GT,C_TA, C_TC, C_TG, C_TT, G_AA, G_AC, G_AG, G_AT, G_CA, G_CC, G_CG, G_CT, G_GA,G_GC, G_GG, G_GT, G_TA, G_TC, G_TG, G_TT, T_AA, T_AC, T_AG, T_AT, T_CA, T_CC,T_CG, T_CT, T_GA, T_GC, T_GG, T_GT, T_TA, T_TC, T_TG, and T_TT of the whole sequence of DNA respectively.

When -kgap=2 then only hundred and twenty eight (128) features will exist for DNA and

RNA, but sixteen thousand (16,000) features will exist for protein. Features will be numbers of A_AA, A_AC,A_AG, A_AT, A_CA, A_CC, A_CG, A_CT, A_GA, A_GC, A_GG, A_GT, A_TA, A_TC, A_TG,A_TT, C_AA, C_AC, C_AG, C_AT, C_CA, C_CC, C_CG, C_CT, C_GA, C_GC, C_GG, C_GT,C_TA, C_TC, C_TG, C_TT, G_AA, G_AC, G_AG, G_AT, G_CA, G_CC, G_CG, G_CT, G_GA,G_GC, G_GG, G_GT, G_TA, G_TC, G_TG, G_TT, T_AA, T_AC, T_AG, T_AT, T_CA, T_CC,T_CG, T_CT, T_GA, T_GC, T_GG, T_GT, T_TA, T_TC, T_TG,T_TT, A__AA, A__AC, A__AG, A__AT, A__CA, A__CC, A__CG, A__CT, A__GA, A__GC,A__GG, A__GT, A__TA, A__TC, A__TG, A__TT, C__AA, C__AC, C__AG, C__AT, C__CA,C__CC, C__CG, C__CT, C__GA, C__GC, C__GG, C__GT, C__TA, C__TC, C__TG, C__TT,G__AA, G__AC, G__AG, G__AT, G__CA, G__CC, G__CG, G__CT, G__GA, G__GC, G__GG,G__GT, G__TA, G__TC, G__TG, G__TT, T__AA, T__AC, T__AG, T__AT, T__CA, T__CC,T__CG, T__CT, T__GA, T__GC, T__GG, T__GT, T__TA, T__TC, T__TG, and T__TT of the whole sequence of DNA respectively.

Protein feature extraction method

SeqFea-Learn contains 31 Protein feature extraction methods.

Protein feature extraction methods	Method Number
Amino acid composition (AAC)	1
Dipeptide composition (DC)	2
Composition of k-spaced amino acid pairs (CKSAAP)	3
Grouped dipeptide composition (GDC)	4
Grouped tripeptide composition (GTC)	5
Conjoint triad (CT)	6
K-spaced conjoint triad (KSCTriad)	7
Composition (C)	8
Transition (T)	9
Distribution (D)	10
Encoding based on grouped weight (EBGW)	11
Auto covariance (AC)	12
Moreau-Broto autocorrelation (Morean-Broto)	13
Moran autocorrelation (Moran)	14
Geary autocorrelation (Geary)	15
Quasi-sequence-order (QSO)	16
Pseudo-amino acid composition (PseAAC)	17
Amphiphilic pseudo-amino acid composition (APAAC)	18
Amino acid composition PSSM (AAC-PSSM)	19
Dipeptide composition PSSM (DPC-PSSM)	20
Bi-gram PSSM (Bi-PSSM)	21
Auto covariance PSSM (AC-PSSM)	22
Pseudo PSSM (PsePSSM)	23
AB-PSSM	24
Secondary structure composition (SSC)	25
Accessible surface area composition (ASA)	26
Torsional angles composition (TAC)	27

Torsional angles bigram (TA-bigram)	28
Structural probabilities bigram (SP-bigram)	29
Torsional angles auto-covariance (TAAC)	30
Structural probabilities auto-covariance (SPAC)	31

Type 1: Amino acid composition information-based methods

1. Amino acid composition (AAC)

The amino acid composition is the fraction of each amino acid type within a protein. The amino acid composition gives 20 features and the fractions of all 20 natural amino acids are calculated as

$$f(r) = \frac{N_r}{N}, \quad r = 1, 2, 3, \ldots, 20$$

where N_r is the number of the amino acid type r and N is the length of the sequence.

2. Dipeptide composition (DC)

The dipeptide composition is used to transform the variable length of proteins to fixed length feature vectors.A dipeptide composition has been used earlier by Grassmann et al. and Reczko and Bohr for the development of fold recognition methods.We adopt the same dipeptide composition-based approach in developing a deep neural networks-based method for predicting protein-protein inter-action.The dipeptide composition gives a fixed pattern length of 400.Dipeptide composition encapsulates information about the fraction of amino acids as well as their local order.The dipeptide composition is defined as

$$fr(r,s) = \frac{N_{(r,s)}}{N}, \quad r, s = 1, 2, 3, \ldots, 20$$

where N the number of dipeptide represented by amino acid type r and s.

3. g -gap dipeptide composition introduces (g-GapDC)

The g-gap dipeptide composition introduces (g-Gap DC) extracts important intrinsic correlation information of protein sequences in multidimensional space. For a protein P, L of the sequence length C, the calculation process of the g-Gap DC can be expressed as

$$f_{\varepsilon}^{g} = \frac{n_{\varepsilon}^{g}}{\sum_{\varepsilon=1}^{400} n_{\varepsilon}^{g}} = \frac{n_{\varepsilon}^{g}}{L-g-1}$$

$$\mathrm{P} = \{ f_1^g, f_2^g, \cdots, f_{\varepsilon}^g, \cdots, f_{400}^g \}^{\mathrm{T}}$$

where g represents the number of residues in the primary structure of the two amino acids, n_{ε}^{g} represents the number of occurrences of the $\varepsilon(\varepsilon = 1, 2, \cdots, 400)$-th feature in the g-gap dipeptide, and f_{ε}^{g} represents the frequency at which the ε-th feature in the g-gap dipeptide appears in the sequences. When $g = 0$, there is no gap between two adjacent amino acid residues, and when $g = 1$, it means that one amino acid residue is between two adjacent amino acid residues. From equation (9), a protein sequence can be represented as a 400-dimensional feature vector.

4. Grouped di-peptide composition (GDC)

The Grouped di-peptide composition encoding is another variation of the DPC descriptor. It is composed of a total of 25 descriptors that are defined as:

$$f(r,s) = \frac{N_{rs}}{N-1}, \quad r,s \in \{g1, g2, g3, g4, g5\}$$

where N_{rs} is the number of the di-peptide type r,s, and N is the length of the sequence.

5. Grouped tri-peptide composition (GTC)

The Grouped tri-peptide composition encoding is also a variation of TPC descriptor, which generates 125 descriptors, defined as:

$$f(r,s,t) = \frac{N_{rst}}{N-2}, \quad r,s,t \in \{g1, g2, g3, g4, g5\}$$

where N_{rst} is the number of the tri-peptide type r,s,t, and N is the length of the sequence.

6. Conjoint triad (CT)

First, 20 amino acids are clustered into seven classes based on dipoles and volumes of side chains. Considering the interaction between the amino acid and its vicinal amino acids, the three continuous amino acids are regarded as a unit, so that we can obtain $7\times7\times7=343$ triad types. We calculate the frequency of occurrence of each triad called $f_i\ (i=1,2,\cdots,343)$. Then the 343-dimensional feature vector is obtained according to equation (6).

$$d_i=\frac{f_i-\min\{f_1,f_2,\cdots,f_{343}\}}{\max\{f_1,f_2,\cdots,f_{343}\}},\ i=1,2,\cdots,343$$

7. *k*-Spaced Conjoint Triad (KSCTriad)

The *k*-spaced conjoint triad descriptor is based on the conjoint ctriad descriptor,

which not only calculates the numbers of three continuous amino acid units, but also considers the continuous amino acid units that are separated by any *k* residues (The default maximum value of *k* is set to 5). For example, AxRxT is a 1-spaced triad. Thus, the dimensionality of the KSCTriad encoded feature vector is 343 (*k*+1).

8. Composition, transition and distribution (CTD)

8.1 Composition

For CTD, taking hydrophobicity as an example, all amino acids are classified into three categories: polar, neutral, and hydrophobic. The replacement sequence consists of three types, and the composition descriptors of the polar, neutral, and hydrophobic residues of the protein can be calculated as follows:

$$C(r)=\frac{N(r)}{N},\ r\in\{polar,neutral,hydropholic\}$$

where $N(r)$ is the number of amino acid type r in the coding sequence and N is sequence length.

8.2 Transition

The transition descriptor first converts the original sequence into a replacement sequence, and T includes three characteristics, the dipeptide composition frequency from the polar group to the neutral group and the composition frequency from the neutral group to the polar group. Transitions between the neutral group and the hydrophobicity and these between hydrophobic group and the polar group are defined in the same way. The T descriptor is defined as follows:

$$T(r,s) = \frac{N(r,s) + N(s,r)}{N-1},\ r,s \in \{(polar, neutral), (neutral, hydrophobic), (hydrophobic, polar)\}$$

Where $N(r,s)$ and $N(s,r)$ are the rs and sr dipeptide frequency, respectively. N is the sequence length.

8.3 Distribution

For each group (polar, neutral and hydrophobic), the D descriptor can generate five values. We obtain the position of the first, 25%, 50%, 75% and 100% of the specific encoded group sequence and then divided the position by the whole sequence. Given sequence MTTTVPKVFAFHEF. It can be represented as '32223213323213' according to Hydrophobicity_PRAM900101. '1' represents polar, '2' represents neutral, '3' represents hydrophobicity. Take '3' for example, there are 6 residues encoded '3'. The first '3' is 1. The second '3' is $25\% \times 6 = 1$. The third '3' is $50\% \times 6 = 3$. The fourth '3' is $75\% \times 6 = 4$. The fifth '3 is $100\% \times 6 = 6$. The position in the first, the second, the third, the fourth, the fifth '3' of whole sequence are 1, 1, 8, 9, 14, respectively. So the distribution descriptor for '3' are $(1/14)$, $(1/14)$, $(8/14)$, $(9/14)$, $(14/14)$.

The C descriptor generates a 39-dimensional feature vector, the T descriptor generates a 39-dimensional feature vector, and the D descriptor generates a 195-dimensional feature vector. For each protein sequence, the CTD generates a 273-dimensional feature vector.

9. Encoding based on grouped weight coding (EBGW)

Studies have shown that different amino acids have different physical and chemical properties. The EBGW can capture the sequence and physicochemical information based on grouped situation. These amino acids are classified into four categories:

neutral and hydrophobic amino acids $C1 = \{G, A, V, L, I, M, P, F, W\}$

neutral and polarity amino acids $C2 = \{Q, N, S, T, Y, C\}$

acidic amino acids $C3=\{D,E\}$

basic amino acids $C4=\{H,K,R\}$.

Thus, we can get three combinations, each of which can partition the 20 amino acid residues into two disjoint group: $\{C1,C2\}$ vs $\{C3,C4\}$, or $\{C1,C3\}$ vs $\{C2,C4\}$, and $\{C1,C4\}$ vs $\{C2,C3\}$. Let $P: R_1R_2\cdots R_L$ be a protein sequence, we can transform it into three binary sequences by three homomorphic maps $\Phi_i(P)=\Phi_i(R_1),\Phi_i(R_2),...,\Phi_i(R_L)(i=1,2,3)$ which are defined as follows:

$$\Phi_1(R_j)=\begin{cases}1 & if\ \ R_j\in C1+C2\\ 0 & if\ \ R_j\in C3+C4\end{cases}\quad (j=1,2,...,L)$$

$$\Phi_2(R_j)=\begin{cases}1 & if\ \ R_j\in C1+C3\\ 0 & if\ \ R_j\in C2+C4\end{cases}\quad (j=1,2,...,L)$$

$$\Phi_3(R_j)=\begin{cases}1 & if\ \ R_j\in C1+C4\\ 0 & if\ \ R_j\in C2+C3\end{cases}\quad (j=1,2,...,L)$$

where $H_i(P)=\Phi_i(P)=h_1^i,h_2^i,...,h_L^i(i=1,2,3)$, and we call $H_i(P)(i=1,2,3)$ as characteristic sequence of the protein sequence.

Then $H_1(P)$, $H_2(P)$, $H_3(P)$ are three binary sequences of length *L*. These sequences are divided into a number of sub-sequences of increasing length successively. A fixed parameter *N* is set and the sub-sequence can be expressed as $\lfloor \underline{\lfloor kL/N} \rfloor (k=1,2,..,N)$, where $\lfloor . \rfloor$ represents the integer operator. Calculate the frequency of 1 in each sub-sequence, each $H_i(P)$ can be converted into an *N*-dimensional feature vector. To sum up, for a protein sequence *P* with length *L*, a 3*N*-dimension vector can be obtained.

Type 2: Physicochemical information-based methods

10. Auto covariance (AC)

Suppose a protein sequence P with *L* amino acid residues; i.e.

$$P=R_1R_2R_3R_4\cdots R_L$$

where R_1 represents the amino acid residue at the sequence position 1, R_2 the amino acid residue at position 2 and so forth.

The AC approach measures the correlation of the same property between two residues separated by a distance of l along the sequence, which can be calculated as:

$$AC(i,l) = \sum_{i=1}^{L-l} (P_u(R_i) - \bar{P}_u)(P_u(R_{i+l}) - \bar{P}_u) / (L-l)$$

where u is a physicochemical index, L is the length of the protein sequence, means the numerical value of the physicochemical index u for the amino acid R_i at position i, $\bar{P}_u$ is the average value for physicochemical index u along the whole sequence. In such a way, the length of AC feature vector is $N \times lag$, where N is the number of physicochemical indices extracted from AAindex; lag is the maximum of sequence.

11. Moreau-Broto autocorrelation (Morean-Broto)

Moreau-Broto autocorrelation descriptor is defined as:

$$NMBA(l) = \frac{NBA(l)}{N-l}, \; l = 1, 2, \cdots, lag$$

where $MBA(l) = \sum_{i=1}^{N-l} P(AA_i) P(AA_{i+l})$, AA_i and AA_{i+l} indicate the i-th and the $i+l$-th amino acids of the protein sequence, respectively. $P(AA_i)$ and $P(AA_{i+l})$ indicate the normalized physicochemical values of AA_i and AA_{i+l}. The lag is the parameter that needs to be adjusted.

12. Moran autocorrelation (Moran)

Moran autocorrelation descriptor is defined as:

$$MA(l) = \frac{\frac{1}{N-l} \sum_{i=1}^{N-l} (P(AA_i) - \tilde{P})(P(AA_{i+l}) - \tilde{P})}{\frac{1}{N} \sum_{i=1}^{N} (P(AA_i) - \tilde{P})^2}, \; l = 1, 2, \cdots, lag$$

where $\bar{P}$ represents the mean value of whole protein sequence for specific physicochemical property.

13. Geary autocorrelation (Geary)

Geary autocorrelation descriptor is defined as:

$$GA(l) = \frac{\frac{1}{2(N-l)}\sum_{i=1}^{N-l}(P(AA_i) - P(AA_{i+l}))^2}{\frac{1}{N}\sum_{i=1}^{N}(P(AA_i) - \bar{P})^2}, l = 1, 2, \cdots, lag$$

14. Quasi-sequence-order descriptors (QSO)

The sequence order features can also be used for representing amino acid distribution patterns of a specific physicochemical property along protein or peptide sequence. These descriptors are derived from both the Schneider-Wrede physicochemical distance matrix and the Grantham chemical distance matrix between each pair of the 20 amino acids. The d-th rank sequence-order-coupling number is defined as

$$\tau_d = \sum_{i=1}^{N-d}\left(d_{i,i+d}\right)^2, \quad d = 1, 2, 3, \ldots, \max lag$$

where $d_{i,i+d}$ is the distance between the two amino acids at position i and $i+d$. Maxlag is the maximum lag and the length of the protein must be not less than maxlag. The maxlag is equal to 30 in the experiment. For each amino acid type, the type-1 quasi-sequence-order descriptor can be defined as

$$X_r = \frac{f_r}{\left(\sum_{r=1}^{20} f_r + w\sum_{d=1}^{\max lag}\tau_d\right)}, r = 1, 2, 3, \ldots, 20$$

where is the normalized occurrence of amino acid type-1 and is a weighting factor $(w = 0.1)$. The type-2 quasi-sequence-order is defined as

$$X_r = \frac{w\tau_{d-20}}{\left(\sum_{r=1}^{20} f_r + w\sum_{d=1}^{\max lag}\tau_d\right)}, r = 21, 22, 23, \ldots, 20 + \max lag$$

In addition to the Schneider-Wrede physicochemical distance matrix used by Chou et al., another chemical distance matrix by Grantham is also used here. The sequence-order features produce a total of $(30+50)\times 2=160$ descriptors.

15. Pseudo-amino acid composition (PseAAC)

Pseudo-amino acid composition are utilized to extract the physicochemical information. Pseudo-amino acid composition (PseAAC) represents the composition information of the protein and sequence order information. The feature vector of PseAAC can be represented:

$$X = [x_1, x_2, \cdots, x_{19}, x_{20}, x_{20+1}, x_{20+\lambda}]^T \ (\lambda < L)$$

where the first 20-dimentional feature vector represents the amino acid composition information, and the latter λ dimensional vector represents the order information of protein sequence. L is the length of amino acid sequence.

$$x_u = \begin{cases} \dfrac{f_u}{\sum_{i=1}^{20} f_i + \omega \sum_{j=1}^{\lambda} \theta_j}, (1 \le u \le 20) \\ \dfrac{\omega \theta_{u-20}}{\sum_{i=1}^{20} f_i + \omega \sum_{j=1}^{\lambda} \theta_j}, (20+1 \le u \le 20+\lambda) \end{cases}$$

where f_i is the normalized frequency of 20 amino acids in protein. θ_j is the layer sequence correlation factor calculated according to the equation (2). Sequence correlation factor can be obtained from the hydrophobicity, hydrophilicity, and side-chain mass of the amino acid.

16. Amphiphilic pseudo amino acid composition (APAAC)

APAAC (http://www. csbio. sjtu. edu. cn/bioinf/PseAAC/type2. htm) are also called type-2 pseudoamino acid composition. The definitions of these qualities are similar to PAAC descriptors. First, two variables are derived from the original hydrophobicity values $H_1^0(i)$ and hydrophilicity value $H_2^0(i)$ of 20 amino acids $(i = 1, 2, \ldots, 20)$:

$$H_1(i) = \frac{H_1^0(i) - \sum_{i=1}^{20} \frac{H_1^0(i)}{20}}{\sqrt{\frac{\sum_{i=1}^{20} \left[H_1^0(i) - \sum_{i=1}^{20} \frac{H_1^0(i)}{20} \right]^2}{20}}}$$

$$H_1(i) = \frac{H_2^0(i) - \sum_{i=1}^{20} \frac{H_2^0(i)}{20}}{\sqrt{\frac{\sum_{i=1}^{20} \left[H_2^0(i) - \sum_{i=1}^{20} \frac{H_2^0(i)}{20} \right]^2}{20}}}$$

where $H_1(i)$ and $H_2(i)$,the hydrophobicity and hydrophilicity correlation functions, are defined respectively as

$$H^1_{i,j} = H_1(i)H_1(j), \quad H^2_{i,j} = H_2(i)H_2(j)$$

where sequence order factors can be defined as

$$\tau_1 = \frac{1}{N-1}\sum_{i=1}^{N-1} H^1_{i,i+1}, \quad \tau_2 = \frac{1}{N-1}\sum_{i=1}^{N-2} H^2_{i,i+1}$$

$$\tau_3 = \frac{1}{N-2}\sum_{i=1}^{N-2} H^1_{i,i+2}, \qquad \tau_4 = \frac{1}{N-2}\sum_{i=1}^{N-2} H^2_{i,i+2}$$

$$\tau_{2\lambda-1} = \frac{1}{N-\lambda}\sum_{i=1}^{N-\lambda} H^1_{i,i+\lambda}, \quad \tau_{2\lambda} = \frac{1}{N-\lambda}\sum_{i=1}^{N-\lambda} H^2_{i,i+\lambda} (\lambda < N)$$

Then a set of descriptors called "Amphiphilic Pseudo Amino Acid Composition" are defined as

$$p^u = \frac{f_u}{\sum_{i=1}^{20} f_i + w\sum_{j=1}^{2\lambda}\tau_j} (1 < u < 20)$$

$$p^u = \frac{w\tau_u}{\sum_{i=1}^{20} f_i + w\sum_{j=1}^{2\lambda}\tau_j} (20+1 < u < 20+2\lambda)$$

where w is the weight factor and is taken as $w=0.5$, and λ is equal to 30 in the experiment. So, we produce a total of $20+2\times 30=80$ descriptors.

Type 3: Evolutionary information-based method

In order to obtain the evolutionary information of the amino acid sequence, all the protein sequences in the dataset are compared with the non-redundant database SwissProt using the PSI-BLAST program. The program can search sequences based on the iterative BLAST search method. Evolutionary information in the position specific scoring matrix (PSSM) plays an important role in biological system analysis.

During the running process, the parameter E-value threshold of PSI-BLAST is set to 0.001, the maximum number of iterations is set to 3, and the remaining parameters are set by default. Then PSSM of each protein sequence is obtained. For a protein sequence whose length is L, PSSM is shown in equation (49).

$$P_{PSSM} = \begin{bmatrix} p_{1,1} & p_{1,2} & \cdots & p_{1,20} \\ \vdots & \vdots & \vdots & \vdots \\ p_{i,1} & p_{i,2} & \cdots & p_{i,20} \\ \vdots & \vdots & \vdots & \vdots \\ p_{L,1} & p_{L,2} & \cdots & p_{L,20} \end{bmatrix}$$

where each row of the PSSM represents a log likelihood score for amino acid substitutions occurring at corresponding positions in the query sequence. Where $P_{i,j}$ represents the i-th position of query sequence being mutated to type j during evolution process. The scores are positive integers or negative integers. A positive integer indicates that more mutations have occurred in the alignment and a negative integer indicates that fewer substitutions have occurred in the alignment.

17. Amino acid composition PSSM (AAC-PSSM)

In this calculating process of amino acid composition PSSM (AAC-PSSM), the PSSM is standardized by the logic function. PSSM elements are map to the interval [0,1].

$$f(x) = \frac{1}{1+e^{-x}}$$

PSSM are converted to feature vector by AAC-PSSM via equation (51)

$$P_{AAC} = (p_1, p_2, \cdots, p_j, \cdots p_{20})^T \quad (j = 1, 2, \cdots, 20)$$

where $P_j = \frac{1}{L}\sum_{i=1}^{L} p_{ij} \quad (j = 1, 2, \cdots 20)$, p_j represents the composition information of the j amino acid residue, which is the average score of j-th amino acid in PSSM.

18. Dipeptide composition PSSM (DPC-PSSM)

The PSSM contains evolutionary information. ACC-PSSM only represents the composition information from PSSM, and loses the order information, which is insufficient to fully represent the evolutionary information. Dipeptide composition PSSM

(DPC-PSSM) can reflect the sequence-order information in the PSSM, which converts the character signal into the numerical signal, and the extracted feature vector can be expressed as

$$P_{DPC} = (D_{1,1}, D_{1,2}, \cdots, D_{1,20}, D_{2,1}, D_{2,2}, \cdots, D_{2,20}, \cdots, D_{20,20})$$

where $D_{i,j} = \frac{1}{L-1}\sum_{k=1}^{L-1} p_{k,i} \times p_{k+1,l}$, the dimension of DPC-PSSM is 400.

19. Bi-gram PSSM (Bi-PSSM)

For Bi-gram PSSM, the frequency of the transition from the m amino acids to the n amino acids is calculated:

$$B_{m,n} = \sum_{i=1}^{L-1} p_{i,m} p_{(i+1),n}, m, n = 1, 2, \cdots, 20$$

Therefore, there are 400 possible cases for $B_{m,n}$, then the Bi-gram PSSM eigenvector for each protein sequence is:

$$F = [B_{1,1}, B_{1,2}, \cdots, B_{1,20}, B_{2,1}, \cdots, B_{2,20}, \cdots, B_{20,1}, \cdots, B_{20,20}]^T$$

20. Auto covariance PSSM (AC-PSSM)

AC-PSSM can transform the PSSMs of different lengths into fixed-length vector. The AC variable measures the correlation of the same property between two residues separated by a distance of lag along the sequence, which can be calculated as:

$$AC(i,l) = \sum_{j=1}^{L-l}\left(S_{i,j} - \bar{S}_i\right)\left(S_{i,j+l} - \bar{S}_i\right) / (L-l)$$

where i is one of the residues, L is the length of the protein sequence, $S_{i,j}$ is the PSSM score of amino acid i at position j , $\bar{S}_i$ is the average score for amino acid i along the whole sequence:

$$\bar{S}_i = \sum_{j=1}^{L} S_{i,j} / L$$

In such a way, the number of AC variables can be calculated as $20 \times lag$, where lag is the maximum of sequence.

21. Cross covariance PSSM (CC-PSSM)

CC-PSSM can transform the PSSMs of different lengths into fixed-length vectors. The CC variable measures the correlation of two different properties between two residues separated by lag along the sequence, which can be calculated by:

$$CC(i1, i2, l) = \sum_{j=1}^{L-l} \left(S_{i1,j} - \bar{S}_{i1} \right) \left(S_{i2,j+l} - \bar{S}_{i2} \right) / (L - l)$$

where $i1, i2$ are two different amino acids and $\bar{S}_{i1} \left(\bar{S}_{i2} \right)$ is the average score for amino acid $i1(i2)$ along the sequence. Since the CC variables are not symmetric, the total number of CC variables is $380 \times lag$.

22. Auto-cross covariance PSSM (ACC-PSSM)

ACC-PSSM as one of the multivariate modeling tools, can transform the PSSMs of different lengths into fixed-length vectors by measuring the correlation between any two properties. ACC results in two kinds of variables: AC between the same property, and cross-covariance (CC) between two different properties. Each protein sequence is represented as a vector of either AC variable or ACC variable that is a combination of AC and CC.

23. Pseudo PSSM (PsePSSM)

According to the pseudo amino acid composition, we obtain the PsePSSM feature vector:

$$\bar{p}_j = \begin{cases} \dfrac{1}{L} \sum_{i=1}^{L} p_{i,j} & j = 1, 2, \cdots, 20, \ \zeta = 0 \\ \dfrac{1}{L - \zeta} \sum_{i=1}^{L-\zeta} (p_{i,j} - p_{i+\zeta,j})^2 & j = 1, 2, \cdots, 20, \ \zeta < L \end{cases}$$

where, each protein sequence can generate $20{+}20 \times \xi$ the dimensional feature vector. The first 20-dimensional vector represents the composition information of the PSSM matrix, and the remaining $20 \times \xi$ dimensional feature vector represents the order evolutionary information. PsePSSM can transform an inconsistent protein sequence into a consistent numerical vector by feature extraction.

24. AB-PSSM

AB-PSSM is based on the averaged PSSM profiles over blocks, each with 5 percent of a sequence. Thus, a protein sequence, regardless of its length, is divided into 20 blocks and each block consists of 20 features (derived from the 20 columns in PSSMs). Mathematically, for the $j\text{-}th$ block, the feature F_j is a 1×20 dimensional feature vector, which is generated by using the following equation:

$$F_j = \frac{1}{B_j}\sum_{i=1}^{B_j} P_i^j$$

where B_j is the size of the $j\text{-}th$ block, which is 5 percent of the length of a sequence and Pej i is a 1×20 vector extracted from the PSSM profile at the $i\text{-}th$ position in the $j\text{-}th$ block. For each sequence, there are a total of 20 blocks; therefore, the final feature is a 400-dimensional vector.

Type 4: Structural information-based methods

25. Secondary structure composition (SSC)

This feature is the normalized count or frequency of the structural motifs present at the amino-acid residue positions. There are three types of motifs: α-helix (H), β-sheet (E) and random coil (C). SPIDER2 returns a vector *SS* of dimension $L \times 1$ containing this information. Thus, we can define this feature as following:

$$SS - Composition(i) = \frac{1}{L}\sum_{j=1}^{L} c_{ij}, 1 \le i \le 3$$

where, *L* is the length of the protein and

$$c_{ij} \begin{cases} 1, & if \quad SS_j = f_i \\ 0, & else \end{cases}$$

where, *SSj* is the structural motif at position *j* of the protein sequence and *fi* is one of the 3 different motif symbols.

26. Accessible surface area composition (ASA)

The accessible surface area composition is the normalized sum of accessible surface area defined by:

$$ASA-Composition=\frac{1}{L}\sum_{i=1}^{L}ASA(i)$$

where ASA is the vector of accessible surface area of dimension $L \times 1$ containing the values of accessible surface area for all the amino acid residues.

27. Torsional angles composition (TAC)

Four different types of torsional angles: ϕ, ψ, τ and θ are returned by SPIDER2 for each residue. First, we convert each of them into radians from degree angles and then take sign and cosine of the angles at each residue position. Thus, we get a matrix of dimension. We denotethis matrix by T. Torsional angles composition is defined as

$$TA-Composition(k)=\frac{1}{L}\sum_{i=1}^{L}T_{i,k}\,(1\le k\le 8)$$

28. Torsional angles bigram (TA-bigram)

The Bigram for the torsional angles is similar to that of the PSSM matrix and is defined as:

$$TA-bigram(k,l)=\frac{1}{L}\sum_{i=1}^{L-1}T_{i,k}T_{i+1,l}\,(1\le k\le 8, 1\le l\le 8)$$

29. Structural probabilities bigram (SP-bigram)

Structural probabilities for each position of the amino-acid residue are given in the SPD2 file as a matrix of dimension $L \times 3$, which we denote by P. The Bigram of the structural probabilities is similar to that of PSSM matrix and is defined as:

$$SP-bigram(k,l)=\frac{1}{L}\sum_{i=1}^{L-1}P_{i,k}P_{i+1,l}\,(1\le k\le 3, 1\le l\le 3)$$

30. Torsional angles auto-covariance (TAAC)

This feature is also derived from the torsional angles and is defined as:

$$TA-Auto-Co\,\mathrm{var}\,iance(k,j)=\frac{1}{L}\sum_{i=1}^{L-k}T_{i,j}T_{i+k,j}\,(1\le j\le 8, 1\le k\le DF)$$

31. Structural probabilities auto-covariance (SPAC)

This feature is also derived from the structural probabilities and is defined as:

$$SP - Auto - Co\,\mathrm{var}\,iance(k, j) = \frac{1}{L}\sum_{i=1}^{L-k} P_{i,j} P_{i+k,j} \, (1 \le j \le 3, 1 \le k \le DF)$$

Feature selection method

SeqFea-Learn contains 21 feature selection methods.

Feature selection methods	Method Number
LASSO	1
Elastic net (EN)	2
L1-SVM	3
L1-Logistic Regression	4
Extra-Trees-RFE	5
XGBosst-RFE	6
SVM-RFE	7
Logistic Regression-RFE	8
Mutual information (MI)	9
Minimum redundancy maximum relevance (MRMR)	10
Joint mutual information (JMI)	11
Maximum relevance maximum distance (MRMD)	12
Information gain (IG)	13
Chi-square test (CHI2)	14
Pearson correlation (Pearson)	15
ReliefF	16
Trace Ratio	17
Gini Index	18
Spectral Feature Selection (SPEC)	19
Fisher Score	20
T-Score	21

1. LASSO

LASSO is a regularization and variable selection method for statistical models. The LASSO minimizes the sum of squared errors, with a upper bound on the sum of the absolute values of the model parameters. The lasso estimate is defined by the solution to the l_1 optimization problem:

$$\text{minimize } \left(\frac{\|\mathbf{Y}-\mathbf{X}\beta\|_2^2}{n}\right) \qquad \text{subject to } \sum_{j=1}^{k}\|\beta\|_1 < t$$

where t is the upper bound for the sum of the coefficients. This optimization problem is equivalent to the parameter estimation that follows

$$\hat{\beta}(\lambda) = \underset{\beta}{\operatorname{argmin}} \left(\frac{\|\mathbf{Y}-\mathbf{X}\beta\|_2^2}{n} + \lambda\|\beta\|_1\right)$$

where $\|Y - X\beta\|^2 = \sum_{i=0}^{n}(Y_i - (X\beta)_i)^2$and $\lambda \geq 0$ is the parameter that controls the strength of the penalty, the larger the value of λ, the greater the amount of shrinkage.

2. Elastic net

Given a dataset $D=\{(x_1,y_1),(x_2,y_2),\cdots,(x_m,y_m)\}$, consider the linear regression model with squared error as the loss function, and the optimization goal is:

$$\min_{\omega}\sum_{i=1}^{m}\left(y_i-\omega^T x_i\right)^2$$

The shortcoming of above loss function is that when there are many features, it is easy to tend to be overfitting, so the equation can be seen as a convex linear combination of L_1 norm and L_2 norm.

$$\min_{w}\frac{1}{2\times n}\|y-Xw\|_2^2-\alpha\times\beta\|w\|_1+\frac{1}{2}\alpha\times(1-\beta)\|w\|_2^2$$

where n is the number of samples. w is the weight coefficient. α, β aer the penalty parameters. Equation is called elastic net (EN). EN has good performance when dealing with the correlation between feature factors.

3. L1-SVM

Support vector machine (SVM) has been an effective and popular method in machine learning, including the application of this method to biomedical problems. Instead of using general L_2-norm for SVM, applying L_1-norm which tends to produce sparse solutions, makes it possible to considerably reduce the number of features of a large feature set. The maximum number of features selected by L_1-norm SVM is bounded by the number of samples. Unlike L_2-norm SVM, the number of features to be reduced is automatically selected by the regularization parameter. The optimization problem of L_1-norm SVM could be described as follows:

$$\min_{w,b} \left\|w\right\|_1 + C\sum_{i=1}^{n} \max\left(0,\ 1 - y_i\left(w^T x_i + b\right)\right)^2.$$

Here, parameter C reflects a regularization parameter that solves the trade-off problem between the training error and the complexity of the model and $\|w\|_1$ denotes the L_1-norm of the weight vector w.

4. L1-LR

The L1-regularized logistic regression (L1-RLR) is an embedded feature selection that combines feature selection with the learner training process. It selects the optimal feature subset during the training process of the learning system. The L1 norm can be solved sparsely, which reduces the computational complexity and the risk of overfitting.

Given the sample data set $D = \{(x_1, y_1), (x_2, y_2), \cdots, (x_m, y_m)\}$, x_i represent the sample feature vector, y_i represent the sample class label. Thus, the L1 logistic regression can be transformed into an unconstrained optimization problem.

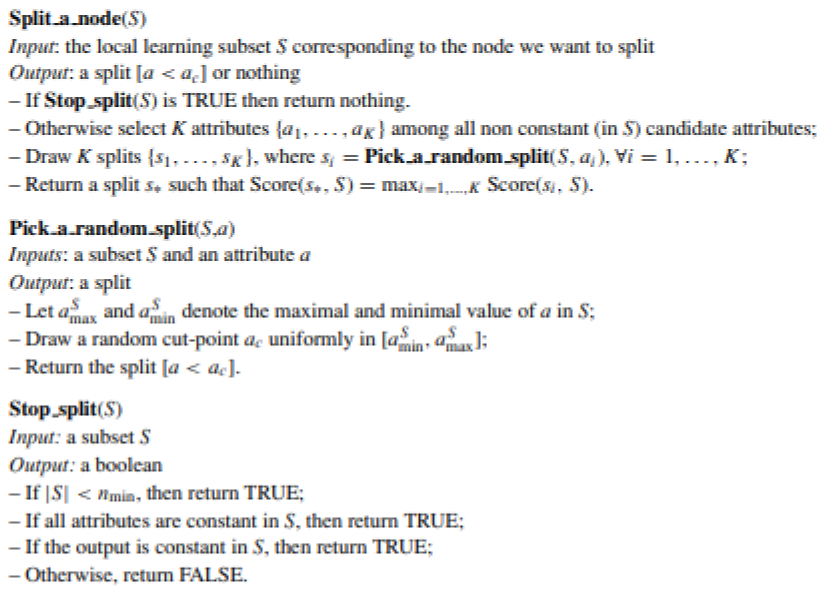
$$\min_{w} \quad f(\omega) = \|\omega\|_1 + C(\sum_{i=1}^{l} \log(1 + e^{-\omega^T x_i}) + \sum_{i:y_i=-1} \omega^T x_i)$$

where $\|\cdot\|_1$ represents L1 norm. ω represents the weight coefficient. C represents the penalty term which determines the number of selected features. The larger penalty term is, the more features are selected.

The Recursive Feature Elimination (RFE) method is a feature selection approach. It works by recursively removing attributes and building a model on those attributes that remain. It uses the model accuracy to identify which attributes (and combination of attributes) contribute the most to predicting the target attribute.

5. Extra-Trees-RFE

The Extra-Trees algorithm builds an ensemble of unpruned decision or regression trees according to the classical top-down procedure. Its two main differences with other treebased ensemble methods are that it splits nodes by choosing cut-points fully at random and that it uses the whole learning sample (rather than a bootstrap replica) to grow the trees.



```
**Split_a_node**($S$)
*Input*: the local learning subset $S$ corresponding to the node we want to split
*Output*: a split $[a < a_c]$ or nothing
– If **Stop_split**($S$) is TRUE then return nothing.
– Otherwise select $K$ attributes $\{a_1, \dots, a_K\}$ among all non constant (in $S$) candidate attributes;
– Draw $K$ splits $\{s_1, \dots, s_K\}$, where $s_i =$ **Pick_a_random_split**($S, a_i$), $\forall i = 1, \dots, K$;
– Return a split $s_*$ such that Score($s_*, S$) = $\max_{i=1,\dots,K}$ Score($s_i, S$).

**Pick_a_random_split**($S$,$a$)
*Inputs*: a subset $S$ and an attribute $a$
*Output*: a split
– Let $a^S_{\max}$ and $a^S_{\min}$ denote the maximal and minimal value of $a$ in $S$;
– Draw a random cut-point $a_c$ uniformly in $[a^S_{\min}, a^S_{\max}]$;
– Return the split $[a < a_c]$.

**Stop_split**($S$)
*Input:* a subset $S$
*Output:* a boolean
– If $|S| < n_{\min}$, then return TRUE;
– If all attributes are constant in $S$, then return TRUE;
– If the output is constant in $S$, then return TRUE;
– Otherwise, return FALSE.
```

The Extra-Trees splitting procedure for numerical attributes is given in Table above.

6. XGBoost-RFE

XGBoost is an efficient and fast gradient boosting decision tree algorithm, which uses weighted quantile sketch, regularized learning, and cache-aware block structure tree learning for ensemble learning. For the given dataset $D = \{(x_i, y_i)(|D| = n, x_i \in R^m, y_i \in \{-1,1\})\}$, the numbers of samples and features are n and m. The objective function can be described as:

$$L(\theta) = \sum_{i}^{n} l(y_i, \hat{y}_i) + \sum_{t=1}^{T} \Omega(f_t)$$

where L is loss function, f_t is the *t-th* tree, $\Omega(f_t)$ represents regularized term. The second-order Taylor term is employed to represent the loss function for *t-th* iteration, and the approximation can be used to optimize the loss function, as the equation (13) show:

$$L^{(t)} \simeq \sum_{i=1}^{k} \left[l\left(y_i, y_i^{(t-1)} + g_i f_t(x_i) + \frac{1}{2} h_i f_t^2(x) \right) \right] + \Omega(f_t)$$

where $g_i = \partial_{y^{(t-1)}} l(y_i, y^{(t-1)})$ represents the first order gradient, $h_i = \partial^2_{y^{(t-1)}} l(y_i, y^{(t-1)})$ is the second order gradient. We can see the loss function only depends on the first and second gradient. In the training process of XGBoost, we use gain to determine the optimal split node.

$$gain = \frac{1}{2} \left[\frac{(\sum_{\in I_L} g_i)^2}{\sum_{\in I_L} h_i + \lambda} + \frac{(\sum_{\in I_R} g_i)^2}{\sum_{\in I_R} h_i + \lambda} - \frac{(\sum_{\in I} g_i)^2}{\sum_{\in I} h_i + \lambda} \right] - \gamma$$

where I_L and I_R represent the number of samples of the left and right nodes after the split node, respectively. $I = I_L \cup I_R$. λ, γ are the penalty parameters. Gain represents the gain score for each split of a tree, and the final feature importance score is calculated by the average gain. The average gain is the total gain of all trees divided by the total number of splits for each feature. The higher the feature importance score of XGBoost is, the more important the corresponding feature is.

7. SVM-RFE

Support vector machine is a machine learning method based on statistical learning theory. It has better generalization ability and higher classification in solving nonlinear and high dimensional data problems. Its basic principle is to map the input sample set to the high-dimensional space, construct the optimal hyperplane, and automatically find out the support vectors that have better classification ability for the classification through the learning algorithm.

For a given sample dataset $(x_i, y_i), i = 1, 2, \cdots n, x \in R^d$, $y \in \{+1, -1\}$

$$y_i\left[\left(\omega^t x_i\right)+b\right]-1 \geq 0, i=1,2,\cdots n$$

Then we can find the optimal classification plane. For the classification problem of high-dimensional space, the SVM model should be able to correctly classify the two types of samples while ensuring the maximum classification interval. Then using $k(x_i, x_j)$ kernel function to obtain the optimal classification plane:

$$f(x)=\operatorname{sgn}\{(\omega, x)+b\}=\operatorname{sgn}\left[\sum_{x_i \in sv} \alpha_i y_i k\left(x_i, x_j\right)+b\right]$$

The kernel functions in SVM include linear kernel functions, polynomial kernel functions, radial basis kernel functions, and sigmoid kernel functions.

8. Logistic Regression-RFE

Logistic regression models the probabilities for classification problems with two possible outcomes. It's an extension of the linear regression model for classification problems. Instead of fitting a straight line or hyperplane, the logistic regression model uses the logistic function to squeeze the output of a linear equation between 0 and 1. The logistic function is defined as:

$$\text{logistic}(\eta)=\frac{1}{1+exp(-\eta)}$$

The step from linear regression to logistic regression is kind of straightforward. In the linear regression model, we have modelled the relationship between outcome and features with a linear equation:

$$\hat{y}^{(i)}=\beta_0+\beta_1 x_1^{(i)}+\ldots+\beta_p x_p^{(i)}$$

For classification, we prefer probabilities between 0 and 1, so we wrap the right side of the equation into the logistic function. This forces the output to assume only values between 0 and 1.

$$P(y^{(i)}=1)=\frac{1}{1+exp(-(\beta_0+\beta_1 x_1^{(i)}+\ldots+\beta_p x_p^{(i)}))}$$

9. Mutual Information

Mutual Information Feature Selection (MIFS) considers both the feature relevance and feature redundancy in the feature selection phase, the feature score for a new unselected feature X_k can be formulated as follows:

$$J_{MIFS}(X_k) = I(X_k;Y) - \beta \sum_{X_j \in S} I(X_k;X_j)$$

In MIFS, the feature relevance is evaluated by $I(X_k;Y)$, while the second term penalizes features that have a high mutual information with the currently selected features such that feature redundancy is minimized.

10. Minimum Redundancy Maximum Relevance

Minimum redundancy maximum relevance (MRMR) criterion is set to the value of β to be the reverse of the number of selected features:

$$J_{MRMR}(X_k) = I(X_k;Y) - \frac{1}{|S|} \sum_{X_j \in S} I(X_k;X_j)$$

Hence, with more selected features, the effect of feature redundancy is gradually reduced.The intuition is that with more non-redundant features selected, it becomes more difficult for new features to be redundant to the features that have already been in S. In [Brown et al. 2012], it gives another interpretation that the pairwise independence between features becomes stronger as more features are added to S, possibly because of noise information in the data. MRMR is also strongly linked to the Conditional likelihoodmaximization framework if we iteratively revise the value of β to be $\frac{1}{|S|}$, and set the other parameter λ to be zero.

11. Joint Mutual Information

MIFS and MRMR reduce feature redundancy in the feature selection process. An alternative criterion, Joint Mutual Information[Yang and Moody 1999; Meyer et al. 2008] is proposed to increase the complementary information that is shared between unselected features and selected features given the class labels. The feature selection criterion is listed as follows:

$$J_{JMI}(X_k) = \sum_{X_j \in S} I(X_k, X_j; Y)$$

The basic idea of JMI is that we should include new features that are complementary

to the existing features given the class labels.JMI cannot be directly reduced to the condition likelihood maximization framework.In [Brown et al. 2012], the authors demonstrate that with simple manipulations, the JMI criterion can be re-written as:

$$J_{JMI}(X_k) = I(X_k; Y) - \frac{1}{|S|}\sum_{X_j \in S} I(X_j; X_k) + \frac{1}{|S|}\sum_{X_j \in S} I(X_j; X_k | Y)$$

Therefore, it is also a special case of the linear combination of Shannon information

terms by iteratively setting β and λ to be $\frac{1}{|S|}$.

12. Maximum Relevance Maximum Distance (MRMD)

Feature selection method has two main part of the decision: 1) Pearson’s correlation coefficient (PCC) is utilized to measure the relevance between features in a subset; 2) Euclidean distance (ED), Cosine distance (CD) and Tanimoto (TO) is utilized to calculate the redundancy among features in a subset.

The Pearson correlation coefficient shows the closely relationship between features and labels. Distance between features is used to measure the redundancy. Finally, MRMD selects features which has strong correlation with labeled and lowest redundancy features subset.

13. Information gain

Information Gain (IG) measures the importance of a feature by its correlation with class labels. It assumes that when a feature has a strong correlation with the class label, it can help achieve good classification performance.

The Mutual information score for feature X_k is:

$$J_{MIM}(X_k) = I(X_k;Y)$$

It can be observed that in MIM, the scores of features are assessed individually. Therefore, only the feature correlation is considered while the feature redundancy is completely ignored. After it obtains the MIM feature scores for all features, we choose the features with the highest feature scores and add them to the selected feature set. The process repeats until the desired number of selected features is obtained.It can also be observed that MIM is a special case of linear combination of Shannon information terms in Eq. (13) where both β and λ are equal to zero.

14. CHI2 Test

Chi-squared test (χ^2 test) is one of statistical method for feature selection. The chi-squared test is applied to determine whether there is significant difference between two events. χ^2 is a measure of how much expected counts E and observed counts N deviate from each other (Chen, et al., 2009). A high value of χ^2 indicates that the hypothesis of independence, which implies that expected and observed counts are similar, is incorrect. This score can be sued to select the n features with the highest values for test chi-square statistic from x, which must contain only non-negative features such as Booleans or frequencies, relative to the classes.

$$\chi^2 = \sum \frac{(A-E)^2}{E}$$

where A is the observed value and E is the expected value.

15. Pearson Correlation

The Pearson correlation is also known as the “product moment correlation coefficient”. Pearson Correlation is one of the simplest methods to explore features’ relation to the response variable. It is a measure of the linear correlation between two variables X and

Y. The resulting value lies in [-1:1], with -1 meaning perfect negative correlation that means one variable increase whereas the other decrease, with +1 meaning perfect positive correlation and 0 meaning no linear correlation between two variables.

The Pearson's correlation is commonly represented by

$$\mathrm{r}_{xy} = \frac{\sum_{i=1}^{n}(x_i - \bar{x})(y_i - \bar{y})}{\sqrt{\sum_{i=1}^{n}(x_i - \bar{x})}\sqrt{\sum_{i=1}^{n}(y_i - \bar{y})^2}}$$

where n is sample size, x_i y_i are the individual sample points indexed with I, $\bar{x} = \frac{1}{n}\sum_{i=1}^{n} x_i$ (the sample mean), and analogously for $\bar{y}$.

16. Relief Algorithm

Relief algorithm is currently the most efficient filter feature evaluation algorithm. It fully considers the correlation between categories and features and solves the problem of multi-class feature dimension reduction. Its main idea is to calculate the correlation between features and categories, and then update the feature weights according to the degree of correlation, and quickly process high-dimensional data to remove unnecessary features effectively. Among them, the higher the weight value, the stronger the classification ability of the feature.

When dealing with multi-class $C(c_1, c_2, c_3)$ feature selection, the ReliefF algorithm first selects d samples with the nearest distance m_i from each category, then the d samples of the same kind as m_i are combined into a set X. According to the class to which the classification belongs, the samples of different classes of m_i respectively constitute the set $Y(c_i)$,; finally the weight $W(f)$ of each feature is updated. The update weight formula is:

$$W(f) = W(f) - \frac{\sum_{x \in X} diff(f, m_i, x_i)}{rd} + \frac{\sum_{c \neq \mathrm{class}(m_i)} \left[\frac{P(C)}{1 - P(class(m_i))} \sum_{x \in Y(c_i)} diff(f, m_i, y_i) \right]}{rd}$$

where f denotes a certain feature, r denotes the number of samples, $diff(f, m_i, x)$ denotes the distance between sample X and sample Y with respect to a certain feature f, $P(\mathrm{C})$ denotes the proportion of C class samples to the total number of samples, and $class(m_i)$ denotes the category to which m_i belongs.

17. Trace Ratio

A feature subset is selected based on the corresponding score (subset-level score), which is calculated in a trace ratio form. Since the number of all possible feature subsets is very huge, it is often prohibitively expensive in computational cost to search in a brute force manner for the feature subset with the maximum subset-level score. Instead of calculating the scores of all the feature subsets, traditional methods calculate the score for each feature, and then select the leading features based on the rank of these feature-level scores. However, selecting the feature subset based on the feature-level score cannot guarantee the optimum of the subset-level score. In this paper, we directly optimize the subset-level score, and propose a novel algorithm to efficiently find the global optimal feature subset such that the subset-level score is maximized.

18. Gini Index

Gini Index transforms the samples space into a feature specific normalized samples space without compromising the intra-class feature distribution. In the second stage of the framework, it identifies the features that discriminates the classes most by applying gini coefficient of inequality.

Gini coefficient of inequality, a popular mechanism to estimate the distribution of income over a population, to analyze distribution of a feature across the classes. If gini = 0, every person in the population receives equal percentage of income and if gini = 1, single person receives 100% of the income. A commonly used approach to represent the inequality and estimate the area under the curve is Lorenz Curve. In Lorenz curve, individuals are sorted by size in increasing order and the cumulative proportion of individuals (x-axis) is plotted against the corresponding cumulative proportion of their total size on y-axis. It has been shown that sample Gini coefficient calculated by Equation below is biased and is to be multiplied by n/(n − 1) to become unbiased.

$$\mathcal{G}(t) = \frac{\sum_{i=1}^{n}(2i - n - 1)wcp(t, c_i)}{n^2\mu}$$

where μ is sample mean. It has been shown that sample Gini coefficient calculated by Equation (3) is biased and is to be multiplied by n/(n − 1) to become unbiased.

19. Spectral Feature Selection

Spectral feature selection studies how to select features according to the structures of the graph induced from S. It employs the spectrum of the graph to measure feature relevance and elaborate how to realize spectral feature selection. The target concept is represented by the graph structures (clusters indicated by the ellipses). Different shapes denote different values assigned by a feature. According to spectral clustering theory, the leading k eigenvectors of L form the optimal soft cluster indicators that separate G into k parts. Therefore, if k is known, we can also use the following function for ranking:

$$\varphi_3(F_i) = \sum_{j=1}^{k-1}(2 - \lambda_j)\alpha_j^2$$

20. Fisher Score

Fisher score typically used in binary classification problems, the Fisher ration (FiR) is defined as the distance between the sample means for each class per feature divided by their variances:

$$\mathrm{FiR}_i = \frac{\left|\overline{X}_i^{(0)} - \overline{X}_i^{(1)}\right|}{\sqrt{\mathrm{var}(X_i)^{(0)} + \mathrm{var}(X_i)^{(1)}}}$$

21. T-Score

T-score is one of the commonly used feature selection methods. This method calculates a relation score by using the sample size, mean and standard deviation values of the features for each class. Features with less score is eliminated from the data set. The formula of t-score is shown in

$$t(x_i) = \frac{\left|\mu_i^+ - \mu_i^-\right|}{\sqrt{\frac{n_i^+(\sigma_i^+)^2 + n_i^-(\sigma_i^-)^2}{n_i^+ + n_i^-}}}$$

The feature selection process of t-score method is executed in the form of features that are ranked by descending order according to the computed scores, then desired number of features are selected starting from the top.

Dimensionality reduction method

SeqFea-Learn contains 12 dimensionality reduction methods.

Dimensionality Reduction Methods	Method Number
Principal component analysis (PCA)	1
Kernel PCA (KPCA)	2
Locally linear embedding (LLE)	3
Multi-dimensional scaling (MDS)	4
t-distributed stochastic neighbor embedding (t-SNE)	5
Truncated singular value decomposition (SVD)	6
Non-negative matrix factorization (NMF)	7
Gaussian random projection (GRP)	8
Sparse random projection (SRP)	9
Independent component analysis (ICA)	10
Factor analysis (FA)	11
Agglomerate feature (AF)	12

1. Principal component analysis (PCA)

PCA is a statistical procedure that uses an orthogonal transformation to convert a set of observations of possibly correlated variables into a set of values of linearly uncorrelated variables called principal components. PCA aims to find the directions of maximum variance in high-dimensional data and projects it onto a new subspace with equal or fewer dimensions than the original one. If we use PCA for dimensionality reduction, we construct a $d * k$ dimensional transformation matrix W that allows us to map a sample vector x onto a new k dimensional feature subspace that has fewer dimensions than the original d-dimensional feature space:

$$\boldsymbol{x} = [x_1, x_2, \ldots, x_d], \qquad \boldsymbol{x} \in \mathbb{R}^d$$
$$\downarrow \boldsymbol{xW}, \quad \boldsymbol{W} \in \mathbb{R}^{d \times k}$$
$$\boldsymbol{z} = [z_1, z_2, \ldots, z_k], \qquad \boldsymbol{z} \in \mathbb{R}^k$$

2. Kernel PCA (KPCA)

PCA is a linear method. That is it can only be applied to datasets which are linearly separable. But, if we use it to non-linear datasets, we might get a result which may not be the optimal dimensionality reduction. Kernel PCA uses a kernel function to project dataset into a higher dimensional feature space, where it is linearly separable. It is similar to the idea of Support Vector Machines.

3. Locally Liner Embedding (LLE)

The LLE algorithm, is based on simple geometric intuitions. Suppose the data consist of N real-valued vectors, each of dimensionality$D$, sampled from some smooth underlying manifold. We can characterize the local geometry of these patches by linear coefficients that reconstruct each data point from its neighbors. In the simplest formulation of LLE, one identifies K nearest neighbors per data point, as measured by Euclidean distance. Reconstruction errors are then measured by the cost function:

$$\mathcal{E}(W) = \sum_i \left| \vec{X}_i - \sum_j W_{ij} \vec{X}_j \right|^2$$

which adds up the squared distances between all the data points and their reconstructions.

4. Multi-dimensional Scaling (MDS)

Multidimensional scaling is a means of visualizing the level of similarity of individual cases of a dataset. MDS is used to translate "information about the pairwise distance among a set of n objects or individuals" into a configuration of n points mapped into an abstract Cartesian space.

It takes an input matrix dissimilarities between pairs of items and outputs a coordinate matrix whose configuration minimizes a loss function called strain. General forms of loss functions called stress in distance MDS and Strain in classical MDS. The strain is given by:

$$Strain_D(x_1, x_2, \ldots, x_N) = \left(\frac{\sum_{i,j} \left(b_{ij} - \langle x_i, x_j \rangle \right)^2}{\sum_{i,j} b_{ij}^2} \right)^{1/2}$$

where b_{ij} are terms of the matrix B defined on step 2 of the following algorithm.

5. t-distributed stochastic neighbor embedding (t-SNE)

t-Distributed Stochastic Neighbor Embedding (t-SNE) is a non-linear technique for dimensionality reduction that is particularly well suited for the visualization of high-dimensional datasets. It is extensively applied in image processing, NLP, genomic data and speech processing.

The algorithms starts by calculating the probability of similarity of points in high-dimensional space and calculating the probability of similarity of points in the corresponding low-dimensional space. The similarity of points is calculated as the conditional probability that a point A would choose point B as its neighbor if neighbors were picked in proportion to their probability density under a Gaussian (normal distribution) centered at A.

It then tries to minimize the difference between these conditional probabilities (or similarities) in higher-dimensional and lower-dimensional space for a perfect representation of data points in lower-dimensional space.

To measure the minimization of the sum of difference of conditional probability t-SNE minimizes the sum of Kullback-Leibler divergence of overall data points using a gradient descent method.

6. Truncated singular value decomposition (SVD)

Dimensionality reduction using truncated SVD is to perform linear dimensionality reduction by means of truncated singular value decomposition. Contrary to PCA, this estimator does not center the data before computing the singular value decomposition. This means it can work with scipy.sparse matrices efficiently. In particular, truncated SVD works on term count/tf-idf matrices as returned by the vectorizers in sklearn.feature_extraction.text. In that context, it is known as latent semantic analysis (LSA). This estimator supports two algorithms: a fast randomized SVD solver, and a “naive” algorithm that uses ARPACK as an eigensolver on (X * X.T) or (X.T * X), whichever is more efficient.

7. Non-negative matrix factorization (NMF)

NMF (Nonnegative Matrix Factorization) is a matrix factorization method where we constrain the matrices to be nonnegative.

In order to understand NMF, we should clarify the underlying intuition between matrix factorization. Suppose we factorize a matrix X into two matrices W and H so that $X \approx WH$. There is no guarantee that we can recover the original matrix, so we will approximate it as best as we can. Now, suppose that X is composed of m rows $x_1, x_2, \dots x_m$, W is composed of k rows $w_1, w_2, \dots w_k$, H is composed of m rows $h_1, h_2, \dots h_m$. Each row in X can be considered a data point.

For instance, in the case of decomposing images, each row in X is a single image, and each column represents some feature. Basically, we can interpret x_i to be a weighted sum of some components (or bases if you are more familiar with linear algebra), where each row in H is a component, and each row in W contains the weights of each component.

8. Gaussian Random Projection (GRP)

Random projection methods are known for their power, simplicity, and low error rates when compared to other methods to reduce the dimensionality. The core idea behind random projection is given in the Johnson-Lindenstrauss lemma, which states that if points in a vector space are of sufficiently high dimension, then they may be projected into a suitable lower-dimensional space in a way which approximately preserves the distances between the points.

In random projection, the original d-dimensional data is projected to a k-dimensional (k<<d) subspace, using a random $k * d$ dimensional matrix R whose columns have unit lengths. Using matrix notation: if X_{dxN} is the original set of N d-dimensional observations, then $X_{k*N}^{RP} = R_{k*d}X_{d*N}$ is the projection of the data onto a lower k-dimensional subspace. Random projection is computationally simple: form the random matrix "R" and project the $d * N$ data matrix X onto K dimensions of order. If the data matrix X is sparse with about c nonzero entries per column, then the complexity of this operation is of order.

GRP reduces the dimensionality by projecting the original input space on a randomly generated matrix where components are drawn from the following distribution $N\left(\frac{0,1}{n_{components}}\right)$.

9. Sparse Random Projection (SRP)

Sparse Random Projection reduces the dimensionality by projecting the original input space using a sparse random matrix. Sparse random metrics are an alternative to dense Gaussian random projection matrix that guarantees similar embedding quality while being much more memory efficient the allowing faster computation of the projected data.

If we define $s = \frac{1}{density}$, the elements of the random matrix are drawn from:

$$\begin{cases} -\sqrt{\frac{s}{n_{\text{components}}}} & & 1/2s \\ 0 & \text{with probability} & 1 - 1/s \\ +\sqrt{\frac{s}{n_{\text{components}}}} & & 1/2s \end{cases}$$

where $n_{components}$ is the size of the projected subspace. By default the density of nonzero elements is set to the minimum density as recommended.

10. Independent component analysis (ICA)

Independent component analysis (ICA) is used to estimate sources given noisy measurements. Unlike principal component analysis which focuses on maximizing the variance of the data points, the independent component analysis focuses on independence.

Linear independent component analysis can be divided into noiseless and noisy cases, where noiseless ICA is a special case of noisy ICA. Nonlinear ICA should be considered as a separate case. The components x_i of the observed random vector $x = (x_1, \ldots, x_m)^T$ are generated as a sum of the independent components $s_k, k = 1, \ldots, n$.

11. Factor Analysis (FA)

Factor analysis is a statistical method used to describe variability among observed, correlated variables in terms of a potentially lower number of unobserved variables called factors. For example, it is possible that variations in six observed variables mainly reflect the variations in two unobserved (underlying) variables. Factor analysis searches for such joint variations in response to unobserved latent variables. The observed variables are modelled as linear combinations of the potential factors, plus "error" terms. Factor analysis aims to find independent latent variables and investigate whether a number of variables of interest $Y_1, Y_2, \dots Y_i$ are linearly related to a smaller number of unobservable factors $F_1, F_2, \dots, F_k$.

12. Agglomerate feature (AF)

Agglomerate feature is similar to Agglomerative Clustering, but recursively merges features instead of samples. In standard agglomerative clustering you receive a matrix M^{n*m} representing n samples of dimension m that you want to cluster. In feature agglomeration the algorithm clusters the transpose of the matrix, M^T so it clusters m samples of dimension n, these samples represent the features. The default distance used to cluster the features is the Euclidean distance, but you can also use l1, cosine and others.

Clustering method

SeqFea-Learn contains 7 clustering methods.

Clustering methods	Method Number
K-means	1
Spectral Clustering	2
Gaussian Mixture Clustering	3
Affinity Propagation Clustering	4
Mean Shift	5
DBSCAN	6
OPTICS	7

1. K-means clustering

K-means clustering is a method of vector quantization, originally from signal processing. K-means clustering aims to partition n observations into k clusters in which each observation belongs to the cluster with the nearest mean, serving as a porotype of the cluster. Given a set of observations (x_1,x_2,…x_n), where each observation is a d-dimensional real vector, k-means is to minimize the within-cluster sum of squares (WCSS):

$$\underset{\mathbf{S}}{\arg\min} \sum_{i=1}^{k} \sum_{\mathbf{x} \in S_i} \left\| \mathbf{x} - \boldsymbol{\mu}_i \right\|^2 = \underset{\mathbf{S}}{\arg\min} \sum_{i=1}^{k} |S_i| \operatorname{Var} S_i$$

where u_i is the mean of points in S_j. This is equivalent to minimizing the pairwise squared deviations of points in the same cluster.

K-means algorithm in data mining starts with a first group of randomly selected centroids, which are used as the beginning points for every cluster, and then performs iterative calculations to optimize the positions of the centroids.

2. Spectral Clustering

Spectral clustering techniques make use of the spectrum of the similarity matrix of the data to perform dimensionality reduction before clustering in fewer dimensions. The similarity matrix is provided as an input and consists of a quantitative assessment of the relative similarity of each pair of points in the dataset.

If the similarity matrix A has not already been explicitly constructed, the efficiency of spectral clustering maybe improved if the solution to the corresponding eigenvalue problem is performed in a matrix-free fashion, as in the Lanczos algorithm. Spectral clustering is related to nonlinear dimensionality reduction, and dimension reduction techniques such as locally-linear embedding can be used to reduce errors from noise or outliers.

3. Gaussian Mixture Clustering

Gaussian mixture clustering is a probabilistic approach to clustering addressing many of these problems. In this approach we describe each cluster by its centroid (mean), covariance , and the size of the cluster(Weight). Here rather than identifying clusters by “nearest” centroids, we fit a set of k gaussians to the data. And we estimate gaussian distribution parameters such as mean and Variance for each cluster and weight of a cluster. After learning the parameters for each data point we can calculate the probabilities of it belonging to each of the clusters.

So mathematically we can define gaussian mixture model as mixture of K gaussian distribution that means it’s a weighted average of K gaussian distribution. So we can write data distribution as

$$p(\boldsymbol{x}) = \sum_{k=1}^{K} \pi_k \mathcal{N}(\boldsymbol{x}|\boldsymbol{\mu}_k, \boldsymbol{\Sigma}_k)$$

where N(x|mu_k,sigma_k) represents cluster in data with mean mu_k and co variance epsilon_k and weight pi_k.

4. Affinity Propagation Clustering

The main drawbacks of K-Means and similar algorithms are having to select the number of clusters, and choosing the initial set of points. Affinity Propagation, instead, takes as input measures of similarity between pairs of data points, and simultaneously considers all data points as potential exemplars. Real-valued messages are exchanged between data points until a high-quality set of exemplars and corresponding clusters gradually emerges. The algorithm requires similarities between data points and preferences. Both similarities and preferences are often represented through a single matrix, where the values on the main diagonal represent preferences. Matrix representation is good for dense datasets. Where connections between points are sparse, it is more practical not to store the whole n x n matrix in memory, but instead keep a list of similarities to connected points. Behind the scene, ‘exchanging messages between points’ is the same thing as manipulating matrices, and it’s only a matter of perspective and implementation.

The algorithm exchanges messages between pairs of data points until a set of exemplars emerges, with each exemplar corresponding to a cluster. The Affinity Propagation algorithm takes as input a real number s(k,k) for each data point k — referred to as a “preference”. Data points with large values for s(k,k) are more likely to be exemplars. The number of clusters is influenced by the preference values and the message-passing procedure.

5. Mean Shift

The mean shift algorithm is a nonparametric clustering technique which does not require prior knowledge of the number of clusters, and does not constrain the shape of the clusters.

Given n data points $x_i, i = 1,2, \ldots$ on a d-dimensional space R^d, the multivariate kernel density estimate obtained with kernel K(x) and window radius h is

$$f(\mathbf{x}) = \frac{1}{nh^d} \sum_{i=1}^{n} K\left(\frac{\mathbf{x} - \mathbf{x}_i}{h}\right)$$

For radially symmetric kernels, it suffices to define the profile of the kernel k(x) satisfying:

$$K(\mathbf{x}) = c_{k,d}\, k(\|\mathbf{x}\|^2)$$

where ck,d is a normalization constant which assures K(x) integrates to 1. The modes of the density function are located at the zeros of the gradient function ∇f(x) = 0.

The gradient of the density estimator is

$$\begin{aligned}\nabla f(\mathbf{x}) &= \frac{2c_{k,d}}{nh^{d+2}}\sum_{i=1}^{n}(\mathbf{x}_i-\mathbf{x})g\left(\left\|\frac{\mathbf{x}-\mathbf{x}_i}{h}\right\|^2\right)\\ &= \frac{2c_{k,d}}{nh^{d+2}}\left[\sum_{i=1}^{n}g\left(\left\|\frac{\mathbf{x}-\mathbf{x}_i}{h}\right\|^2\right)\right]\left[\frac{\sum_{i=1}^{n}\mathbf{x}_i g\left(\|\frac{\mathbf{x}-\mathbf{x}_i}{h}\|^2\right)}{\sum_{i=1}^{n}g\left(\|\frac{\mathbf{x}-\mathbf{x}_i}{h}\|^2\right)}-\mathbf{x}\right]\end{aligned}$$

The first term is proportional to the density estimate at x computed and the second term is mean shift.

$$\mathbf{m}_h(\mathbf{x}) = \frac{\sum_{i=1}^{n}\mathbf{x}_i g\left(\|\frac{\mathbf{x}-\mathbf{x}_i}{h}\|^2\right)}{\sum_{i=1}^{n}g\left(\|\frac{\mathbf{x}-\mathbf{x}_i}{h}\|^2\right)}-\mathbf{x}$$

6. DBSCAN

Density-based spatial clustering of applications with noise (DBSCAN) is a well-known data clustering algorithm that is commonly used in data mining and machine learning. Based on a set of points (let's think in a bidimensional space as exemplified in the figure), DBSCAN groups together points that are close to each other based on a distance measurement (usually Euclidean distance) and a minimum number of points. It also marks as outliers the points that are in low-density regions. The DBSCAN algorithm basically requires 2 parameters: eps and minPoints.

DBSCAN finds core samples of high density and expands clusters from them. Good for data which contains clusters of similar density.

7. OPTICS

Ordering Points To Identify the Clustering Structure (OPTICS), closely related to DBSCAN, finds core sample of high density and expands clusters from them. Unlike DBSCAN, keeps cluster hierarchy for a variable neighborhood radius. Better suited for usage on large datasets than the current sklearn implementation of DBSCAN.

This implementation deviates from the original OPTICS by first performing k-nearest-neighborhood searches on all points to identify core sizes, then computing only the distances to unprocessed points when constructing the cluster order. Note that we do not employ a heap to manage the expansion candidates, so the time complexity will be O(n^2).

Sampling method

SeqFea-Learn contains 5 sampling methods.

Sampleing methods	Method Number
Random over sampling (ROS)	1
Synthetic minority oversampling technique (SMOTE)	2
Adaptive synthetic (ADASYN)	3
Random under sampling (RUS)	4
Neighbourhood cleaning rule (NCR)	5

1. Random over sampling (ROS)

Suppose the feature vectors of a certain minority sample to be x_i , $x_i \in \{1,2\cdots T\}$ .The process of random over sampling can be shown as:

(i) For the samples x_i in the minority samples, we calculate the Euclidean distance from this sample to other samples in the minority samples, and find k nearest neighbor samples, denoted as $x_{i(n)}, n \in \{1,2\cdots k\}$.

(ii) A sample $x_{i(nn)}$ is randomly selected from the k nearest neighbors, and then generate a random value from 0 to 1. The new sample x_{i1} could be synthesized using linear interpolation between $x_{i(nn)}$ and x_i .

(iii) Repeat step 2 for N iterations to synthesize N new samples $x_{inew}, i \in 1,2\cdots N$.

2. Synthetic minority oversampling technique (SMOTE)

SMOTE is an oversampling algorithm proposed, which aims to synthesize some new positive samples to reduce the class imbalance. k nearest neighbor samples. If the oversampling ratio is N , then N nearest neighbor samples are selected from the k nearest neighbor samples, denoted as $c_1, c_2, \cdots, c_N$. A random linear interpolation can be performed between the positive samples X and $c_1, c_2, \cdots, c_N$, and a new positive sample P_j is generated:

$$P_j = X + rand(0,1) * (c_j - X),\ j = 1,2,\cdots,N$$

where $rand(0,1)$ represents the random number within $(0,1)$.

3. Adaptive synthetic (ADASYN)

ADASYN focuses on generating samples next to the original samples which are wrongly classified using a k-Nearest Neighbors classifier while the basic implementation of SMOTE will not make any distinction between easy and hard samples to be classified using the nearest neighbors rule. Therefore, the decision function found during training will be different among the algorithms.

4. Random under sampling (RUS)

Let X be an imbalanced dataset with $X_{\min}$ and X_{maj} being the subset of samples belonging to the minority and majority class, respectively. The balancing ratio of the dataset is defined as:

$$r_X = \frac{|X_{\min}|}{|X_{maj}|}$$

where | | denotes the cardinality of a set. The balancing process is equivalent to resample into a new dataset such that $r_X > r_{res}$.

Under-sampling Under-sampling refers to the process of reducing the number of samples in maj. The implemented methods can be categorized into 2 groups: (i) X_{ed} under-sampling and (ii) cleaning under-sampling. Fixed under-sampling refer to the methods which perform under-sampling to obtain the appropriate balancing ratio r_{res}. Contrary to the previous methods, cleaning under-sampling do not allow to reach specically the balancing ratio r_{res}, but rather clean the feature space based on some empirical criteria.

5. Neighbourhood cleaning rule (NCR)

The basic idea of our neighborhood cleaning rule (NCL) is the same as in one-sided selection. NCL emphasizes ore data cleaning than data reduction. The calculation process of NCL is described as:

(i) Split data T into the class of interest C and the rest of data O.

(ii) Identify noisy data A_1 in O with edited nearest neighbor rule.

```
(iii) For each class $C_i$ in $O$
    if ( $x \in C_i$ in 3-nearest neighbors of misclassified $y \in C$ )
    and ( $|C_i| \ 0.5|C|$ ) then $A_2 = \{x\} \cup A_2$
(iv) Reduced data $S = T - (A_1 \cup A_2)$
```

Classification method

SeqFea-Learn integrated 13 classification methods to make predictions.

Classifier	Method Number
Support vector machine (SVM)	1
K-nearest neighbor (KNN)	2
Random forest (RF)	3
Extremely randomized trees (Extra-Trees)	4
Gradient boosting decision tree (GBDT)	5
XGBoost	6
LightGBM	7
Bagging classifier (Bagging)	8
AdaBoost	9
Gaussian Naïve Bayes (GNB)	10
Deep neural network (DNN)	11
Convolutional neural network (CNN)	12
Recurrent neural network (RNN)	13

1. Support vector machine (SVM)

Support vector machine is a machine learning method based on statistical learning theory. It has better generalization ability and higher classification in solving nonlinear and high dimensional data problems. Its basic principle is to map the input sample set to the high-dimensional space, construct the optimal hyperplane, and automatically find out the support vectors that have better classification ability for the classification through the learning algorithm.

For a given sample dataset $(x_i, y_i), i = 1, 2, \cdots n, x \in R^d$, $y \in \{+1, -1\}$

$$y_i \left[\left(\omega^t x_i \right) + b \right] - 1 \geq 0, i = 1, 2, \cdots n$$

Then we can find the optimal classification plane. For the classification problem of high-dimensional space, the SVM model should be able to correctly classify the two types of samples while ensuring the maximum classification interval. Then using $k(x_i, x_j)$ kernel function to obtain the optimal classification plane:

$$f(x) = \operatorname{sgn}\left\{ (\omega, x) + b \right\} = \operatorname{sgn}\left[\sum_{x_i \in sv} \alpha_i y_i k\left(x_i, x_j \right) + b \right]$$

The kernel functions in SVM include linear kernel functions, polynomial kernel functions, radial basis kernel functions, and sigmoid kernel functions.

2. K-nearest neighbor (KNN)

The idea of the KNN algorithm is to calculate the similarity of each sample between the test set and the training set. Then count the most similar samples to classify the prediction via the majority voting method. The specific steps of the KNN algorithm can be describe as:

Step 1: Input the sample dataset and calculate neighbor samples according to the feature information.

Step 2: calculate the sample weight in order, using the equation:

$$p(\bar{x}, C_j) = \sum_{\bar{d}_i \in KNN} Sim(\bar{x}, \bar{d}_i) y(\bar{d}_i, C_j)$$

where, $\bar{x}$ is the variable of the new sample, $Sim(\bar{x}, \bar{d}_i)$ is the similarity score and $y(\bar{d}_i, C_j)$ is the category attribute function.

Step 3 Compare the weights of the two categories and classify the samples the category with the largest weight.

3. Random forest (RF)

RF is a classifier based on decision tree and Bagging algorithm. First, the training sets are generated using the bootstrap method. Secondly, for each training set, the decision tree model is constructed. At each step of split selection, RF determines the optimal split node from a subset of features according to Gini coefficient. Then the ensemble learning method can be built up based on the majority voting principle

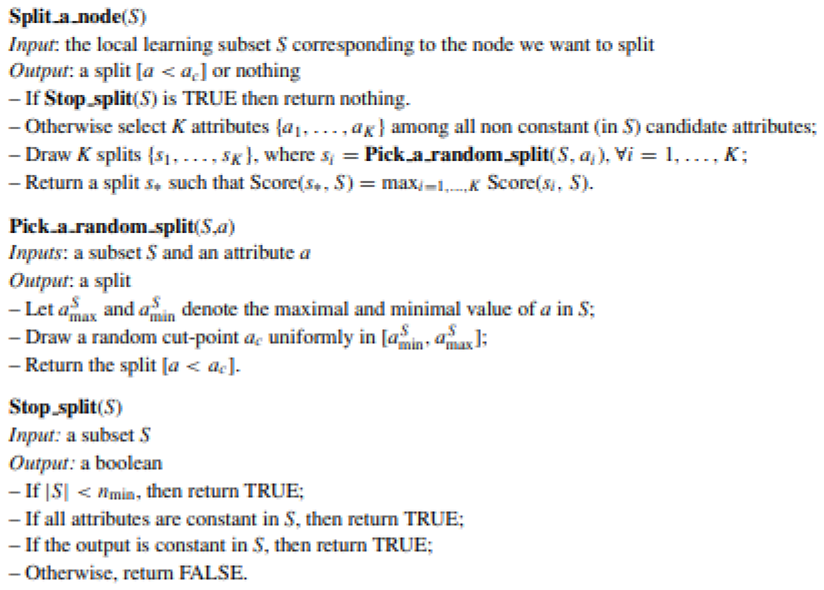
$$H(x) = \arg\max_{Y} \sum_{i=1}^{k} I(h_i(x) = Y)$$

where, h_i represents single decision tree, and Y is the output label.

4. Extremely randomized trees (ET)

ET is similar to RF, but RF applies the Bagging algorithm, and ET uses all training samples to construct each decision tree. Random forest obtains the optimal split attribute from a random subset, and the ET is completely random to obtain the split node.

The ET algorithm builds an ensemble of unpruned decision or regression trees according to the classical top-down procedure. Its two main differences with other treebased ensemble methods are that it splits nodes by choosing cut-points fully at random and that it uses the whole learning sample (rather than a bootstrap replica) to grow the trees.



```
Split_a_node($S$)
Input: the local learning subset $S$ corresponding to the node we want to split
Output: a split $[a < a_c]$ or nothing
– If Stop_split($S$) is TRUE then return nothing.
– Otherwise select $K$ attributes $\{a_1, \ldots, a_K\}$ among all non constant (in $S$) candidate attributes;
– Draw $K$ splits $\{s_1, \ldots, s_K\}$, where $s_i$ = Pick_a_random_split($S, a_i$), $\forall i = 1, \ldots, K$;
– Return a split $s_*$ such that Score($s_*, S$) = $\max_{i=1,\ldots,K}$ Score($s_i, S$).

Pick_a_random_split($S$,$a$)
Inputs: a subset $S$ and an attribute $a$
Output: a split
– Let $a^S_{\max}$ and $a^S_{\min}$ denote the maximal and minimal value of $a$ in $S$;
– Draw a random cut-point $a_c$ uniformly in $[a^S_{\min}, a^S_{\max}]$;
– Return the split $[a < a_c]$.

Stop_split($S$)
Input: a subset $S$
Output: a boolean
– If $|S| < n_{\min}$, then return TRUE;
– If all attributes are constant in $S$, then return TRUE;
– If the output is constant in $S$, then return TRUE;
– Otherwise, return FALSE.
```

The Extra-Trees splitting procedure for numerical attributes is given in Table above.

5. Gradient boosting decision tree (GBDT)

Gradient boosting decision tree is an ensemble learning classification algorithm for multiple decision trees with excellent learning ability, which has been successfully applied in many fields. The residual is the predicted value of the tree minus the residual by the previous tree which multiplied by a learning rate η. In general, the smaller the η, the higher the accuracy of the resulting GTB model.

Training set $\{(x_1, y_1), (x_2, y_2), \cdots, (x_n, y_n)\}$, given the x value and the corresponding value y, according to the principle of risk experience minimization, find the approximate value $F(x)$ of the objective function $F(x)$, and minimize the expected value of loss function $L(y, F(x))$.

$$F = \arg\min_{F} E_{x,y}[L(y, F(x))]$$

Suppose $h_m(x)$ is the base decision tree of step m and J_m is the number of leaf nodes in the base decision tree.The input space was divided into J_m disjoint regions $R_{1m}, R_{2m}, \cdots, R_{J_m m},$ and the output value in each region was predicted. The output $h_m(x)$ is expressed as a linear combination of input x:

$$h_m(x) = \sum_{j=1}^{J_m} b_{jm} I_{R_{jm}}(x)$$

where b_{jm} is the predicted value in the region R_{jm}.

Then, the coefficient b_{jm} is multiplied by the learning rate r_m, the value of leaf node region is estimated by linear search, the approximate value of residual is fitted, and the loss function is minimized. The model is iteratively updated as follows:

$$F_m(x) = F_{m-1}(x) + r_m h_m(x), \quad r_m = \arg\min_{r} \sum_{i=1}^{n} L(y_1, F_{m-1}(x_i) + r h_m(x_i))$$

6. XGBoost

XGBoost is an ensemble learning algorithm based on gradient boosting, which is an optimization model that combines a linear model with a boosting tree model. It uses not only the first derivative but also the second derivative of the loss function for second-order derivation.

For a given n sample and m feature datasets $D = \{(x_i, y_i)(|D| = n, x_i \in R^m, y_i \in R)\}$, the XGBoost algorithm objective function is defined as

$$obj(\theta) = \sum_{i}^{n} l(y_i, \hat{y}_i) + \sum_{t=1}^{T} \Omega(f_t)$$

where L is the loss function, the smaller L is, the better the performance of the algorithm. f_t is the t-th tree, $\Omega(f_t)$ is the regular term, used to control the complexity of the model, $\Omega(f) = \gamma T + \frac{1}{2}\lambda\|\omega\|^2$, ω is the vector of the score in the leaf, λ is the regularization parameter, γ is the minimum loss required to further segment the leaf nodes. Then, according to Taylor expansion optimization of the objective function, the second-order Taylor of the loss function after the t iteration is obtained.

$$L^{(t)} \simeq \sum_{i=1}^{k} \left[l\left(y_i, y_i^{(t-1)} + g_i f_t(x_i) + \frac{1}{2} h_i f_t^2(x) \right) \right] + \Omega(f_t)$$

where $g_i = \partial_{y^{(t-1)}} l(y_i, y^{(t-1)})$ represents the first derivative of each sample and $h_i = \partial^2_{y^{(t-1)}} l(y_i, y^{(t-1)})$ represents the second derivative of each sample, and the loss function depends only on the first and second derivatives of each data point.

7. LightGBM

LightGBM is a variant of gradient tree boosting. As we can know, when the number of samples is large or the feature dimension is high, the efficiency and accuracy of GTB still cannot obtain satisfactory results. Ke et al proposed a highly efficient gradient boosting decision tree using gradient-based one-side sampling (GOSS) and exclusive feature bundling (EFB) called LightGBM. This algorithm uses GOSS to determine the split point via calculating variance gain. First, sorting the absolute values of the gradients of the training examples in descending order and the top $a \times 100\%$ data samples of gradient values are selected called A. Then the subset B whose size is $b \times |A^c|$ is randomly selected from the retained samples A^c. Finally, the instances are split through the estimated variance $V_j(d)$ on $A \cup B$.

$$V_j(d) = \frac{1}{n}\left(\frac{(\sum_{x_i \in A_l} g_i + \frac{1-a}{b}\sum_{x_i \in B_l} g_i)^2}{n_l^j(d)} + \frac{(\sum_{x_i \in A_r} g_i + \frac{1-a}{b}\sum_{x_i \in B_r} g_i)^2}{n_r^j(d)} \right)$$

where $A_l = \left\{x_i \in A\text{:}\ x_{ij} \le d\right\}$, $A_r = \left\{x_i \in A\text{:}\ x_{ij} > d\right\}$, $B_l = \left\{x_i \in B\text{:}\ x_{ij} \le d\right\}$, $B_r = \left\{x_i \in B\text{:}\ x_{ij} > d\right\}$, g_i represents the negative gradient of the loss function, $\frac{1-a}{b}$ is employed to normalize the sum of gradients.

8. Bagging Classifier

A Bagging classifier is an ensemble meta-estimator that fits base classifiers each on random subsets of the original dataset and then aggregate their individual predictions (either by voting or by averaging) to form a final prediction. Such a meta-estimator can typically be used as a way to reduce the variance of a black-box estimator (e.g., a decision tree), by introducing randomization into its construction procedure and then making an ensemble out of it.

This algorithm encompasses several works from the literature. When random subsets of the dataset are drawn as random subsets of the samples, then this algorithm is known as Pasting. If samples are drawn with replacement, then the method is known as Bagging. When random subsets of the dataset are drawn as random subsets of the features, then the method is known as Random Subspaces.

Finally, when base estimators are built on subsets of both samples and features, then the method is known as Random Patches.

9. AdaBoost

An AdaBoost classifier is a meta-estimator that begins by fitting a classifier on the original dataset and then fits additional copies of the classifier on the same dataset but where the weights of incorrectly classified instances are adjusted such that subsequent classifiers focus more on difficult cases. This class implements the algorithm known as AdaBoost-SAMME.

Ada-boost classifier combines weak classifier algorithm to form strong classifier. A single algorithm may classify the objects poorly. But if we combine multiple classifiers with selection of training set at every iteration and assigning right amount of weight in final voting, we can have good accuracy score for overall classifier.

10. Gaussian Naïve Bayes (GNB)

Naive Bayes methods are a set of supervised learning algorithms based on applying Bayes’ theorem with the “naive” assumption of conditional independence between every pair of features given the value of the class variable. Bayes’ theorem states the following relationship, given class variable y and dependent feature vector x_1 through x_n. The relationship is simplified to

$$P(y \mid x_1, \ldots, x_n) = \frac{P(y) \prod_{i=1}^{n} P(x_i \mid y)}{P(x_1, \ldots, x_n)}$$

Since $P(x_1, \ldots, x_n)$ is constant given the input, we can use the following classification rule:

$$P(y \mid x_1, \ldots, x_n) \propto P(y) \prod_{i=1}^{n} P(x_i \mid y)$$

$$\Downarrow$$

$$\hat{y} = \arg\max_{y} P(y) \prod_{i=1}^{n} P(x_i \mid y),$$

and we can use Maximum A Posteriori (MAP) estimation to estimate P(y) and P(xi|y); the former is then the relative frequency of class y in the training set. GNB implements the Gaussian Naïve Bayes algorithm for classification. The likelihood of features is assumed to be Gaussian:

$$P(x_i \mid y) = \frac{1}{\sqrt{2\pi\sigma_y^2}} \exp\left(-\frac{(x_i - \mu_y)^2}{2\sigma_y^2}\right)$$

11. Deep neural network (DNN)

Deep neural network (DNN) is a machine learning method based on layer-by-layer learning. Unlike traditional neural networks, deep neural network is a single-transport multi-hidden layer artificial network. The neural network consists of an input layer, one or more hidden layers, and an output layer. The output features of the upper layer are used as the input of the next layer for feature learning. After layer-by-layer feature mapping, the existing spatial samples are used. The feature is mapped to another feature space to learn to have a better characterization of existing inputs.

In general, the first layer is the input layer, the last layer is the output layer, and the middle layer is the hidden layer, and the adjacent layers are fully connected, that is, any one of the neurons in the i-th layer and any one of the neurons in the i+1-th layer. The yuan is connected. The DNN receives the data at the input layer, combines the input data with the weights in each node to convert the data in a non-linear manner, calculates the average gradient and adjusts the weights and activation functions accordingly, and finally calculates the final output at the output layer.

From the local model, the DNN consists of a linear relationship plus a nonlinear activation function, and the output of the first layer is represented by the matrix method:

$$a^l = \delta(Z^i) = \delta(w^l a^{l-1} + b^l)$$

Where $l = 1, 2, \cdots, N$, a^l indicates the input data representing l-th layer is the connection weight matrix between the $(l-1)$ layer and the l layer, and is the offset of the first layer, δ indicates the activation function of the l-th layer.

Currently, in DNN, ReLU (Rectified linear unit) is usually used as an activation function of neurons. ReLU has a one-sided suppression feature that turns all negative values to zero and a positive value. This unilateral inhibition makes the neurons in the neural network sparsely activating. The sparse model can better mine the relevant features and fit the training data. The ReLU function can be expressed as follows:

$$\delta(z) = \max(0, z)$$

The DNN constructed in this paper consists of input layer, hidden layer and output layer. The input layer is extracted from the selected feature as the input vector. The hidden layer has three layers. The activation function is selected as ReLU, and the output layer is composed of two neurons. The number of categories of dataset target variables, and finally, created using a softmax function to solve the two-class problem.

12. Convolutional neural network (CNN)

We use convolution layer, pooling layer, and fully connected layer to fulfill the construction of convolutional neural network. This paper use $X = [v_1, v_2, \cdots v_l]$ to denote an input vector sequence that corresponds to the embedded amino acids or the outputs of a previous neural layer.

A convolution layer applies a weight-sharing kernel $M_c \in R^{b\times k}$ to generate a k-dimension latent vector h_t^1 from a window $v_{t:t+b-1}$ of the input vector sequence X :

$$h_t^{(1)} = Conv(v_{t:t+b-1}) = M_c v_{t:t+b-1} + b_c$$

for which b is the kernel size, and b_c is a bias vector. The convolution layer applies the kernel as a sliding window to produce a sequence of latent vectors

$$H^{(1)} = [h_1^{(1)}, h_2^{(1)}, \cdots, h_{l-b+1}^{(1)}]$$

where each latent vector combines the local features from each h-gram of the input sequence. The n-max-pooling mechanism is applied to every consecutive n-length subsequence (i.e. non-overlapped n-strides) of the convolution outputs, which takes the maximum value along each dimension j by $h_{ij}^{(2)} = \max(h_{i:n+i-1,j}^{(1)})$. Finally three fully connected layers are added to the convolutional neural network model.

13. Recurrent neural network (RNN)

Recurrent neural network can in principle use their feedback connections to store representations, which is effective to process the sequence data. Especially, long short term memory (LSTM) paly an important role in many areas. LSTM provides a different way to compute the hidden states.

The $k\text{-}th$ LSTM unit consists of an input gate i_k, forget gate f_k, an output gate o_k, a memory cell c_k and hidden state h_k. The input to this unit is a n-dimensional input vector x_k, the previous hidden state h_{k1}, and the memory cell h_{k1}, and computes the new hidden states as follows:

$$\begin{aligned}
i_k &= \sigma(W_1^{(i)} x_k + W_2^{(i)} h_{k-1} + b^{(i)}) \\
f_k &= \sigma(W_1^{(f)} x_k + W_2^{(f)} h_{k-1} + b^{(f)}) \\
o_k &= \sigma(W_1^{(o)} x_k + W_2^{(o)} h_{k-1} + b^{(o)}) \\
u_k &= \tanh(W_1^{(u)} x_k + W_2^{(u)} h_{k-1} + b^{(u)}) \\
c_k &= i_k \odot u_k + f_k \odot c_{k-1} \\
h_k &= o_k \odot \tanh(c_k)
\end{aligned}$$

where $\sigma, \odot$ denote the sigmoid function and element-wise multiplication, respectively. The W_1, W_2 and b are the weight-metrics and bias vectors, respectively. So the LSTM hidden unit can be described as :

$$h_k, c_k = LSTM(x_k, c_{k-1}, h_{k-1})$$

After the LSTM layer, we add three fully connected layers to perform the binary or multi-class problems.