User Manual for *iFeatureOmega*

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1. Introduction

iFeatureOmega is a comprehensive platform for generating, analyzing and visualizing more than 170 representations for biological sequences, 3D structures and ligands. To the best of our knowledge, *iFeatureOmega* supplies the largest number of feature extraction and analysis approaches for most molecule types compared to other pipelines. Three versions (i.e. *iFeatureOmega-Web*, *iFeatureOmega-GUI* and *iFeatureOmega-CLI*) of *iFeatureOmega* have been made available to cater to both experienced bioinformaticians and biologists with limited programming expertise. *iFeatureOmega* also expands its functionality by integrating 15 feature analysis algorithms (including ten cluster algorithms, three dimensionality reduction algorithms and two feature normalization algorithms) and providing nine types of interactive plots for statistical features visualization (including histogram, kernel density plot, heatmap, boxplot, line chart, scatter plot, circular plot, protein three dimensional structure plot and ligand structure plot). *iFeatureOmega* is an open-source platform for academic purposes. The web server can be accessed through http://ifeatureomega.erc.monash.edu and the GUI and CTL versions can be download at: https://github.com/Superzchen/iFeatureOmega-GUI and https://github.com/Superzchen/iFeatureOmega-CLI, respectively.

2. Installing and running *iFeatureOmega*

Installation

iFeatureOmega is an open-source Python-based toolkit, which operates in the Python environment (Python version 3.7.4) and can run on multiple operating systems (e.g. Windows, Mac, and Linux). Prior to installing and running *iFeatureOmega*, all the third-party packages should be installed in the Python environment, including Biopython (v.1.78), Pandas (v.1.3.4), Numpy (v.1.21.4), NetworkX (v.2.5), RDKit (v. 2020.03.3.0), Matplotlib (v.3.4.3), DSSP (v.3.0.0) and MSMS (v.2.6.1). The GUI of *iFeatureOmega-GUI* was implemented by PyQt5 (v.5.9.2). For convenience, we strongly recommend users install the Anaconda Python environment in their local computers, which can be freely downloaded from https://www.anaconda.com/. The detailed steps of installing these dependencies are provided as follows:

Step 1. Download and install the anaconda platform:

- Download from: https://repo.anaconda.com/archive/ and download the software package (version: 2020.02) according to your operating system.

Step 2. Install anaconda environment on your own machine and make sure the "Add Anaconda to the system PATH environment variable" option is selected when installation.

Step 3. Install biopython, rdkit, dssp, msms and networkx

```
$ conda install biopython
$ conda install -c rdkit rdkit
$ conda install -c saliab dssp
$ conda install -c bioconda msms
$ conda install networkx
```

Note: dssp and msms can not be installed in Windows system.

Step 4. Install *iFeatureOmega* by pip:

- *For GUI version:*

```
$ pip3 install iFeatureOmegaGUI
```

- *For CLI version:*

```
$ pip3 install iFeatureOmegaCLI
```

Running for GUI version

To run *iFeatureOmega-GUI*:

```
$ python
>>> from iFeatureOmegaGUI import runiFeatureOmegaGUI
>>> runiFeatureOmegaGUI()
```

Once *iFeatureOmega* has started, the interface will show as demonstrated in **Figure 1**.

Running for CLI version

The CLI version of *iFeatureOmega* can be import as a python package as follows:

```
$ python
>>> import iFeatureOmegaCLI
>>> dna = iFeatureOmegaCLI.iDNA('<abs_path>/data_examples/DNA_sequences.txt')
>>> dna.import_parameters('<abs_path>/parameters/DNA_parameters_setting.json')
>>> dna.get_descriptor('Kmer')
```

Note: <abs_path> indicates the absolute path of iFeatureOmegaCLI package.

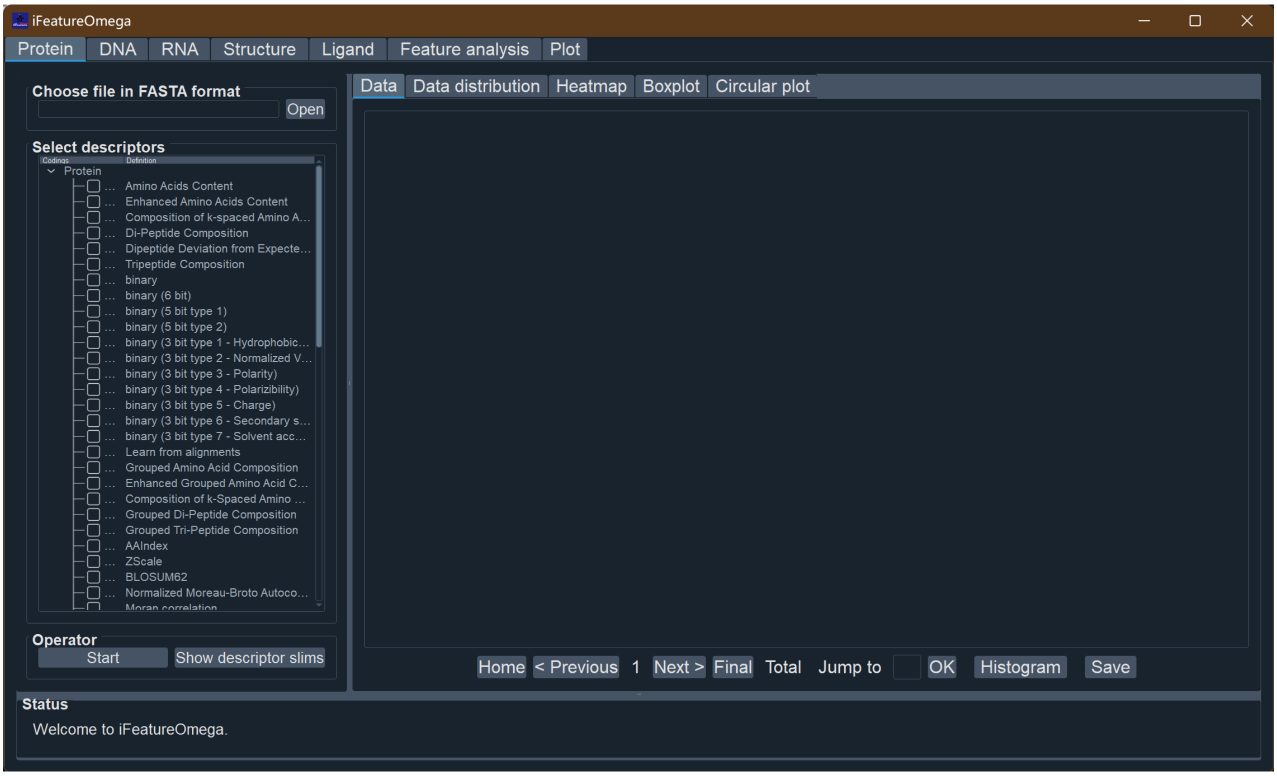


Figure 1. The main interface of *iFeatureOmega-GUI*.

3. The workflow of *iFeatureOmega-GUI*

Here we provide a step-by-step user instruction to demonstrate the workflow of *iFeatureOmega-GUI* toolkit by running the examples provided in the “examples” directory. Seven tab-widgets are included in the GUI-based version of *iFeatureOmega* (**Figure 1**), and different functionalities are accessible by switching among the tabs. (**Table 1**).

Table 1. Functions of the seven tab-widgets in *iFeatureOmega*.

Tab-widgets		Function
Protein	1)	Extraction of 65 different types of feature descriptors for protein sequences.
	2)	Data visualization (Histogram and kernel density plot, heatmap, boxplot and circular plot)
DNA	1)	Extraction of 43 different types of feature descriptors for DNA sequences.
	2)	Data visualization (Histogram and kernel density plot, heatmap, boxplot and circular plot)
RNA	1)	Extraction of 33 different types of feature descriptors for RNA sequences.
	2)	Data visualization (Histogram and kernel density plot, heatmap, boxplot and circular plot)
Structure	1)	Extraction of 14 different types of feature descriptors for protein structures.
	2)	Data visualization (Histogram and kernel density plot, heatmap, boxplot and circular plot)
Ligand	1)	Extraction of 18 different types of feature descriptors for protein structures.
	2)	Data visualization (histogram and kernel density plot, heatmap, Boxplot and circular plot)

Feature analysis	1)	15 feature analysis algorithms (ten feature clustering, three dimensionality reduction, and two feature normalization algorithms).
	2)	Data visualization (Scatter plot, kernel density plot)
Plot	1)	Generate histogram and kernel density plot, boxplot, heatmap, scatter plot and circular plot by using user-defined data.

4. The workflow of *iFeatureOmega-CLI*

There were seven main python class in *iFeatureOmega-CLI*, including "iProtein", "iDNA", "iRNA", "iStructure" and "iLigand", which are feature extraction methods for protein sequences, DNA sequences, RNA sequences, protein structures and ligand molecules, respectively. "iAnalysis" class is also equipped for feature analysis, while "iPlot" class is used to generate the corresponding plots.

5. The input and output format of *iFeatureOmega*

To calculate features for protein, DNA and RNA sequences, a set of DNA, RNA or protein sequences in FASTA format is used as input. To calculate analyze protein structural features, users need to provide the protein structure of interest, which must comply with the PDB(1) (https://www.rcsb.org/) format by either providing a PDB accession or uploading your own structure file (i.e., in PDB or CIF format). For analyzing ligands, candidate ligand molecules can be provided with SMILES format or SDF format.

6. *iFeatureOmega-GUI* usage

Seven tab-widgets are included and different functionalities are accessible by switching among tabs.

DNA/RNA/Protein sequences feature descriptor extraction

Taking feature descriptor extraction of DNA sequences as an example:

Step 1: Open the sequences file

Click the "Open" button and select the DNA sequences file (e.g. "DNA_sequences.txt" in "data" directory of *iFeatureOmega* package).

Step 2: Select the feature descriptor and configure the descriptor parameters

Select one or more feature descriptor(s) and set the corresponding parameters with the parameter dialog box.

Step 3: Run the program

Click the "Start" button to calculate the descriptor features. The feature encoding and graphical presentation will be displayed in the "Data", "Data distribution", "Heatmap", "Boxplot" and "Circular plot" panels, respectively (**Figure 2**).

Step 4: Save the results and plots

Click the "Save" button to save the generated feature encodings. *iFeatureOmega* supports four formats for saving the calculated features, including LIBSVM, CSV, TSV, and WEKA format, so as to facilitate direct use of the features in the following analysis, prediction model construction and the third-party computational tools, such as scikit-learn and WEKA. In addition, *iFeatureOmega* provides the TSV1 format, which includes the sample and feature labels. All the plots in *iFeatureOmega* are generated by the matplotlib library and can be saved to a variety of image formats, such as PNG, JPG, PDF, TIFF etc).

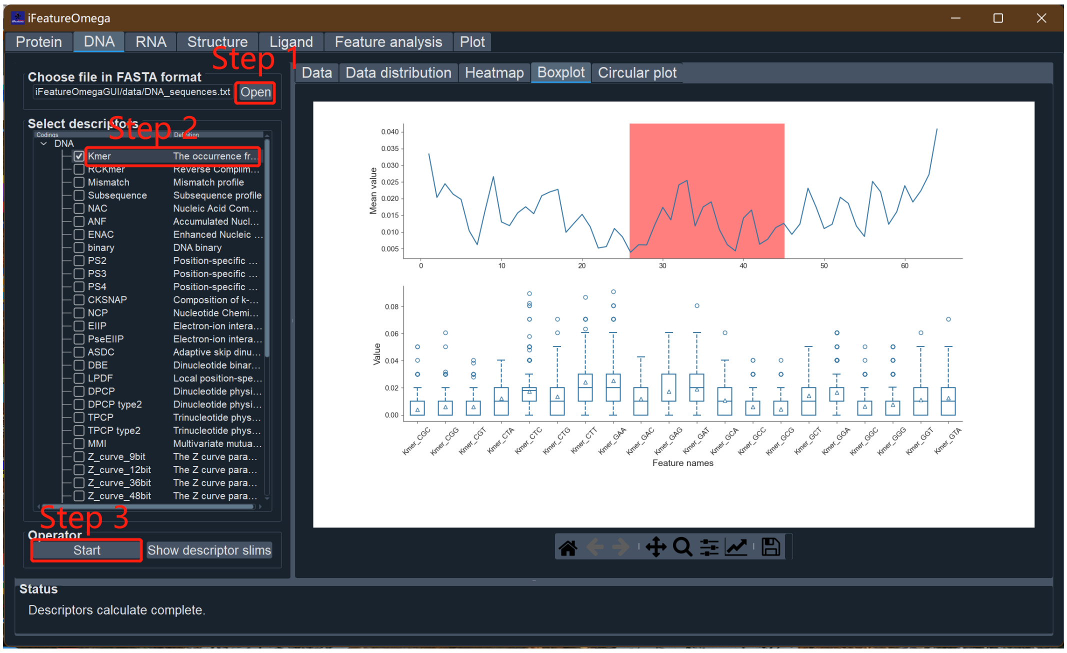


Figure 2. An example of extracting feature descriptor.

Protein structure feature descriptor extraction

Step 1: Open a PDB file or enter PDB ID

Click the “Open” button and select a PDB file (e.g. “1iir.pdb” in “data” directory of *iFeatureOmega* package), or enter a PDB ID (e.g. “1iir”) and then click the “Download” button, then the program will download the PDB file automatically.

Step 2: Select the feature descriptor type and run the program.

Please refer to the steps 2-4 in “DNA/RNA/Protein sequences feature descriptor extraction”.

Ligands feature descriptor extraction

Step 1: Open a file with SMILES format

Click the “Open” button and select a file (e.g. “Chemical_SMILES.txt” in “data” directory of *iFeatureOmega* package). In this file, each row is a molecule with SMILES format (**Figure 3**).

Step 2: Select the feature descriptor type and run the program.

Please refer to the steps step 2-4 in “DNA/RNA/Protein sequences feature descriptor extraction”.

```
CN(C)C(=O)c1cnn(-c2nc(N)c3ncn(C4OC(CO)C(O)C4O)c3n2)c1
OC1C(O)C(n2cnc3c(NCc4cccc5ccccc45)nc(Cl)nc32)C2CC12
Cc1ccc(-c2nc(NC(=O)CN3CCN(C)CC3)cc(-n3nccc3C)n2)o1
Cc1nc(C(=O)NCc2ccccn2)cc(-c2ccc(C)o2)n1
CCNC(=O)C1OC(n2cnc3c(NCC(c4ccccc4)c4ccccc4)nc(C(=O)NCCNC(=O)NCCN4CCc5ccccc5C4)nc32)C(O)C1O
CN(CCc1ccc(F)cc1)c1cc2nc(-c3ccco3)nn2c(N)n1
CCNc1cc2nc(NCc3cccnc3)nc(C(=O)c3cccs3)c2s1
CCCn1c(=O)c2nc(-c3ccc(OCC(=O)Nc4ccc([N+](=O)[O-])cc4)cc3)[nH]c2n(CCC)c1=O
CCN(CC)c1ncnc2sc(Nc3ccccc3)nc12
CCCn1cc2c(nc(NC(=O)Nc3ccc([N+](=O)[O-])cc3)n3nc(-c4ccco4)nc23)n1
Cc1ccc(OCC(=O)Nc2cc(-c3nccs3)nc(-c3ccc(C)o3)n2)cc1
C#CC1(O)CCC2C3CCc4cc(O)ccc4C3CCC21C
CCn1cc2c(nc(NC(=O)Cc3ccsc3)n3nc(-c4ccco4)nc23)n1
COCCCn1c(NC(=O)c2ccccc2Cl)nc2cc(C(=O)NCc3cccc(OC)c3)ccc21
Cc1ccccc1Cn1nnc2c(-c3ccco3)nc(N)nc21
CCCCCN(CCCCC)c1nc2nn(C)cc2c2nc(-c3ccco3)nn12
CCNC(=O)C1OC(n2cnc3c(NCCNc4ccc([N+](=O)[O-])c5nonc45)ncnc32)C(O)C1O
Cn1cc2c(nc(NCCCNC(=S)Nc3ccc(C4c5ccc(O)cc5OC5=CC(=O)C=CC54)c(C(=O)O)c3)n3nc(-c4ccco4)nc23)n1
CNC(=O)C1OC(n2cnc3c(NCc4cccc(Cl)c4)nc(N)nc32)C(O)C1O
```

Figure 3. An example of the input file for ligand feature descriptor extraction.

Feature analysis

iFeatureOmega provides multiple options to facilitate feature analysis, including ten feature clustering, three dimensionality reduction and two feature normalization (**Table S5** in our paper).

The “Feature analysis” panel is used to deploy the feature analysis function. Taking the clustering as an example:

Step 1: Load data

There are two ways to load the data for analysis: 1) open a coding file and 2) select the data generated from other panels. Here we load the data from file. Click the “Open [without sample label]” button and open the “data_without_labels.csv” in the “data” directory.

Step 2: Select the analysis algorithm and set the corresponding parameter(s)

Select “kmeans” clustering algorithm and set the cluster number as 3.

Step 3: Run the program

Click the “Start” button to start the analysis progress. The clustering result and graphical presentation will be displayed in the “Cluster/Dimensionality reduction result” and “Scatter plot” panels, respectively. Here, we used the scatter plot to display the clustering result.

Step 4: Save the result and plot

Click the “Save” button to save the generated clustering results (**Figure 4**).

Figure 4. An example of implement the clustering algorithm using *iFeatureOmega*.

For feature dimensionality reduction analysis, *iFeatureOmega* also support data with sample labels (i.e. The sample labels should be integers in the first column of the data file):

Step 1: Load data with sample labels for dimensionality reduction analysis

Click the “Open [with sample label]” button and open the “data_with_labels.csv” in the “data” directory.

Step 2: Select the analysis algorithm and set the corresponding parameter(s)

Select “PCA” algorithm and set the cluster number as 2.

Step 3: Run the program

Click the “Start” button to start the analysis progress. The dimensionality reduction result and graphical presentation will be displayed in the “Cluster/Dimensionality reduction result” and “Scatter plot” panels, respectively. Each dot represents a sample, and the color of the dots corresponds to the sample category (i.e. Samples with the same label have the same color).

Step 4: Save the result and plot

Click the “Save” button to save the generated clustering results.

Plot with user-defined data

For convenience, *iFeatureOmega* allows generate plots with user-defined data. Take the box plot as an example:

Step 1: Load data

Click the “Open [with sample label]” button and open the “data_with_labels.csv” in the “data” directory.

Step 2: Select plot type

Select “Box plot”.

Step 3: Run the program

Click the “Draw plot” button to start the analysis progress. The plot will be displayed in the “Plot viewer” panel.

Figure 5. An example of boxplot generated by *iFeatureOmega*.

7. *iFeatureOmega-CLI* usage

The CLI-based version, which was developed and implemented as a python package. This version accepts the JSON format configuration file, allowing users to conveniently specify the parameter values of individual features and analysis algorithms.

The classes in iFeatureOmega-CLI are:

- *iDNA*: extract feature descriptors for DNA sequences
- *iRNA*: extract feature descriptors for RNA sequences
- *iProtein*: extract feature descriptors for protein sequences
- *iLigand*: extract feature descriptors for chemical molecules.
- *iStructure*: extract feature descriptors for protein structure
- *iAnalysis*: implement feature analysis for extracted feature descriptors
- *iPlot*: generate various statistical plots for generated feature descriptors

Extract feature descriptors

In each class, we provide the example code, users can run the following command view the example code for “iDNA” class.

```
$ python
>>> import iFeatureOmegaCLI
>>> print(iFeatureOmegaCLI.iDNA.__doc__)
```

Take the DNA feature descriptors extraction as an example:

Step 1: running python and import iFeatureOmega

Run python from the command line.

Step 2: import iFeatureOmega

```
$ python
>>> import iFeatureOmegaCLI
```

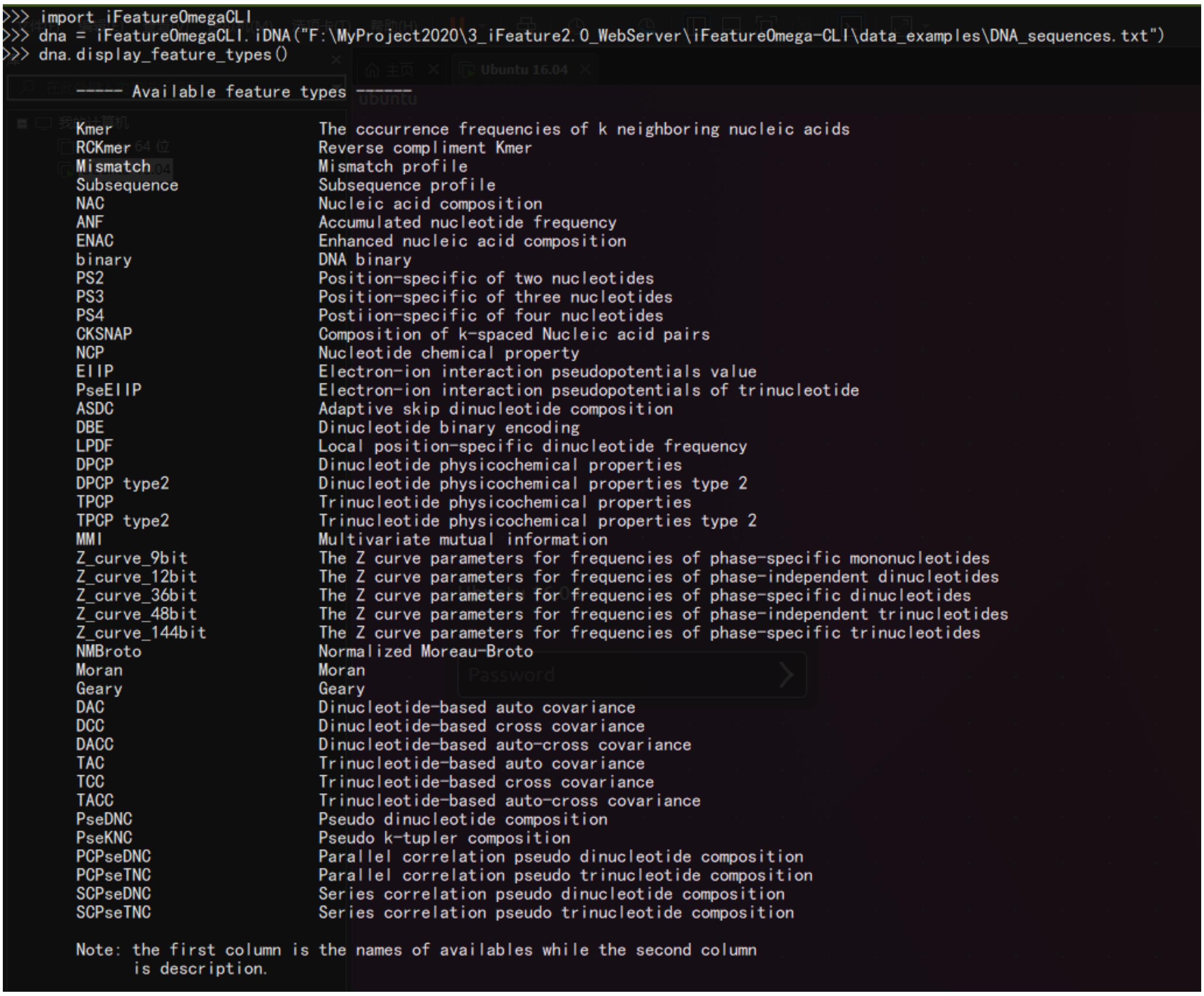
Step 3: Load data file

```
>>> dna = iFeatureOmegaCLI.iDNA("<abs_path>/data_examples/DNA_sequences.txt")
```

“iDNA” is used to extract feature descriptors for DNA sequences, and the class should be initialized with the sequence file (i.e. “<abs_path>/data_examples/DNA_sequences.txt” in this example, <abs_path> indicates the absolute path of “data_examples” directory.)

Step 4: Display the available feature descriptor types

For “iDNA”, “iRNA”, “iProtein”, “iLigand” and “iStructure”, each of these classes has a function named “display_feature_types”, which is used to display the names of available feature extraction methods (**Figure 6**).



```
>>> import iFeatureOmegaCLI
>>> dna = iFeatureOmegaCLI.iDNA("F:\MyProject2020\3_iFeature2.0_WebServer\iFeatureOmega-CLI\data_examples\DNA_sequences.txt")
>>> dna.display_feature_types()

        ----- Available feature types ------

        Kmer                          The cccurrence frequencies of k neighboring nucleic acids
        RCKmer                        Reverse compliment Kmer
        Mismatch                      Mismatch profile
        Subsequence                   Subsequence profile
        NAC                           Nucleic acid composition
        ANF                           Accumulated nucleotide frequency
        ENAC                          Enhanced nucleic acid composition
        binary                        DNA binary
        PS2                           Position-specific of two nucleotides
        PS3                           Position-specific of three nucleotides
        PS4                           Postiion-specific of four nucleotides
        CKSNAP                        Composition of k-spaced Nucleic acid pairs
        NCP                           Nucleotide chemical property
        EIIP                          Electron-ion interaction pseudopotentials value
        PseEIIP                       Electron-ion interaction pseudopotentials of trinucleotide
        ASDC                          Adaptive skip dinucleotide composition
        DBE                           Dinucleotide binary encoding
        LPDF                          Local position-specific dinucleotide frequency
        DPCP                          Dinucleotide physicochemical properties
        DPCP type2                    Dinucleotide physicochemical properties type 2
        TPCP                          Trinucleotide physicochemical properties
        TPCP type2                    Trinucleotide physicochemical properties type 2
        MMI                           Multivariate mutual information
        Z_curve_9bit                  The Z curve parameters for frequencies of phase-specific mononucleotides
        Z_curve_12bit                 The Z curve parameters for frequencies of phase-independent dinucleotides
        Z_curve_36bit                 The Z curve parameters for frequencies of phase-specific dinucleotides
        Z_curve_48bit                 The Z curve parameters for frequencies of phase-independent trinucleotides
        Z_curve_144bit                The Z curve parameters for frequencies of phase-specific trinucleotides
        NMBroto                       Normalized Moreau-Broto
        Moran                         Moran
        Geary                         Geary
        DAC                           Dinucleotide-based auto covariance
        DCC                           Dinucleotide-based cross covariance
        DACC                          Dinucleotide-based auto-cross covariance
        TAC                           Trinucleotide-based auto covariance
        TCC                           Trinucleotide-based cross covariance
        TACC                          Trinucleotide-based auto-cross covariance
        PseDNC                        Pseudo dinucleotide composition
        PseKNC                        Pseudo k-tupler composition
        PCPseDNC                      Parallel correlation pseudo dinucleotide composition
        PCPseTNC                      Parallel correlation pseudo trinucleotide composition
        SCPseDNC                      Series correlation pseudo dinucleotide composition
        SCPseTNC                      Series correlation pseudo trinucleotide composition

        Note: the first column is the names of availables while the second column
              is description.
```

Figure 6. A snapshot of the available feature extraction methods in "iDNA" class.

Step 5: Extract feature descriptor

We use the "get_descriptor" function to extract the feature descriptors. Take the "Kmer" feature descriptor as an example (**Figure 7**):

```
>>> status = dna.get_descriptor("Kmer")
>>> print(dna.encodings)
                 Kmer_AAA  Kmer_AAC  Kmer_AAG  Kmer_AAT  Kmer_ACA  ...  Kmer_TGT  Kmer_TTA  Kmer_TTC  Kmer_TTG  Kmer_TT
T
AT1G22840.1_532  0.040404  0.010101  0.000000  0.050505  0.000000  ...  0.020202  0.030303  0.020202  0.050505  0.14141
4
AT1G44000.1_976  0.020202  0.000000  0.020202  0.010101  0.030303  ...  0.050505  0.020202  0.060606  0.020202  0.10101
0
AT1G09770.1_2698 0.030303  0.010101  0.040404  0.000000  0.020202  ...  0.010101  0.020202  0.010101  0.050505  0.05050
5
AT1G09645.1_586  0.020202  0.010101  0.020202  0.010101  0.010101  ...  0.060606  0.030303  0.010101  0.040404  0.06060
6
AT1G22850.1_1097 0.050505  0.020202  0.040404  0.010101  0.010101  ...  0.010101  0.000000  0.000000  0.040404  0.03030
3
...                   ...       ...       ...       ...       ...  ...       ...       ...       ...       ...       ..
.
AT5G22920.1_138  0.090909  0.020202  0.050505  0.030303  0.010101  ...  0.010101  0.010101  0.020202  0.030303  0.04040
4
AT5G12960.1_581  0.020202  0.030303  0.020202  0.010101  0.000000  ...  0.010101  0.010101  0.010101  0.020202  0.03030
3
AT5G11230.1_249  0.030303  0.000000  0.010101  0.020202  0.000000  ...  0.010101  0.020202  0.020202  0.010101  0.03030
3
AT5G32481.1_4454 0.060606  0.020202  0.070707  0.020202  0.000000  ...  0.000000  0.010101  0.000000  0.000000  0.00000
0
AT5G59305.1_468  0.123288  0.041096  0.013699  0.054795  0.041096  ...  0.041096  0.027397  0.013699  0.013699  0.00000
0

[300 rows x 64 columns]
```

Figure 7. A snapshot of DNA feature descriptor extraction.

The calculated feature descriptors will be stored in the "encodings" variable of the "iDNA" class, which is a pandas dataframe.

Step 6: Save the feature descriptor values to file

Four functions including "to_csv", "to_tsv", "to_svm" and "to_arff", are provided to save the calculated feature descriptor values to the "CSV", "TSV", "SVM" and "arff", respectively.

```
>>> dna.to_csv("Kmer.csv", index=False, header=False)
```

Feature analysis

Run the following command to view the example code for feature analysis (**Figure 8**):

```
>>> print(iFeatureOmegaCLI.iAnalysis.__doc__)
```

```
# Running examples:

>>> import iFeatureOmegaCLI
>>> import pandas as pd

# read data to pandas DataFrame
>>> df = pd.read_csv('data_examples/data_without_labels.csv', sep=',', header=None, index_col=None)

# Initialize a instance of iAnalysis
>>> data = iFeatureOmegaCLI.iAnalysis(df)

# kmeans clustering
>>> data.kmeans(nclusters=3)
>>> data.cluster_result

# other clustering algorithm
>>> data.MiniBatchKMeans(nclusters=2)   # Mini-Batch K-means
>>> data.GM()                           # Gaussian mixture
>>> data.Agglomerative()                # Agglomerative
>>> data.Spectral()                     # Spectral
>>> data.MCL()                          # Markov clustering
>>> data.hcluster()                     # Hierarchical clustering
>>> data.APC()                          # Affinity propagation clustering
>>> data.meanshift()                    # Mean shift
>>> data.DBSCAN()                       # DBSCAN

# save cluster result
>>> data.cluster_to_csv(nclusters=2)

# dimensionality reduction
>>> data.t_sne(n_components=2)          # t-distributed stochastic neighbor embedding
>>> data.PCA(n_components=2)            # Principal component analysis
>>> data.LDA(n_components=2)            # Latent dirichlet allocation

# save dimensionality reduction result
>>> data.dimension_to_csv(file="dimension_reduction_result.csv")

# feature normalization
>>> data.ZScore()                       # ZScore
>>> data.MinMax()                       # MinMax

# save feature normalization result
>>> data.normalization_to_csv(file="feature_normalization_result.csv")
```

Figure 8. A snapshot of running example for "iAnalysis" class.

Step 1: Open a data file

```
>>> import iFeatureOmegaCLI
>>> import pandas as pd

# read data to pandas DataFrame
>>> df = pd.read_csv('data_examples/data_without_labels.csv', sep=',', header=None,
index_col=None)
```

Step 2: Create an instance for "iAnalysis" class

```
# Initialize an instance of iAnalysis
>>> data = iFeatureOmegaCLI.iAnalysis(df)
```

Step 3: Implement an analysis algorithm and save analysis result

```
>>> data.kmeans(nclusters=3)           # k-means clustering
>>> data.MiniBatchKMeans(nclusters=2)   # Mini-Batch K-means
>>> data.GM()                          # Gaussian mixture
>>> data.Agglomerative()               # Agglomerative
>>> data.Spectral()                    # Spectral
>>> data.MCL()                         # Markov clustering
>>> data.hcluster()                    # Hierarchical clustering
>>> data.APC()                         # Affinity propagation clustering
>>> data.meanshift()                   # Mean shift
>>> data.DBSCAN()                      # DBSCAN

# save cluster result
>>> data.cluster_to_csv(nclusters=2)

# dimensionality reduction
>>> data.t_sne(n_components=2)         # t-distributed stochastic neighbor embedding
>>> data.PCA(n_components=2)           # Principal component analysis
>>> data.LDA(n_components=2)           # Latent dirichlet allocation

# save dimensionality reduction result
>>> data.dimension_to_csv(file="dimension_reduction_result.csv")

# feature normalization
>>> data.ZScore()                      # ZScore
>>> data.MinMax()                      # MinMax

# save feature normalization result
>>> data.normalization_to_csv(file="feature_normalization_result.csv")
```

Data visualization

Run the following command to view the running code for data visualization (**Figure 9**):

```
>>> print(iFeatureOmegaCLI.iPlot.__doc__)
```

```
# Running examples:

>>> import iFeatureOmegaCLI
>>> import pandas as pd

# read data to pandas DataFrame
>>> df = pd.read_csv('data_examples/data_with_labels.csv', sep=',', header=None, index_col=None)

# Initialize an instance of iPlot
>>> myPlot = iFeatureOmegaCLI.iPlot(df, label=True)

# scatter plot
myPlot.scatterplot(method="PCA", xlabel="PC1", ylabel="PC2", output="scatterplot.pdf")

# histogram and kernel density
myPlot.hist()

# headmap
myPlot.heatmap(samples=(0, 50), descriptors=(0, 100), output='heatmap.pdf')

# line chart
myPlot.line(output='linechart.pdf')

# boxplot
myPlot.boxplot(descriptors=(0, 10), output='boxplot.pdf')
```

Figure 9. A snapshot of running example for "iPlot" class.

Step 1: Open a data file

```
>>> df = pd.read_csv('data_examples/data_with_labels.csv', sep=',', header=None,
index_col=None)
```

Step 2. Initialize an instance of "iPlot"

```
>>> myPlot = iFeatureOmegaCLI.iPlot(df, label=True)
```

Note: The first column of the data file we be taken as sample labels when label is True.

Step 3. Scatter plot

```
# scatter plot
myPlot.scatterplot(method="PCA", xlabel="PC1", ylabel="PC2", output="scatterplot.pdf")
```

For scatter plot, the dimensionality reduction algorithm was used to decompose the data to two-dimensional space. And the dimension reduced data will be plotted as points in a plane. Three dimensionality reduction algorithms can be selected (i.e. PCA, t_sne and LDA).

The parameters of "scatterplot":

- *method*: dimensionality reduction algorithm (select from PCA, t_sne, LDA)
- *xlabel*: the name of abscissa label of scatter plot
- *ylabel*: the name of ordinate label of scatter plot
- *output*: the name of output file

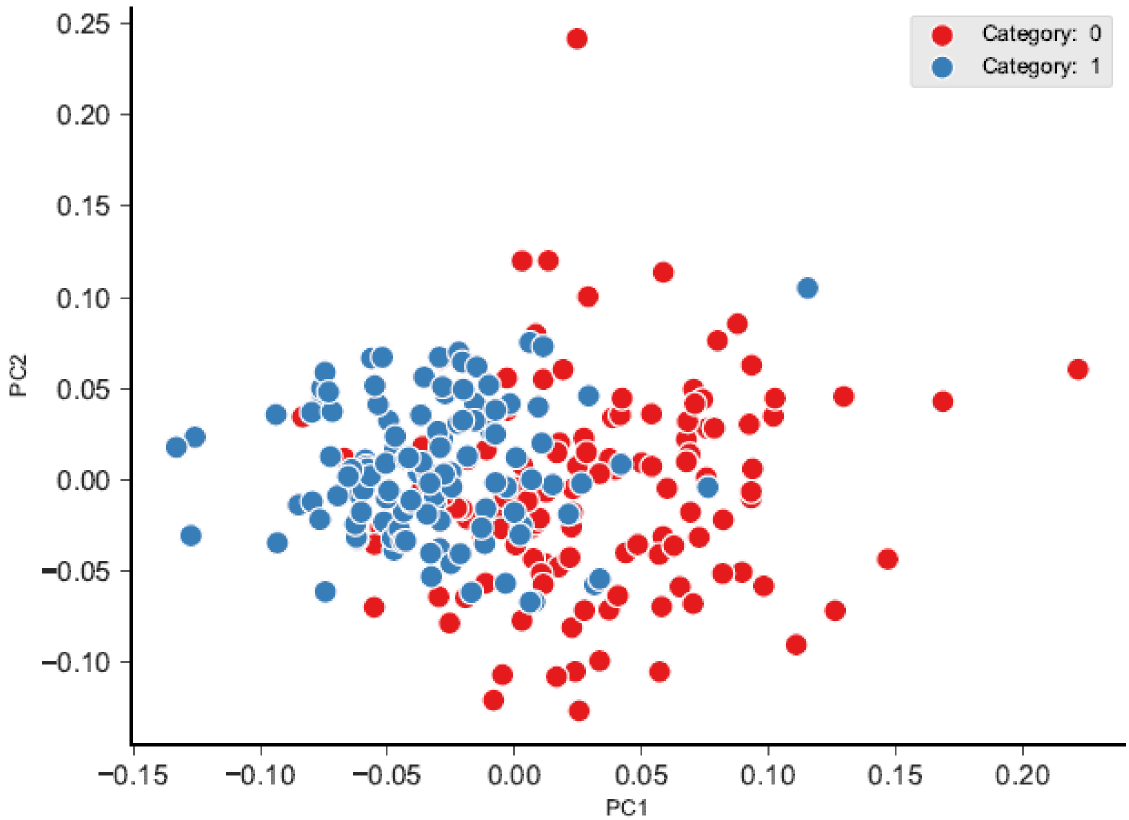


Figure 10. An example of scatter plot.

Step 4. *Histogram and kernel density plot*

```
# histogram and kernel density
myPlot.hist()
```

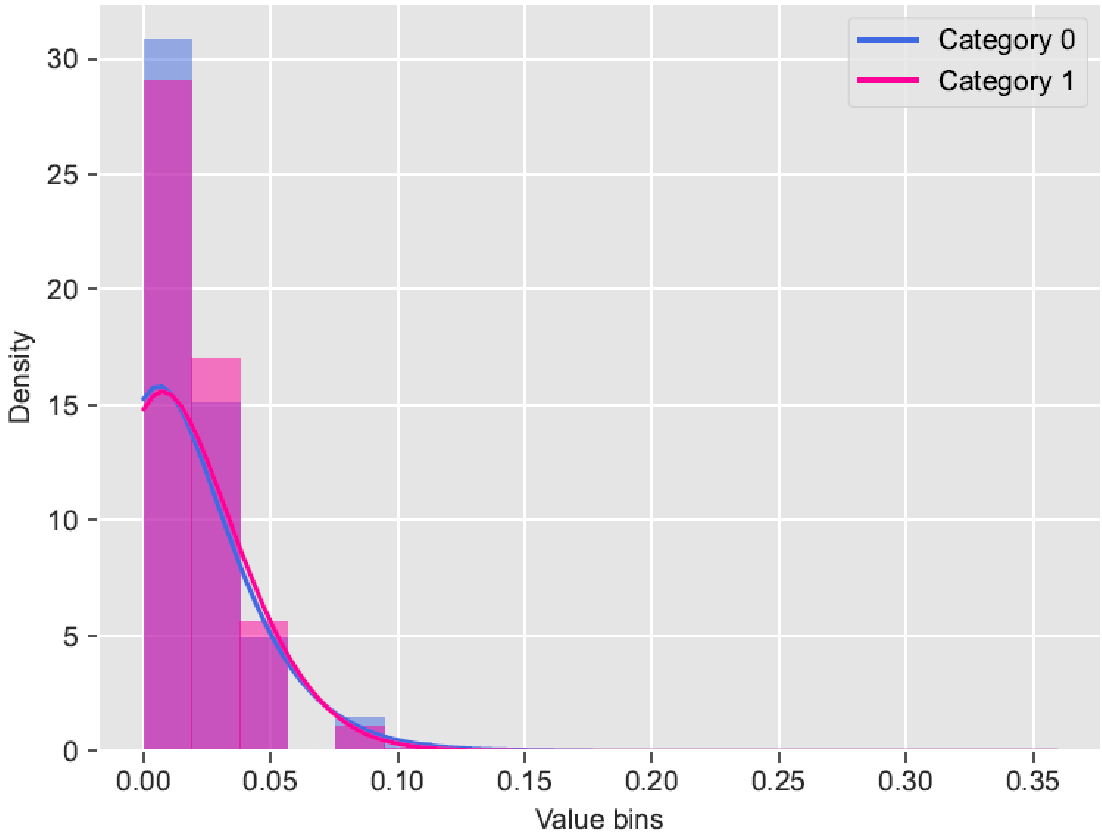


Figure 11. An example of histogram and kernel density plot.

Step 5. Heatmap

```
# heatmap
myPlot.heatmap(samples=(0, 50), descriptors=(0, 100), output='heatmap.pdf')
```

The parameters of "heatmap":

- *samples*: the range of displayed samples (i.e. rows of the data matrix)
- *descriptors*: the range of displayed descriptors (i.e. columns of the data matrix)
- *output*: the name of output file

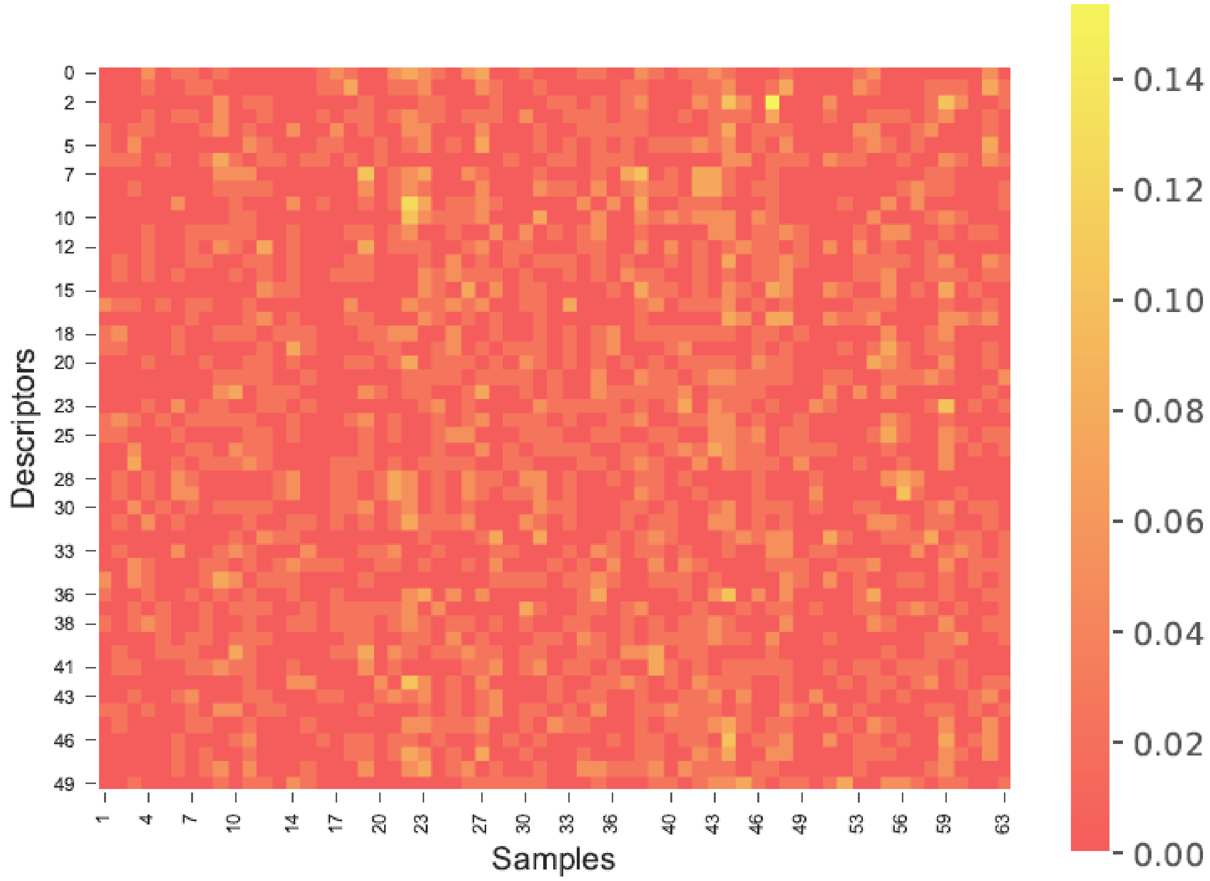


Figure 12. An example of heatmap.

Step 6. Line chart

```
# line chart
myPlot.line(output='linechart.pdf')
```

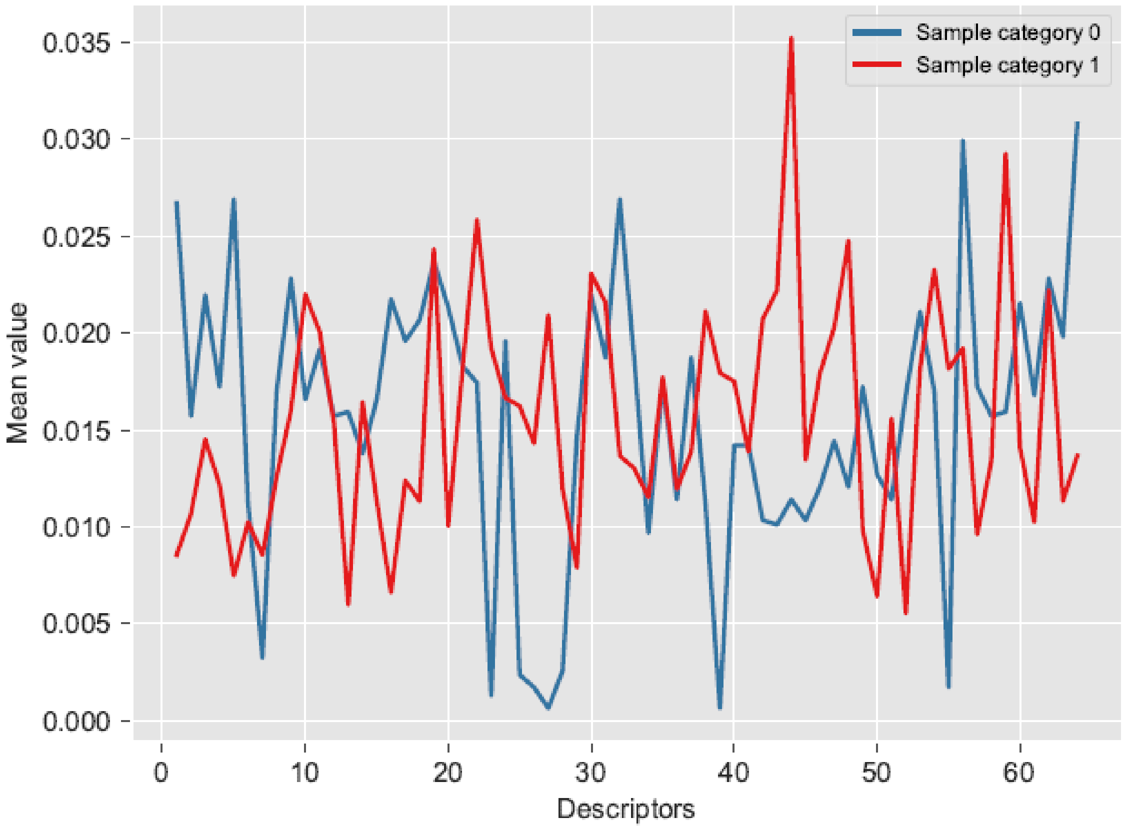


Figure 13. An example of line chart.

Step 7. Boxplot

```
# boxplot
myPlot.boxplot(descriptors=(0, 10), output='boxplot.pdf')
```

The parameters of "boxplot":

- *descriptors*: the range of displayed descriptors (i.e. columns of the data matrix)

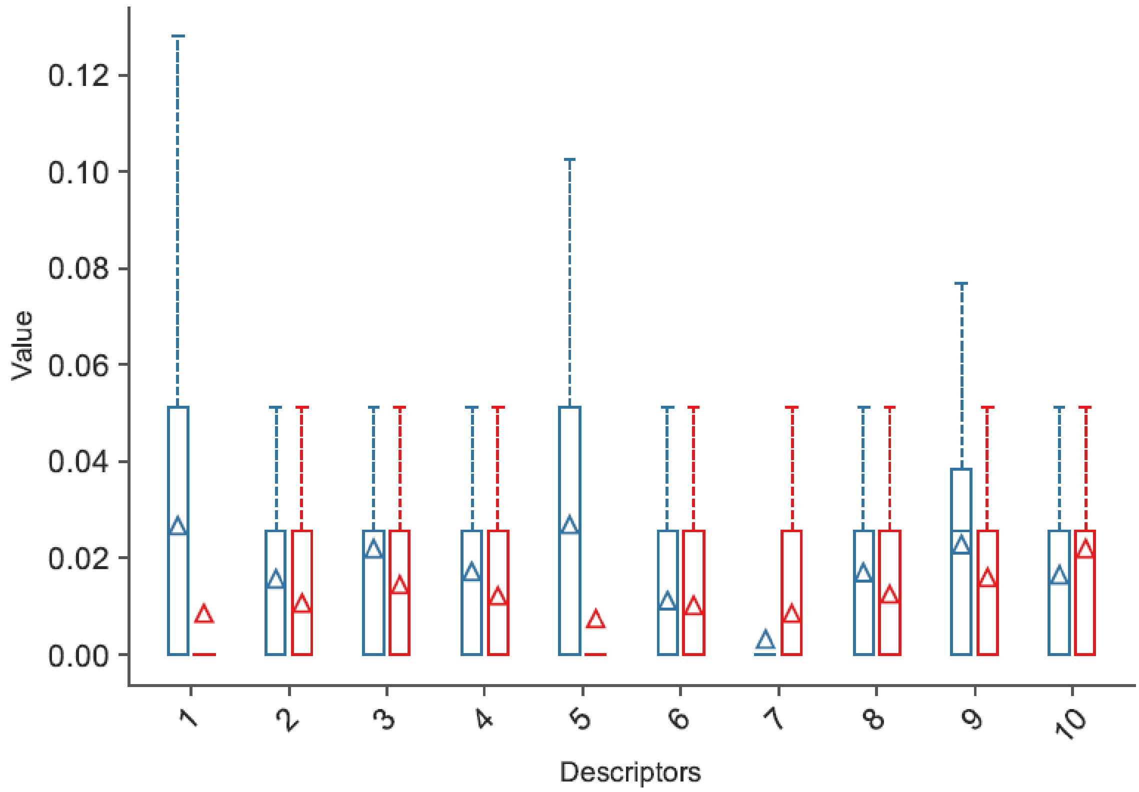
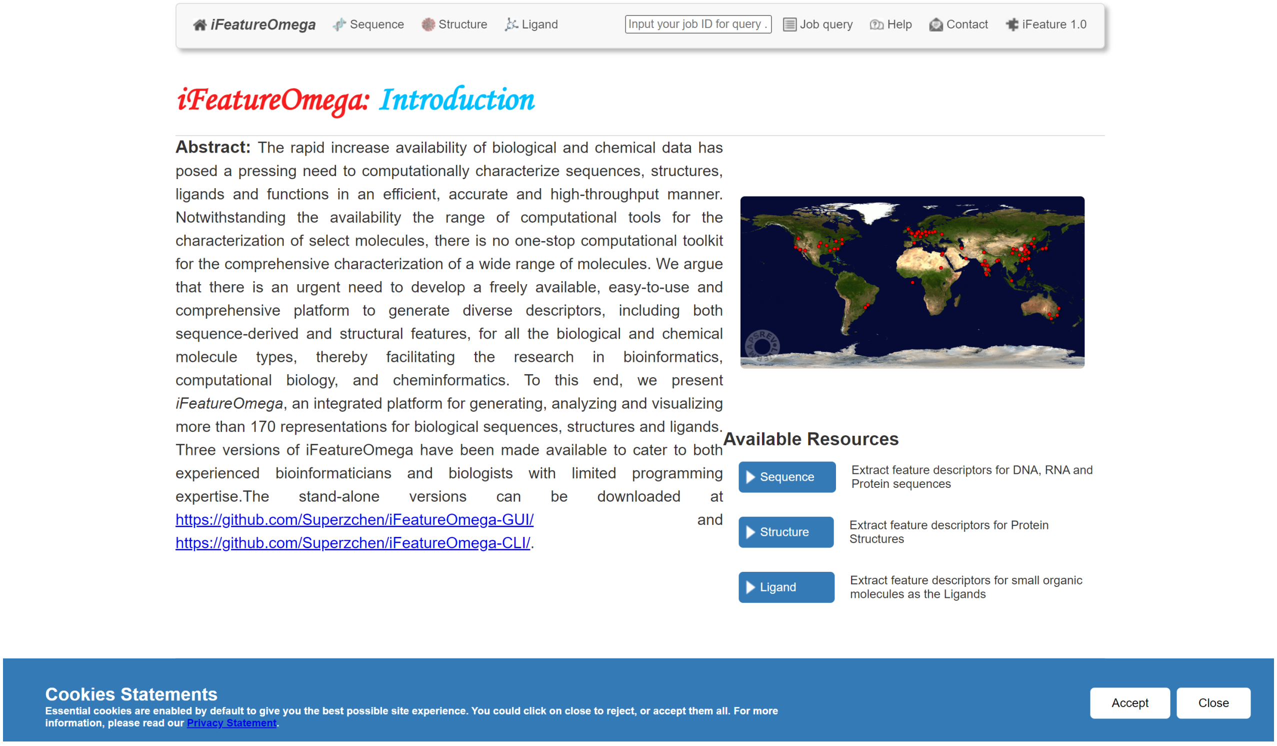


Figure 14. An example of boxplot.

8. Online web server

The *iFeatureOmega* server is freely accessible at https://ifeatureomega.erc.monash.edu/, which resides on the Nectar (The National eResearch Collaboration Tools and Resources) infrastructure and managed by the eResearch Centre at Monash University. The *iFeatureOmega* server was implemented based on 'Linux+Apache+Django' framework and is equipped with 16 cores, 64 GB memory and a 2 TB hard disk. The server has been tested across five commonly used browsers, including Internet Explorer (version ≥7.0), Microsoft Edge, Mozilla Firefox, Google Chrome and Safari. The step-by-step of usage instructions is as follows:

Type “http://ifeatureomega.erc.monash.edu” on your browser.



Five webpages have been designed and implemented and are accessible via the navigation bar at the top of the website.

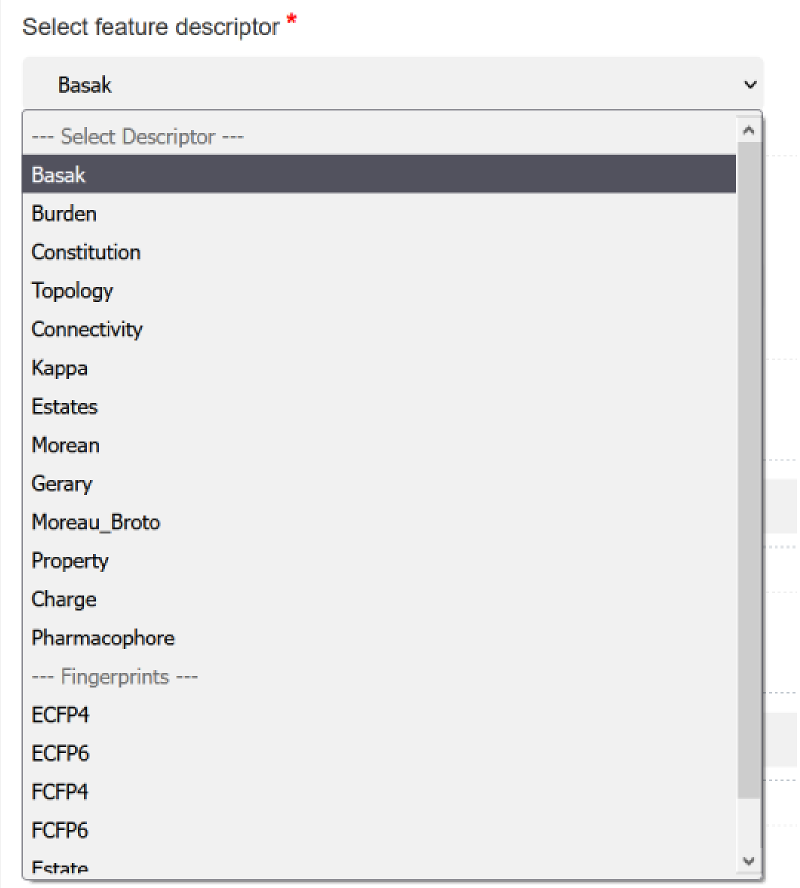
Take ligand page as an example:

Step 1: Click “Ligand” in the navigation bar and open the page for ligand molecule feature extraction.

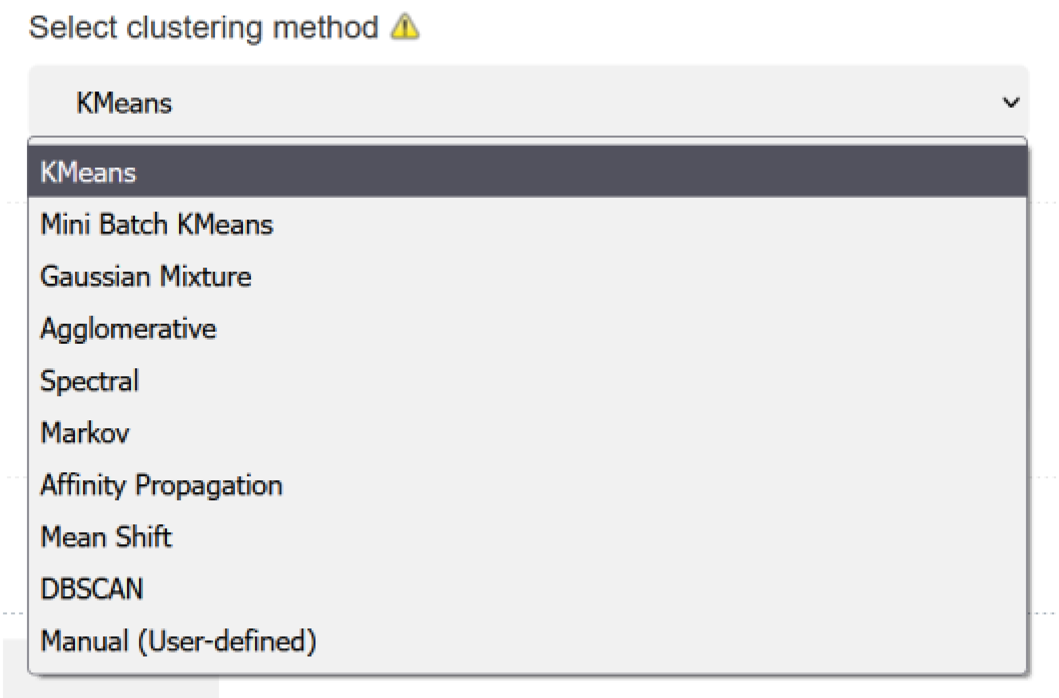
Step 2. Paste ligands in SMILES format or upload a file with SDF format.

```
Cc1cc(-c2csc(N=C(N)N)n2)cn1C
Brc1cccc(Nc2ncnc3ccncc23)c1NCCN1CCOCC1
COc1c(O)cc(O)c(C(=N)Cc2ccc(O)cc2)c1O
CCOC(=O)c1cc2cc(C(=O)O)ccc2[nH]1
O=C(NO)c1ccc(I)cc1
C=CCc1ccc(OC(=O)C23CC4CC(CC(C4)C2)C3)c(OC)c1
Cc1cccc(N2CCN(CCCON3C(=O)c4ccccc4C3=O)CC2)c1
N=c1sc2ccccc2n1CCN1CCC(c2ccc(F)cc2)CC1
O=C(Nc1ncc(F)s1)[C@H](CC1CCOCC1)c1ccc(S(=O)(=O)C2CC2)cc1
c1ccccc1Br
```

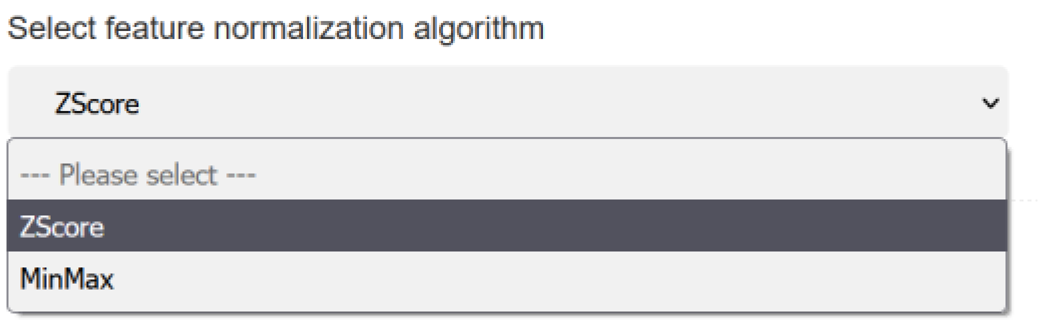
Step 2: Select the descriptor type.



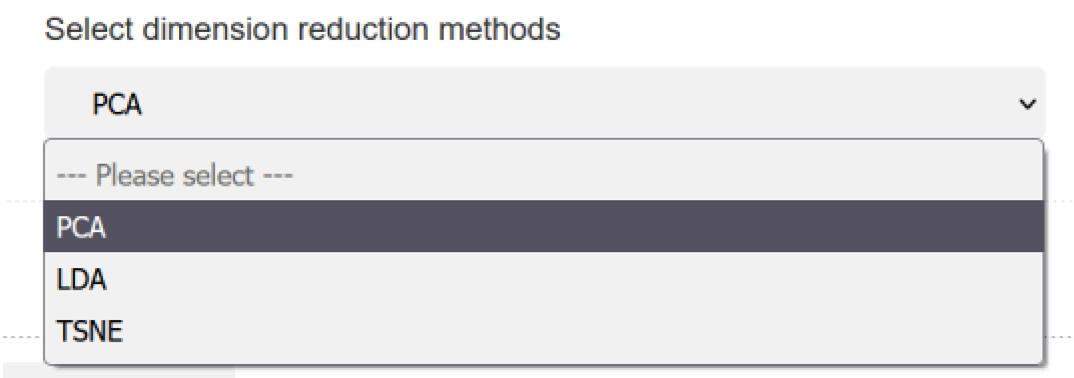
Step 3: Select the clustering method.



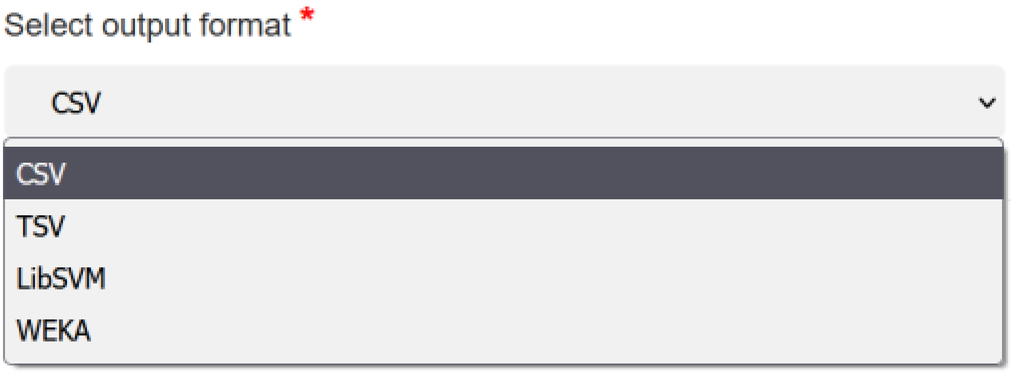
Step 4: Select the feature normalization algorithm.



Step 5: Select the dimension reduction methods.

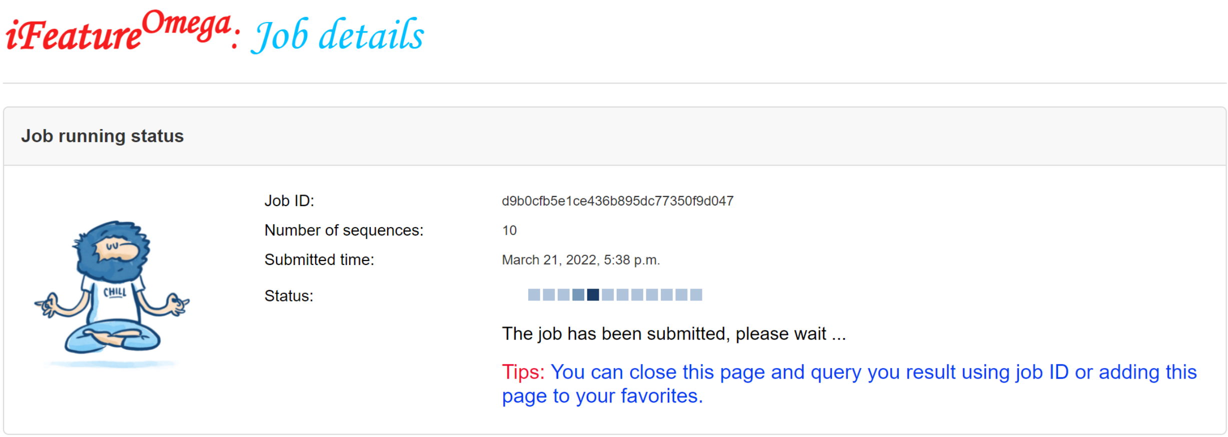


Step 6: Select the output format.



Finally, click the 'Submit' button to calculate the descriptors and run the feature analysis algorithms.

Step 7. Wait for the results.



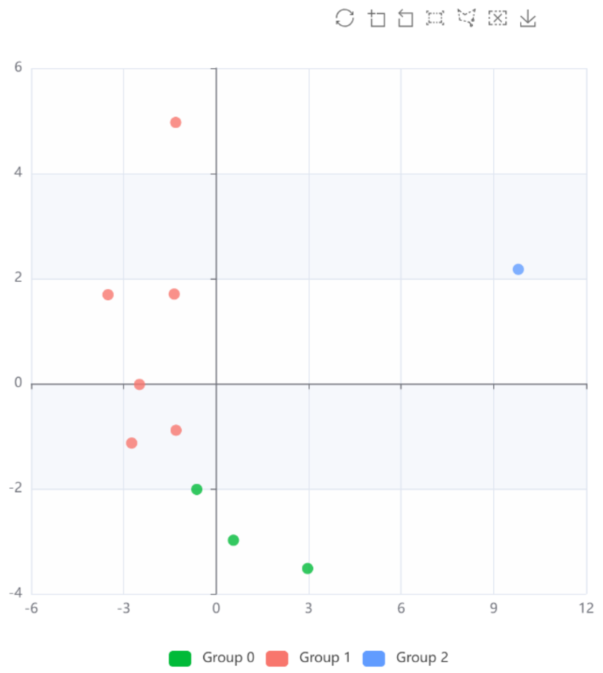
Job result

Detailed results (ID: d9b0cfb5e1ce436b895dc77350f9d047)

Basic information

Data type:	Ligand	**Samples size:**	10
Descriptor method:	Basak	**Normalization method:**	ZScore
Clustering method:	KMeans	**Dimension reduction:**	PCA
Output file format:	CSV	**All generated files:**	Download

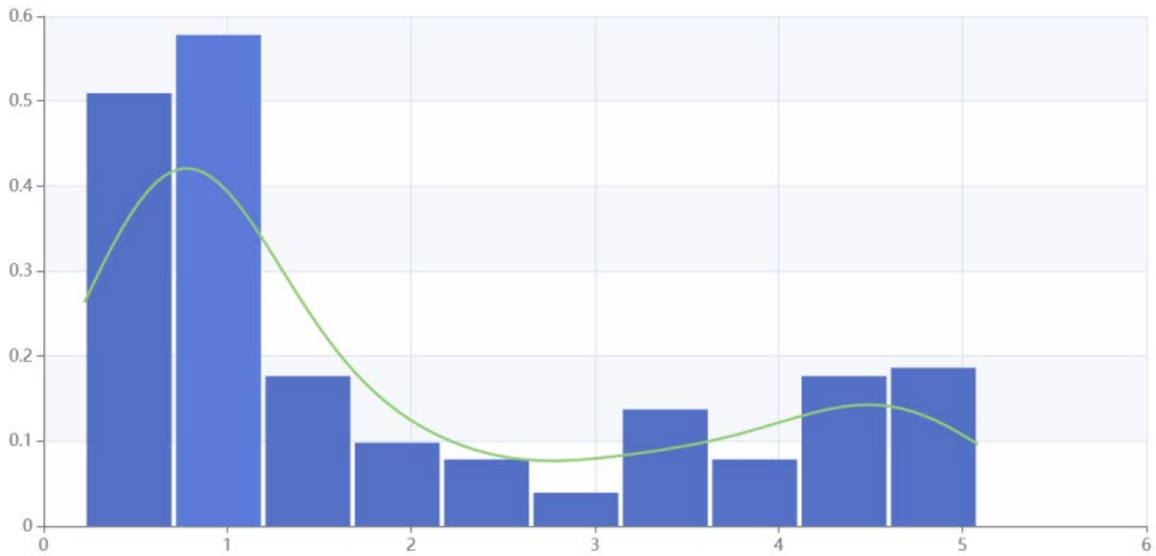
Scatter Plot | Distribution | Feature Matrix | Sample Similarity | Feature Similarity



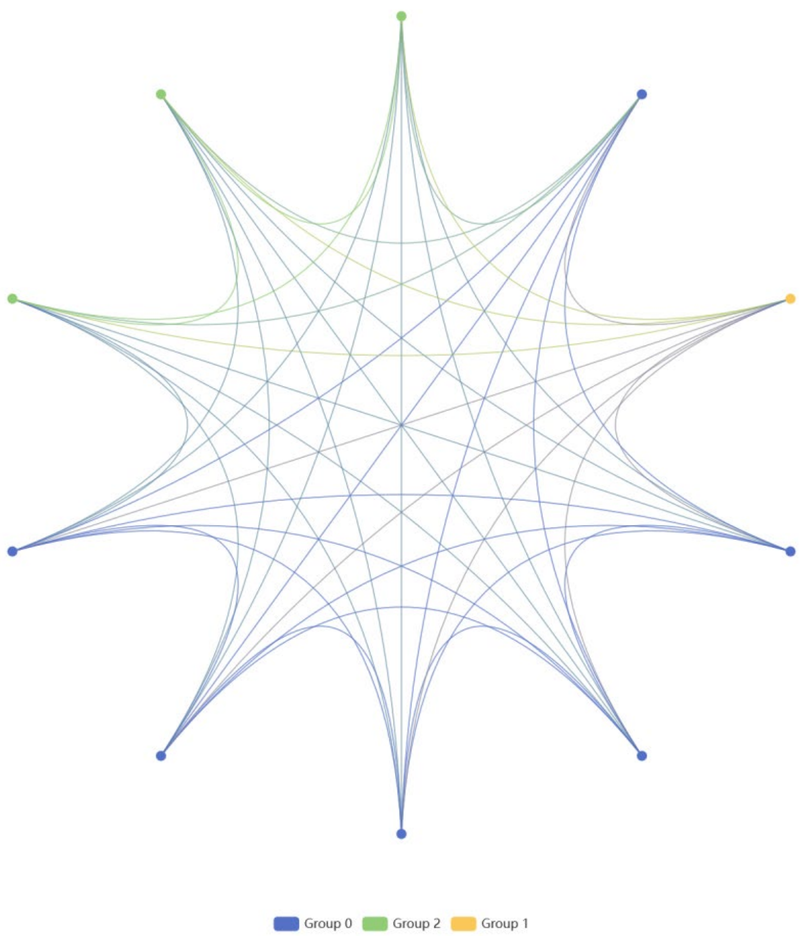
Show 10 entries Search:

ID	Name	Group
0	Cc1cc(-c2csc(N=C(N)N)n2)cn1C	Group 1
1	Brc1cccc(Nc2ncnc3ccncc23)c1NCCN1CCOCC1	Group 1
2	COc1c(O)cc(O)c(C(=N)Cc2ccc(O)cc2)c1O	Group 1
3	CCOC(=O)c1cc2cc(C(=O)O)ccc2[nH]1	Group 1
4	O=C(NO)c1ccc(I)cc1	Group 1
5	C=CCc1ccc(OC(=O)C23CC4CC(CC(C4)C2)C3)c(OC)c1	Group 0
6	Cc1cccc(N2CCN(CCCON3C(=O)c4ccccc4C3=O)CC2)c1	Group 0
7	N=c1sc2ccccc2n1CCN1CCC(c2ccc(F)cc2)CC1	Group 0
8	O=C(Nc1ncc(F)s1)[C@H](CC1CCOCC1)c1ccc(S(=O)(=O)C2CC2)cc1	Group 1
9	c1ccccc1Br	Group 2

Showing 1 to 10 of 10 entries Previous 1 Next


0.6
0.5
0.4
0.3
0.2
0.1
0
0
1
2
3
4
5
6


Outlier
Boxplot
2
1
0
-1
-2
CIC0
CIC1
CIC2
CIC3



Step 8: Query your results.

You can query your jobs by inputting the job ID in the query form. An incorrect ID will return an error message.

iFeatureOmega Sequence Structure Ligand d9b0cfb5e1ce436b895dc77 Job query Help Contact iFeature 1.0

iFeature^{Omega}: Job list

Show 10 entries

Search:

Job Name	Data Type	Data Size	Time (Time zone: Australia/Sydney)	Status	Detail
chemcals	Ligand	10	March 21, 2022, 5:38 p.m.	Done	Click
Job Name	**Data Type**	**Data Size**	**Time (Time zone: Australia/Sydney)**	**Status**	**Detail**

Showing 1 to 1 of 1 entries

Previous 1 Next

9. List of Integrated Feature Descriptors, Feature Analysis Plots in iFeatureOmega

Table 2. Feature descriptors calculated by *iFeatureOmega* for protein sequences

Feature group	Features (Abbreviation)	Reference
Amino acid composition	Amino acid composition (AAC)	(2)
	Enhanced amino acid composition (EAAC)	(3,4)
	Composition of *k*-spaced amino acid pairs (CKSAAP)	(5,6)
	Kmer (dipeptides and tripeptides) composition (DPC and TPC)	(2,7)
	Dipeptide deviation from expected mean (DDE)	(7)
	Composition (CTDC)	(8-12)
	Transition (CTDT)	(8-12)
	Distribution (CTDD)	(8-12)
	Conjoint triad (CTriad)	(13)
	Conjoint *k*-spaced Triad (KSCTriad)	(3,4)
	Adaptive skip dipeptide composition (ASDC)	(14)
	PseAAC of distance-pairs and reduced alphabet (DistancePair)	(15,16)
Grouped amino acid composition	Grouped amino acid composition (GAAC)	(3,4)
	Enhanced grouped amino acid composition (EGAAC)	(3,4)
	Composition of *k*-spaced amino acid group pairs (CKSAAGP)	(3,4)
	Grouped dipeptide composition (GDPC)	(3,4)
	Grouped tripeptide composition (GTPC)	(3,4)
Autocorrelation	Moran (Moran)	(17,18)
	Geary (Geary)	(19)
	Normalized Moreau-Broto (NMBroto)	(20)
	Auto covariance (AC)	(21-23)
	Cross covariance (CC)	(21-23)
	Auto-cross covariance (ACC)	(21-23)
Quasi-sequence-order	Sequence-order-coupling number (SOCNumber)	(24-26)
	Quasi-sequence-order descriptors (QSOrder)	(24-26)
Pseudo-amino acid composition	Pseudo-amino acid composition (PAAC)	(27,28)
	BPAAC (APAAC)	(27,28)
	Pseudo *K*-tuple reduced amino acids composition (PseKRAAC type 1 to type 16)	(29)
Residue representation	Binary - 20bit (binary)	(30,31)
	Binary - 6bit (binary_6bit)	(16,32)
	Binary - 5bit (binary_5bit_type 1 and type 2)	(16,33)
	Binary - 3bit (binary_3bit_type 1 to type 7)	(14)
	Learn from alignments (AESNN3)	(16,34)
	Overlapping property features - 10 bit (OPF_10bit)	(14)
	Overlapping property features - 7 bit (OPF_7bit type 1 to type 3)	(14)
Physicochemical property	AAindex (AAindex)	(35)
BLOSUM matrix	BLOSUM62 (BLOSUM62)	(36)
Z-Scales index	Z-Scales (ZSscale)	(37)

Table 3. Feature descriptors calculated by *iFeatureOmega* for DNA and RNA sequences

Feature group	Features (Abbreviation)	Sequence type	Reference
Nucleic acid composition	Nucleic acid composition (NAC)	DNA/RNA	(4)
	Enhanced nucleic acid composition (ENAC)	DNA/RNA	(4)
	k-spaced nucleic acid pairs (CKSNAP)	DNA/RNA	(4)
	Basic kmer (Kmer)	DNA/RNA	(38)
	Reverse compliment kmer (RCKmer)	DNA	(39,40)
	Accumulated nucleotide frequency (ANF)	DNA/RNA	(41)
	Nucleotide chemical property (NCP)	DNA/RNA	(41)
	The occurrence of kmers, allowing at most m mismatches (Mismatch)	DNA/RNA	(16)
	The occurrences of kmers, allowing non-contiguous matches (Subsequence)	DNA/RNA	(16)
	Adaptive skip dinucleotide composition (ASDC)	DNA/RNA	(14)
	Local position-specific dinucleotide frequency (LPDF)	DNA/RNA	(42)
	The Z curve parameters for frequencies of phase-specific mononucleotides (Z_curve_9bit)	DNA/RNA	(43)
	The Z curve parameters for frequencies of phase-independent dinucleotides (Z_curve_12bit)	DNA/RNA	(43)
	The Z curve parameters for frequencies of phase-specific dinucleotides (Z_curve_36bit)	DNA/RNA	(43)
	The Z curve parameters for frequencies of phase-independent trinucleotides (Z_curve_48bit)	DNA/RNA	(43)
	The Z curve parameters for frequencies of phase-specific trinucleotides (Z_curve_144bit)	DNA/RNA	(43)
Position-specific of n-nucleotides	Binary (binary)	DNA/RNA	(30,31)
	Dinucleotide binary encoding (DBE)	DNA/RNA	(42)
	Position-specific of two nucleotides (PS2)	DNA/RNA	(16,44)
	Position-specific of three nucleotides (PS3)	DNA/RNA	(16,44)
	Position-specific of four nucleotides (PS4)	DNA/RNA	(16,44)
Electron-ion interaction pseudopotentials	Electron-ion interaction pseudopotentials value (EIIP)	DNA	(45,46)
	Electron-ion interaction pseudopotentials of trinucleotide (PseEIIP)	DNA	(45,46)
Autocorrelation and cross-covariance	Dinucleotide-based auto covariance (DAC)	DNA/RNA	(21-23)
	Dinucleotide-based cross covariance (DCC)	DNA/RNA	(21-23)
	Dinucleotide-based auto-cross covariance (DACC)	DNA/RNA	(21-23)
	Trinucleotide-based auto covariance (TAC)	DNA	(21)
	Trinucleotide-based cross covariance (TCC)	DNA	(21)
	Trinucleotide-based auto-cross covariance (TACC)	DNA	(21)
	Moran (Moran)	DNA/RNA	(17,18)
	Geary (Geary)	DNA/RNA	(19)
	Normalized Moreau-Broto (NMBroto)	DNA/RNA	(20)
Physicochemical property	Dinucleotide physicochemical properties (DPCP type 1 and type 2)	DNA/RNA	(47)
	Trinucleotide physicochemical properties (TPCP type 1 and type 2)	DNA	(47)
Mutual information	Multivariate mutual information (MMI)	DNA/RNA	(48)
Pseudo nucleic acid composition	Pseudo dinucleotide composition (PseDNC)	DNA/RNA	(21,49)
	Pseudo *k*-tupler composition (PseKNC)	DNA/RNA	(21,49)
	Parallel correlation pseudo dinucleotide composition (PCPseDNC)	DNA/RNA	(21,49)
	Parallel correlation pseudo trinucleotide composition (PCPseTNC)	DNA	(21,49)
	Series correlation pseudo dinucleotide composition (SCPseDNC)	DNA/RNA	(21,49)
	Series correlation pseudo trinucleotide composition (SCPseTNC)	DNA	(21,49)

Table 4. Feature descriptors calculated by *iFeatureOmega* for ligands

Feature group	Features (Abbreviation)	Reference
Constitution	Molecular constitutional descriptors	(50,51)
Topology	Topological descriptors	(50,51)
	Molecular connectivity indices	(50,51)
E-State	E-state descriptors	(50,51)
Basak	Basak descriptors	(50,51)
Burden	Burden descriptors	(50,51)
Kappa	Kappa shape descriptors	(50,51)
Autocorrelation	Moreau–Broto autocorrelation	(50,51)
	Moran autocorrelation	(50,51)
	Geary autocorrelation	(50,51)
Charge	Charge descriptors	(50,51)
Property	Molecular property	(50,51)
Pharmacophore	Potential pharmacophore point descriptors	(50,51)
MOE-type	MOE-type descriptors	(50,51)
Fingerprints	MACCS fingerprints	(50,51)
	Morgan fingerprints	(50,51)
	E-state fingerprints	(50,51)

Table 5. Feature descriptors calculated by *iFeatureOmega* for protein structures.

Descriptor group	Descriptor (Abbreviation)
Amino acids composition	Amino acids content type 1 (AAC_type1)
	Amino acids" content type 2 (AAC_type2)
Grouped amino acids composition	Grouped amino acids content type 1 (GAAC_type1)
	Grouped amino acids content type 2 (GAAC_type2)
Secondary structure	Secondary structure elements (3) type 1 (SS3_type1)
	Secondary structure elements (3) type 2 (SS3_type2)
	Secondary structure elements (8) type 1 (SS8_type1)
	Secondary structure elements (8) type 2 (SS8_type2)
Half sphere exposure	Half sphere exposure α (HSE_CA)
	Half sphere exposure β (HSE_CB)
Residue depth	Residue depth (Residue depth)
Atom composition	Atom content type 1 (AC_type1)
	Atom content type 2 (AC_type2)
Network-based index	Network-based index

Table 6. The feature analysis approaches provided in iFeatureOmega

Method	Algorithm (Abbreviation)	Reference
Clustering	*k*-means (kmeans)	(52,53)
	Mini-Batch *K*-means (MiniBatchKMeans)	(52,53)
	Gaussian mixture (GM)	(52,53)
	Agglomerative (Agglomerative)	(54)
	Spectral (Spectral)	(55)
	Markov clustering (MCL)	(56)
	Hierarchical clustering (hcluster)	(52,57)
	Affinity propagation clustering (APC)	(58)
	Mean shift (meanshift)	(59)
	DBSCAN (dbscan)	(60)
Dimensionality reduction	Principal component analysis (PCA)	(61)
	Latent dirichlet allocation (LDA)	(62)
	t-distributed stochastic neighbor embedding (*t*_SNE)	(63)
Feature normalization	ZScore (ZScore)	(4)
	MinMax (MinMax)	(4)

Table 7. Graphical display options in *iFeatureOmega*

Category	Type	Purpose
Feature descriptor visualization	Histogram	Display data distribution
	Kernel density plot	Display data distribution
	Heatmap	Display data distribution
	Boxplot	Display data distribution
	Line chart	Display data distribution
	Scatter plot	Display clustering and dimensionality reduction result
	Circular plot	Display the correlation of samples or descriptors
Protein structure visualization		Display the 3-D protein structure
Ligand structure visualization		Display chemical structure

10. Descriptions of feature descriptors for nucleotide sequences

Let us assume that a nucleotide sequence with L residues can be generally represented as $\{R_1, R_2, \ldots, R_L\}$, where R_i represents the base at the *i-th* position in the sequence. The following commonly used feature descriptors can be described as follows:

Kmer

For kmer descriptor, the DNA or RNA sequences are represented as the occurrence frequencies of k neighboring nucleic acids (38), which has been successfully applied to human gene regulatory sequence prediction (39) and enhancer identification (38). 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. The Kmer descriptor has been successfully applied to lncRNA prediction (64,65).

Parameter(s):

- *Kmer size: The number of neighboring nucleic acids, default: 3.*

RCKmer (Reverse compliment kmer)

The reverse compliment kmer (39,40) 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'). It has been used to predict the *in vivo* signature of human gene regulatory sequences (39) and human nucleosome occupancy (40).

Parameter(s):

- *Kmer size: The number of neighboring nucleic acids, default: 3.*

Mismatch (The occurrence of kmers, allowing at most m mismatches)

The mismatch profile also calculates the occurrences of kmers (16), but allows max *m* inexact matching ($m < k$). There are two parameters for this descriptor, *k* neighboring nucleic acids and *m* inexact matching. The mismatch descriptor is defined as:

$$f_{k,m} = (\sum_{j=0}^{m} c_{1,j}, \sum_{j=0}^{m} c_{2,j}, \dots, \sum_{j=0}^{m} c_{4^k,j},),$$

where $c_{i,j}$ represents the occurrences of i-th kmer type with j mismatches, $i = 1, 2, 3, \dots, 4^k$; $j = 0, 1, 2, \dots, m$. The mismatch descriptor has been successfully applied to protein classification prediction (66), B-cell epitopes identification (67) and transposon-derived piRNA prediction (68).

Parameter(s):

- *Kmer size: The number of k neighboring nucleic acids, default: 3.*
- *Mismatch value: the nucleotide number of inexact matching (< kmer size), default: 1.*

Subsequence (The occurrences of kmers, allowing non-contiguous matches)

The subsequence descriptor allows non-contiguous matching (16). For example, the 3-mer "AAC" in the sequence "AACTACG". By exact and non-contiguous matching, we can obtain AAC, AA-C, A-AC, A-AC ("-" means the gap in non-contiguous matching). AAC is the exact form of "AAC", and AA-C, A-AC, A-AC are non-contiguous forms of "AAC". The occurrences of non-contiguous forms are penalized with their length *l* and the factor δ ($0 \leq \delta \leq 1$), defined as δ^l. Therefore, the occurrence of "AAC" in above example is $1 + 2\delta^6 + \delta^5$. The subsequence descriptor has been successfully applied to B-cell epitopes identification (67), transposon-derived piRNA prediction (68).

Parameter(s):

- *Kmer size: the number of k neighboring nucleic acids, default: 3.*
- *Delta value: the penalty factor, range from 0 to 1, default: 0.*

NAC (Nucleic Acid Composition)

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:

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

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

Di-Nucleotide Composition (DNC)

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

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

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

Tri-Nucleotide Composition (TNC)

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

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

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

ANF (Accumulated nucleotide frequency)

The Accumulated Nucleotide Frequency (ANF) encoding (41) include the nucleotide frequency information and the distribution of each nucleotide in the RNA sequence, the density d_i of any nucleotide s_i at position i in RNA sequence by the following formula:

$$d_i = \frac{1}{|s_i|}\sum_{j=1}^{l} f(s_i), \quad f(q) = \begin{cases} 1 & if\ s_i = q \\ 0 & other\ case \end{cases},$$

where l is the sequence length, $|S_i|$ is the length of the i-th prefix string $\{s_1, s_2, \ldots, s_i\}$ in the sequence, $q \in \{\text{A, C, G or U}\}$. Suppose an example sequence "UCGUUCAUGG". The density of 'U' is 1 (1/1), 0.5 (2/4), 0.6 (3/5), 0.5 (4/8) at positions 1, 4, 5, and 8, respectively. The density of 'C' is 0.5 (1/2), 0.33 (2/6) at positions 2 and 6, respectively. The density of 'G' is 0.33 (1/3), 0.22 (2/9), 0.3 (3/10) at positions 3, 9, and 10, respectively. The density of 'A' is 0.14 (1/7) at position 7.

By integrating both the nucleotide chemical property and accumulated nucleotide information, the sample sequence "UCGUUCAUGG" can be represented by {(0, 0, 1, 1), (0, 1, 0, 0.5), (1, 0, 0, 0.33), (0, 0, 1, 0.5), (0, 0, 1, 0.6), (0, 1, 0, 0.33), (1, 1, 1, 0.14), (0, 0, 1, 0.5), (1, 0, 0, 0.22), (1, 0, 0, 0.3)}. By doing so, not only the chemical property was considered, but also the long-range sequence order information was incorporated. Therefore, the samples in the benchmark dataset were encoded in terms of both nucleotide chemical property and nucleotide densities. The ANF descriptor has been successfully applied to N(6)-methyldenosine site prediction (41).

ENAC (Enhanced nucleic acid composition)

The Enhanced Nucleic Acid Composition (ENAC) calculates the NAC based on the sequence window of fixed length (the default value is 5) that continuously slides from the 5' to 3' terminus of each nucleotide sequence and can be usually applied to encode the nucleotide sequence with an equal length, which has been successfully applied to N(6)-methyldenosine site prediction (69).

Parameter(s):

- *Sliding window size: the length of the sliding window, default: 5.*

Binary (also termed one-hot)

In the Binary encoding, each amino acid is represented by a 4-dimensional binary vector, e.g. A is encoded by (1000), C is encoded by (0100), G is encoded by (0010) and T(U) is encoded by (0001), respectively. This encoding scheme is often used to encode nucleotide sequence with an equal length. The binary descriptor has been successfully applied to N(6)-methyldenosine sites prediction (69), RNA pseudouridylation sites prediction (70), DNA- and RNA-binding proteins prediction (71) and noncoding variants effect prediction (72).

PS2 (Position-specific of two nucleotides)

There are 4 × 4 = 16 pairs of adjacent pairwise nucleotides, such as AA/AT/AG …, thus a single variable representing one such pair gets one-hot (i.e. binary) encoded into 16 binary variables (16). For example, e.g. AA is encoded by (1000000000000000), AC is encoded by (0100000000000000) …, and the sequence AAC is encoded as (10000000000000000100000000000000). PS2 has been successfully applied to off-target effects of CRISPR-Cas9 prediction (44). Both PS3 and PS4 are encoded for three adjacent nucleotides (4 × 4 × 4 = 64) and four adjacent nucleotides (4 × 4 × 4 × 4 = 256) in a similar way.

CKSNAP (Composition of *k*-spaced nucleic acid pairs)

The CKSNAP feature encoding calculates the frequency of nucleic acid pairs separated by any k nucleic acid (k = 0, 1, 2, … , 5) (4). Taking k = 0 as an example, there are 16 0-spaced nucleic acid pairs (i.e. 'AA', 'AC', 'AG', 'AT', 'CA', 'CC', 'CG', 'CT', 'GA', 'GC', 'GG', 'GT', 'TA', 'TC', 'TG', 'TT'). Then, a feature vector can be defined as:

$$(\frac{N_{AA}}{N_{total}}, \frac{N_{Ac}}{N_{total}}, \frac{N_{AG}}{N_{total}}, \dots, \frac{N_{TT}}{N_{total}},)_{16}.$$

The value of each descriptor denotes the composition of the corresponding nucleic acid pair in the nucleotide sequence. For instance, if the nucleic acid pair AA appears m times in the nucleotide sequence, the composition of the nucleic acid pair AA is equal to m divided by the total number of *0*-spaced nucleic acid pairs (N_{total}) in the nucleotide sequence. For k = 0, 1, 2, 3, 4 and 5, the value of N_{total} is $P-1$, $P-2$, $P-3$, $P-4$, $P-5$ and $P-6$ for a nucleotide sequence of length P, respectively.

Parameter(s):

- *Gap value: the length of k-spaced nucleic acid, default is 5.*

NCP (Nucleotide chemical property)

There are four different kinds of nucleotides in RNA, i.e., adenine (A), guanine (G), cytosine (C) and uracil (U). Each nucleotide has different chemical structure and chemical binding. The four kinds of nucleotides can be classified into three different groups in terms of these chemical properties (**Table 8**).

Table 8. Chemical structure of each nucleotide (41).

Chemical property	Class	Nucleotides
Ring Structure	Purine	A, G
	Pyrimidine	C, U
Functional Group	Amino	A, C
	Keto	G, U
Hydrogen Bond	Strong	C, G
	Weak	A, U

Based on chemical properties, A can be represented by coordinates (1, 1, 1), C can be represented by coordinates (0, 1, 0), G can be represented by coordinates (1, 0, 0), U can be represented by coordinates (0, 0, 1). The NCP descriptor has been successfully applied to N(6)-methyldenosine site prediction (41).

EIIP (Electron-ion interaction pseudopotentials)

Dragutin (46) came up with electron-ion interaction pseudopotentials (EIIP) value of nucleotides A, G, C, T (A: 0.1260, C: 0.1340, G: 0.0806, T:0.1335). The EIIP directly use the EIIP value represent the nucleotide in the DNA sequence. Therefore, the dimension of the EIIP descriptor is the length of the DNA sequence. The EIIP descriptor has been successfully applied to DNA N4-methylcytosine site prediction (73) and subcellular location prediction (74).

PseEIIP (Electron-ion interaction pseudopotentials of trinucleotide)

In these encoding, let $EIIP_A$, $EIIP_T$, $EIIP_G$, and $EIIP_C$ denote the EIIP values of nucleotides A, T, G and C, respectively. Then, the mean EIIP value of trinucleotides in each sample to construct feature vector, which can be formulated as:

$$\mathrm{V} = [EIIP_{AAA} \cdot f_{AAA}, EIIP_{AAC} \cdot f_{AAC}, \dots, EIIP_{TTT} \cdot f_{TTT}],$$

where f_{xyz} is the normalized frequency of the i-th trinucleotide, $EIIP_{xyz} = EIIP_x + EIIP_y + EIIP_z$ expresses the *EIIP* value of one trinucleotide and X, Y, Z∈ [A, C, G, T]. Obviously, the dimension of vector V is 64. The EIIP descriptor has been successfully applied to 5-Methylcytosine prediction (75) and non-coding RNA promoter identification (76).

ASDC (Adaptive skip dinucleotide composition)

The adaptive skip dipeptide composition is a modified dinucleotide composition, which sufficiently considers the correlation information present not only between adjacent residues but also between intervening residues (77). For given a sequence, the feature vector for ASDC is represented by:

$$ASDC = (f_{v1}, f_{v1}, \dots, f_{v16}),$$

where f_{vi} is calculated by

$$f_{vi} = \frac{\sum_{g=1}^{L-1} O_i^g}{\sum_{i=1}^{16} \sum_{g=1}^{L-1} O_i^g},$$

where f_{vi} denotes the occurrence frequency of all possible dinucleotide with $\leq L$-1 intervening nucleotides. The ASDC descriptor has been successfully applied to anti-cancer peptide (77) and cell-penetrating peptide predictions (78).

DBE (Dinucleotide binary encoding)

The dinucleotide binary encoding descriptor encapsulates the positional information of the dinucleotide at each position in the sequence. There are a total of 16 possible dinucleotides. In this descriptor, each dinucleotide can be encoded into a 4-dimensional 0/1 vector. For example, AA is encoded as (0,0,0,0); AT is encoded as (0,0,0,1); AC is encoded as (0,0,1,0); and so forth, GG is encoded as (1,1,1,1). Therefore, using the dinucleotide binary encoding, we can yield a 160 (=40×4)-dimensional 0/1 vector for the given sequence. The DBE descriptor has been successfully applied to N6-Methyladenosine site prediction (42).

LPDF (Local position-specific dinucleotide frequency)

The local position-specific dinucleotide frequency descriptor can be denoted as ($f_2, f_3, \ldots, f_l$), where f_i is calculated as follows:

$$f = \frac{1}{|N_i|} C(X_{i-1}X_i), 2 \leq i \leq l,$$

where l is the length of the given sequence, $|N_i|$ is the length of the i-th prefix string $\{X_1X_2...X_i\}$ in the sequence, and C ($X_{i-1}X_i$) is the occurrence number of the dinucleotide $X_{i-1}X_i$ in position i of the i-th prefix string. The LPDF descriptor has been successfully applied to N6-Methyladenosine site prediction (42).

DPCP (Dinucleotide physicochemical properties)

The dinucleotide physicochemical properties descriptor can be devised as:

$$V = [DPCP_{AA} \times f_{AA}, DPCP_{AC} \times f_{AC}, \ldots, DPCP_{TT} \times f_{TT}],$$

where $DPCP_i$ is one of the i-th physicochemical properties of a dinucleotide. The 148 physicochemical properties for DNA dinucleotide and 22 physicochemical properties for RNA dinucleotide are listed in **Tables 9** and **10**, respectively. The DPCP descriptor has been successfully applied to DNA N4-Methylcytosine sites prediction (47).

Parameter(s):

- *Di-DNA physicochemical indices: the names of used physicochemical dinucleotides indices. (For DNA sequences)*

- *Di-RNA physicochemical indices: the names of used physicochemical dinucleotides indices. (For RNA sequences)*

Table 9. The names of the 148 physicochemical dinucleotides indices for DNA.

Base stacking	Protein induced deformability	B-DNA twist	Propeller twist	Duplex stability:(freeenergy)
Duplex tability(disruptenergy)	Protein DNA twist	Stabilising energy of Z-DNA	Aida_BA_transition	Breslauer_dS
Electron_interaction	Hartman_trans_free_energy	Lisser_BZ_transition	Polar_interaction	SantaLucia_dG
Sarai_flexibility	Stability	Stacking_energy	Sugimoto_dS	Watson-Crick_interaction
Twist	Shift	Slide	Rise	Twist stiffness
Tilt stiffness	Shift_rise	Twist_shift	Enthalpy1	Twist_twist
Shift2	Tilt3	Tilt1	Slide (DNA-protein complex) 1	Tilt_shift
Twist_tilt	Roll_rise	Stacking energy	Stacking energy1	Propeller Twist
Roll11	Rise (DNA-protein complex)	Roll2	Roll3	Roll1
Slide_slide	Enthalpy	Shift_shift	Flexibility_slide	Minor Groove Distance
Rise (DNA-protein complex)1	Roll (DNA-protein complex)1	Entropy	Cytosine content	Major Groove Distance
Twist (DNA-protein complex)	Purine (AG) content	Tilt_slide	Major Groove Width	Major Groove Depth
Free energy6	Free energy7	Free energy4	Free energy3	Free energy1
Twist_roll	Flexibility_shift	Shift (DNA-protein complex) 1	Thymine content	Tip
Keto (GT) content	Roll stiffness	Entropy1	Roll_slide	Slide (DNA-protein complex)
Twist2	Twist5	Twist4	Tilt (DNA-protein complex)1	Twist_slide
Minor Groove Depth	Persistance Length	Rise3	Shift stiffness	Slide3
Slide2	Slide1	Rise1	Rise stiffness	Mobility to bend towards minor groove
Dinucleotide GC Content	A-philicity	Wedge	DNA denaturation	Bending stiffness
Free energy5	Breslauer_dG	Breslauer_dH	Shift (DNA-protein complex)	Helix-Coil_transition
Ivanov_BA_transition	Slide_rise	SantaLucia_dH	SantaLucia_dS	Minor Groove Width
Sugimoto_dG	Sugimoto_dH	Twist1	Tilt	Roll
Twist7	Clash Strength	Roll_roll	Roll (DNA-protein complex)	Adenine content
Direction	Probability contacting nucleosome core	Roll_shift	Shift_slide	Shift1
Tilt4	Tilt2	Free energy8	Twist (DNA-protein complex)1	Tilt_rise
Free energy2	Stacking energy2	Stacking energy3	Rise_rise	Tilt_tilt
Roll4	Tilt_roll	Minor Groove Size	GC content	Inclination
Slide stiffness	Melting Temperature1	Twist3	Tilt (DNA-protein complex)	Guanine content
Twist6	Major Groove Size	Twist_rise	Rise2	Melting Temperature
Free energy	Mobility to bend towards major groove	Bend		

Table10. The names of the 22 physicochemical dinucleotides indices for RNA.

Shift (RNA)	Hydrophilicity (RNA)	Hydrophilicity (RNA)	GC content	Purine (AG) content
Keto (GT) content	Adenine content	Guanine content	Cytosine content	Thymine content
Slide (RNA)	Rise (RNA)	Tilt (RNA)	Roll (RNA)	Twist (RNA)
Stacking energy (RNA)	Enthalpy (RNA)	Entropy (RNA)	Free energy (RNA)	Free energy (RNA)
Enthalpy (RNA)	Entropy (RNA)			

DPCP type2 (Dinucleotide physicochemical properties)

For DPCP type2 descriptor, it can be encoded into the following matrix:

$$V = \begin{bmatrix} PC^1(N_1N_2) & \dots & PC^1(N_{L-1}N_L) \\ \dots & \dots & \dots \\ PC^j(N_1N_2) & \dots & PC^j(N_{L-1}N_L) \end{bmatrix},$$

where $PC_j(N_i, N_{i+1})$ is the j-th physicochemical dinucleotides value of the dinucleotide N_iN_{i+1}. L is the length of sequence. The 148 physicochemical properties for DNA dinucleotide and 22 physicochemical properties for RNA dinucleotide are listed in **Tables 9** and **10**, respectively. The DPCP type2 descriptor has been successfully applied to DNA N4-Methylcytosine sites prediction (48).

Parameter(s):

- *Di-DNA physicochemical indices: the names of used physicochemical dinucleotides indices. (For DNA sequences)*
- *Di-RNA physicochemical indices: the names of used physicochemical dinucleotides indices. (For RNA sequences)*

TPCP (Trinucleotide physicochemical properties)

The trinucleotide physicochemical properties descriptor can be devised as:

$$V = [TPCP_{AAA} \times f_{AAA}, TPCP_{AAC} \times f_{AAC}, \dots, DPCP_{TTT} \times f_{TTT}],$$

where $TPCP_i$ is one of the i-th physicochemical properties of a trinucleotide listed in **Table 11**, and f_{NNN} denotes the trinucleotide normalized frequency. The 12 physicochemical properties for DNA trinucleotide are listed in **Table 11**. The TPCP descriptor has been successfully applied to DNA N4-Methylcytosine site prediction (47).

Parameter(s):

- *Tri-DNA physicochemical indices: the names of used physicochemical trinucleotides indices.*

Table 11. The names of the 12 physicochemical trinucleotides indices for DNA.

Dnase I	Bendability (DNAse)	Bendability (consensus)	Trinucleotide GC Content
Nucleosome positioning	Consensus_roll	Consensus-Rigid	Dnase I-Rigid
MW-Daltons	MW-kg	Nucleosome	Nucleosome-Rigid

TPCP type2 (Trinucleotide physicochemical properties)

For TPCP type2 descriptor, it can be encoded into the following matrix:

$$V = \begin{bmatrix} PC^1(N_1N_2N_3) & \dots & PC^1(N_{L-2}N_{L-1}N_L) \\ \dots & \dots & \dots \\ PC^j(N_1N_2N_3) & \dots & PC^j(N_{L-2}N_{L-1}N_L) \end{bmatrix}$$

Where $PC_j(N_i, N_{i+1},N_{i+2})$ is the j-th physicochemical value of the trinucleotide N_iN_{i+1},N_{i+2}. L is the length of sequence. The 12 physicochemical properties for DNA trinucleotide are listed in **Table 11**. The TPCP type2 descriptor has been successfully applied to DNA N4-Methylcytosine site prediction (48).

Parameter(s):

- *Tri-DNA physicochemical indices: the names of used physicochemical trinucleotides indices.*

MMI (Multivariate mutual information)

In order to use multivariate mutual information on a DNA/RNA sequence, the '2-mer' set T2 = { AA, AC, AG, AT, CC, CG, CT, GG, GT, TT} and '3-mer' set T3 = {AAA, AAC, AAG, AAT, ACC, ACG, ACT, AGG, AGT, ATT, CCC, CCG, CCT, CGG, CGT, CTT, GGG, GGT, GTT and TTT} were defined, and then the mutual information can be calculated as follows:

$$I(N_1N_2) = f(N_1N_2)ln\frac{f(N_1N_2)}{f(N_1)f(N_2)}$$

$$I(N_1N_2N_3) = f(N_1N_2)ln\frac{f(N_1N_2)}{f(N_1)f(N_2)} + \frac{f(N_1N_3)}{f(N_3)}ln\frac{f(N_1N_3)}{f(N_3)} - \frac{f(N_1N_2N_3)}{f(N_2N_3)}ln\frac{f(N_1N_2N_3)}{f(N_2N_3)}$$

where $f(N_i)$ is the frequency of N_i in the sequence; $f(N_i, N_j)$ is the frequency of the T2's element N_iN_j; $f(N_i, N_j, N_k)$ are the frequency of the T3's element $N_iN_jN_k$. The MMI descriptor has been successfully applied to DNA N4-Methylcytosine site prediction (48,79).

Z_curve_9bit (The Z curve parameters for frequencies of phase-specific mononucleotides)

The frequencies of bases A, C, G and T occurring in an open reading frame or a fragment of DNA sequence with base at position 1, 4, 7, …; 2, 5, 8, …; 3, 6, 9, …, are denoted by a_1, c_1, g_1, t_1; a_2, c_2, g_2, t_2; a_3, c_3, g_3, t_3, respectively. They are in fact the frequencies of bases at the 1st, 2nd and 3rd codon positions. a_i, c_i, g_i, t_i are mapped onto a point P_i in a three-dimensional space V_i, i=1, 2, 3. The coordinates of P_i, denoted by x_i, y_i, z_i, are determined by the Z-transform of DNA sequences:

$$\begin{cases} x_i = (a_i + g_i) - (c_i + t_i), \\ y_i = (a_i + c_i) - (g_i + t_i), \\ z_i = (a_i + t_i) - (g_i + c_i), \\ x_i, y_i, z_i, \in [-1, 1], i = 1,2,3. \end{cases}$$

Z_curve_12bit (The Z curve parameters for frequencies of phaseindependent di-nucleotides)

The Z_curve_12bit descriptor consider the frequency of dinucleotides, denoted by *p(XY)*, where X, Y = A, C, G and T. This descriptor can be calculated as follows:

$$\begin{cases} x_X = (p(XA) + p(XG)) - (p(XC) + p(XT)), \\ y_X = (p(XA) + p(XC)) - (p(XG) + p(XT)), \\ z_X = (p(XA) + p(XT)) - (p(XG) + p(XC)), \\ \qquad X = A, C, G, T, \end{cases}$$

Z_curve_36bit (The Z curve parameters for frequencies of phase-specific di-nucleotides)

Using similar notations, the Z_curve_36bit descriptor can be calculated as follows:

$$\begin{cases} x_X^k = (p^k(XA) + p^k(XG)) - (p^k(XC) + p^k(XT)), \\ y_X^k = (p^k(XA) + p^k(XC)) - (p^k(XG) + p^k(XT)), \\ z_X^k = (p^k(XA) + p^k(XT)) - (p^k(XG) + p^k(XC)), \\ \qquad X = A, C, G, T; k = 1,2,3, \end{cases}$$

Z_curve_48bit (The Z curve parameters for frequencies of phaseindependent tri-nucleotides)

Using similar notations, the Z_curve_48bit descriptor can be calculated as follows:

$$\begin{cases} x_{XY} = (p(XYA) + p(XYG)) - (p(XYC) + p(XYT)), \\ y_{XY} = (p(XYA) + p(XYC)) - (p(XYG) + p(XYT)), \\ z_{XY} = (p(XYA) + p(XYT)) - (p(XYG) + p(XYC)), \\ \qquad X = A, C, G, T; Y = A, C, G, T \end{cases}$$

Z_curve_144bit (The Z curve parameters for frequencies of phase-specific tri-nucleotides)

Using similar notations, the Z_curve_144bit descriptor can be calculated as follows:

$$\begin{cases} x_{XY}^{k} = (p^{k}(XYA) + p^{k}(XYG)) - (p^{k}(XYC) + p^{k}(XYT)), \\ y_{XY}^{k} = (p^{k}(XYA) + p^{k}(XYC)) - (p^{k}(XYG) + p^{k}(XYT)), \\ z_{XY}^{k} = (p^{k}(XYA) + p^{k}(XYT)) - (p^{k}(XYG) + p^{k}(XYC)), \\ \qquad X = A, C, G, T; Y = A, C, G, T; k = 1,2,3. \end{cases}$$

The Z_curve descriptor has been successfully applied to short coding sequence identification of human genes (43).

Autocorrelation

The Autocorrelation encoding (21) can transform the nucleotide/protein sequences of different lengths into fixed-length vectors by measuring the correlation between any two properties. Autocorrelation encoding can generate two kinds of variables (i.e. The autocorrelation (AC) between the same property, and the cross-covariance (CC) between two different properties). There are six types of autocorrelation encodings for nucleotide sequence, including dinucleotide-based auto covariance (DAC), dinucleotide-based cross covariance (DCC), dinucleotide-based auto-cross covariance (DACC), trinucleotide-based auto covariance (TAC), trinucleotide-based cross covariance (TCC), and trinucleotide-based auto-cross covariance (TACC). The used 148 physicochemical properties for DNA dinucleotide and 22 physicochemical properties for RNA dinucleotide are listed in **Tables 9** and **10**, respectively. The used 12 physicochemical properties for DNA trinucleotide are listed in **Table 11**.

DAC (Dinucleotide-based auto covariance)

The Dinucleotide-based Auto Covariance (DAC) encoding (21) measures the correlation of the same physicochemical index between two dinucleotide separated by a distance of *lag* along the sequence. The DAC can be calculated as:

$$DAC(u, lag) = \sum_{i=1}^{L-lag-1} ((P_u(R_i R_{i+1}) - \overline{P_u})(P_u(R_{i+lag} R_{i+lag+1}) - \overline{P_u})/(L - lag - 1)),$$

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

$$\overline{P_u} = \sum_{j=1}^{L-1} P_u(R_jR_{j+1}) / (L-1).$$

The dimension of the DAC feature vector is $N \times$ LAG, where N is the number of physicochemical indices and LAG is the maximum of *lag* (*lag* = 1, 2, …, LAG).

Parameter(s):

- *Di-DNA physicochemical indices: the names of used physicochemical dinucleotides indices. (For DNA sequences)*
- *Di-RNA physicochemical indices: the names of used physicochemical dinucleotides indices. (For RNA sequences)*
- *Lag value: the number of nucleotides between two di-nucleotides.*

DCC (Dinucleotide-based Cross Covariance)

The Dinucleotide-based Cross Covariance (DCC) encoding (21) measures the correlation of two different physicochemical indices between two dinucleotides separated by *lag* nucleic acids along the sequence. The DCC encoding is calculated as:

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

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

$$\bar{P}_{u_a} = \sum_{j=1}^{L-1} P_{u_a}(R_jR_{j+1}) / (L-1).$$

The dimension of the DCC feature vector is $N \times (N\text{-}1) \times$ LAG, where N is the number of physicochemical indices and LAG is the maximum of *lag* (*lag* = 1, 2, …, LAG).

Parameter(s):

- *Di-DNA physicochemical indices: the names of used physicochemical dinucleotides indices. (For DNA sequences)*
- *Di-RNA physicochemical indices: the names of used physicochemical dinucleotides indices. (For RNA sequences)*
- *Lag value: the number of nucleotides between two di-nucleotides.*

DACC (Dinucleotide-based Auto-Cross Covariance)

The Dinucleotide-based Auto-Cross Covariance (DACC) encoding (21) is a combination of DAC and DCC encoding. Thus, the dimension of the DACC encoding is $N \times N \times$LAG, where N is the number of physicochemical indices and LAG is the maximum of the *lag* (*lag* = 1, 2, …, LAG).

Parameter(s):

- *Di-DNA physicochemical indices: the names of used physicochemical dinucleotides indices. (For DNA sequences)*
- *Di-RNA physicochemical indices: the names of used physicochemical dinucleotides indices. (For RNA sequences)*
- *Lag value: the number of nucleotides between two di-nucleotides.*

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TAC (Trinucleotide-based Auto Covariance)

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:

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

where u is a physicochemical index, L is the length of the nucleotide sequence, $P_u(R_i R_{i+1} R_{i+2})$ is the numerical value of the physicochemical index u for the trinucleotide $R_i R_{i+1} R_{i+2}$ at position i, $\overline{P_u}$ is the average value for physicochemical index u along the whole sequence:

$$\bar{P_u} = \sum_{j=1}^{L-2} P_u(R_i R_{i+1} R_{i+2}) \,/(L-2).$$

The dimension of the TAC feature vector is $N\times$LAG, where N is the number of physicochemical indices and LAG is the maximum of *lag* (*lag* = 1, 2, …, LAG).

Parameter(s):

- *Tri-DNA physicochemical indices: the names of used physicochemical trinucleotides indices.*
- *Lag value: the number of nucleotides between two tri-nucleotides.*

TCC (Trinucleotide-based Cross Covariance)

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:

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

where u_1 and u_2 are different physicochemical indices, L is the length of the nucleotide sequence, $R_i R_{i+1} R_{i+2}$ is the numerical value of the physicochemical index u_a for the dinucleotide $R_iR_{i+1}R_{i+2}$ at position *i*, $\bar{P}_{u_a}$ is the average value for physicochemical index u_a along the whole sequence:

$$\bar{P}_{u_a} = \sum_{j=1}^{L-1} P_{u_a}\left(R_j R_{j+1} R_{j+2}\right) /(L-2)$$

The dimension of the DCC feature vector is $N \times (N\text{-}1) \times$ LAG, where N is the number of physicochemical indices and LAG is the maximum of *lag* (*lag* = 1, 2, …, LAG).

Parameter(s):

- *Tri-DNA physicochemical indices: the names of used physicochemical trinucleotides indices.*
- *Lag value: the number of nucleotides between two tri-nucleotides.*

TACC (Trinucleotide-based Auto-Cross Covariance)

Like DAC encoding, the Trinucleotide-based Auto-Cross Covariance (TACC) encoding (21) 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 the *lag* (*lag* = 1, 2, …, LAG). There are three types of autocorrelation encodings for protein sequence, including auto covariance (AC), cross covariance (CC), auto-cross covariance (ACC), The amino acid properties used here are different types of amino acids index, which is retrieved from the AAindex Database (80) available at http://www.genome.jp/dbget/aaindex.html. The Autocorrelation descriptor has been successfully applied to protein fold recognition (22) and protein-protein interaction prediction (23).

Parameter(s):

- *Tri-DNA physicochemical indices: the names of used physicochemical trinucleotides indices.*
- *Lag value: the number of nucleotides between two tri-nucleotides.*

PseDNC (Pseudo dinucleotide composition)

The Pseudo Dinucleotide Composition (PseDNC) encoding (81) incorporate contiguous local sequence-order information and the global sequence-order information into the feature vector of the nucleotide sequence. The PseDNC encoding is defined:

$$D = [d_1, d_2, \dots, d_{16}, d_{16+1}, \dots, d_{16+1}, \dots, d_{16+\lambda}]^T,$$

where

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

where f_k (k=1, 2, …, 16) is the normalized occurrence frequency of dinucleotide in the nucleotide sequence, λ represent the highest counted rank (or tie) of the correlation along the nucleotide sequence, w is the weight factor ranged from 0 to 1, and θ_j (j =1,2, …, λ) is the j-tier correlation factor and is defined:

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

where the correlation function is defined:

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

where μ is the number of physicochemical indices. $P_u(R_iR_{i+1})$ is the numerical value of the u-th (u=1, 2, …, μ) physicochemical index of the dinucleotide R_iR_{i+1} at position i and $P_u(R_jR_{j+1})$ represents the corresponding value of the dinucleotide R_jR_{j+1} at position j. The PseDNC descriptor has been successfully applied to recombination spot identification (81).

Parameter(s):

- *Lambda value: the highest counted rank of the correlation along the nucleotide sequence, default is 2.*
- *Weight value: weight factor, ranged from 0 to 1, default is 0.1.*

PCPseTNC (Parallel correlation pseudo trinucleotide composition)

The Parallel Correlation Pseudo Trinucleotide Composition (PCPseTNC) encoding (82,83) is defined as:

$$D = [d_1, d_2, \dots, d_{64}, d_{64+1}, \dots, d_{64+\lambda}]^T,$$

where

$$d_k = \begin{cases} \frac{f_k}{\sum_{i=1}^{64} f_i + w\sum_{j=1}^{\lambda}\theta_j}, (1 \le k \le 64) \\ \frac{w\theta_{k-64}}{\sum_{i=1}^{64} f_i + w\sum_{j=1}^{\lambda}\theta_j}, (65 \le k \le 64+\lambda) \end{cases},$$

where f_k (k=1, 2, …, 64) is the normalized occurrence frequency of trinucleotide in the DNA sequence, λ represent the highest counted rank (or tie) of the correlation along the DNA sequence, w is the weight factor ranged from 0 to 1, and θ_j (j =1,2, …, λ) is the j-tier correlation factor and is defined:

$$\begin{cases} \theta_1 = \frac{1}{L-3}\sum_{i=1}^{L-3} \Theta(R_iR_{i+1}R_{i+2}, R_{i+1}R_{i+2}R_{i+3}) \\ \theta_2 = \frac{1}{L-4}\sum_{i=1}^{L-4} \Theta(R_iR_{i+1}R_{i+2}, R_{i+2}R_{i+3}R_{i+4}) \\ \theta_3 = \frac{1}{L-5}\sum_{i=1}^{L-5} \Theta(R_iR_{i+1}R_{i+2}, R_{i+3}R_{i+4}R_{i+5}) \qquad (\lambda < L), \\ \quad \cdots \\ \theta_\lambda = \frac{1}{L-2-\lambda}\sum_{i=1}^{L-2-\lambda} \Theta(R_iR_{i+1}R_{i+2}, R_{i+\lambda}R_{i+\lambda+1}R_{i+\lambda+2}) \end{cases}$$

where the correlation function is defined:

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

where μ is the number of physicochemical indices. $P_u(R_iR_{i+1}R_{i+2})$ is the numerical value of the u-th (u=1, 2, …, μ) physicochemical index of the dinucleotide $R_iR_{i+1}R_{i+2}$ at position i and $P_u(R_jR_{j+1}R_{j+2})$ represents the corresponding value of the dinucleotide $R_jR_{j+1}R_{j+2}$ at position j. The PCPseTNC descriptor has been successfully applied to recombination spot identification (83).

Parameter(s):

- *Lambda value: the highest counted rank of the correlation along the nucleotide sequence, default is 2.*
- *Weight value: weight factor, ranged from 0 to 1, default is 0.1.*
- *Tri-DNA physicochemical indices: the names of used physicochemical trinucleotides indices.*

SCPseDNC (Series correlation pseudo dinucleotide composition)

The Series Correlation Pseudo Dinucleotide Composition (SCPseDNC) encoding (82) is defined as:

$$D = [d_1, d_2, \dots, d_{16}, d_{16+1}, \dots, d_{16+\lambda}, d_{16+\lambda+1}, \dots, d_{16+\lambda\Lambda}]^T,$$

where

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

where f_k (k=1, 2, …, 16) is the normalized occurrence frequency of dinucleotide in the nucleotide sequence, λ represent the highest counted rank (or tie) of the correlation along the nucleotide sequence, w is the weight factor ranged from 0 to 1, Λ is the number of physicochemical indices and θ_j (j =1,2, …, λ) is the j-tier correlation factor and is defined:

$$\begin{cases} \theta_1 = \dfrac{1}{L-3} \sum_{i=1}^{L-3} J_{i,i+1}^{1} \\ \theta_2 = \dfrac{1}{L-3} \sum_{i=1}^{L-3} J_{i,i+1}^{2} \\ \quad \cdots \\ \theta_\Lambda = \dfrac{1}{L-3} \sum_{i=1}^{L-3} J_{i,i+1}^{\Lambda} \qquad (\lambda < L-2), \\ \quad \cdots \\ \theta_{\lambda\Lambda} = \dfrac{1}{L-\lambda-2} \sum_{i=1}^{L-\lambda-2} J_{i,i+\lambda}^{\Lambda-1} \\ \theta_{\lambda\Lambda} = \dfrac{1}{L-\lambda-2} \sum_{i=1}^{L-\lambda-2} J_{i,i+\lambda}^{\Lambda} \end{cases}$$

where the correlation function is defined:

$$\begin{cases} J_{i,i+m}^{\zeta} = P_u(R_i R_{i+1}) P_u(R_{i+m} R_{i+m+1}) \\ \zeta = 1,2,\ldots,\Lambda; m = 1,2,\ldots,\lambda; i = 1,2,\ldots,L-\lambda-2 \end{cases},$$

where μ is the number of physicochemical indices. $P_u(R_i R_{i+1})$ is the numerical value of the u-th (u=1, 2, …, μ) physicochemical index of the dinucleotide $R_i R_{i+1}$ at position i and $P_u(R_j R_{j+1})$ represents the corresponding value of the dinucleotide $R_j R_{j+1}$ at position j. The SCPseDNC descriptor has been successfully applied to recombination spot identification (83).

Parameter(s):

- *Lambda value: the highest counted rank of the correlation along the nucleotide sequence, default is 2.*
- *Weight value: weight factor, ranged from 0 to 1, default is 0.1.*
- *Di-DNA physicochemical indices: the names of used physicochemical dinucleotides indices. (For DNA sequences)*

- *Di-RNA physicochemical indices: the names of used physicochemical dinucleotides indices. (For RNA sequences)*

SCPseTNC (Series correlation pseudo trinucleotide composition)

The Series Correlation Pseudo Trinucleotide Composition (SCPseTNC) encoding (82) is defined as:

$$D = [d_1, d_2, \dots, d_{64}, d_{64+1}, \dots, d_{64+\lambda}, d_{64+\lambda+1}, d_{64+\lambda+1}, \dots, d_{64+\lambda\Lambda}]^T,$$

where

$$d_k = \begin{cases} \dfrac{f_k}{\sum_{i=1}^{64} f_i + w\sum_{j=1}^{\lambda}\theta_j}, (1 \le k \le 64) \\ \dfrac{w\theta_{k-64}}{\sum_{i=1}^{64} f_i + w\sum_{j=1}^{\lambda\Lambda}\theta_j}, (65 \le k \le 64 + \lambda\Lambda) \end{cases},$$

where f_k (k=1, 2, …, 64) is the normalized occurrence frequency of trinucleotide in the DNA sequence, λ represent the highest counted rank (or tie) of the correlation along the DNA sequence, w is the weight factor ranged from 0 to 1, Λ is the number of physicochemical indices and θ_j (j =1,2, …, λ) is the j-tier correlation factor and is defined:

$$\begin{cases} \theta_1 = \dfrac{1}{L-4}\sum_{i=1}^{L-4} J_{i,i+1}^{1} \\ \theta_2 = \dfrac{1}{L-4}\sum_{i=1}^{L-4} J_{i,i+1}^{2} \\ \quad \dots \\ \theta_\Lambda = \dfrac{1}{L-4}\sum_{i=1}^{L-4} J_{i,i+1}^{\Lambda} \qquad (\lambda < L-3), \\ \quad \dots \\ \theta_{\lambda\Lambda} = \dfrac{1}{L-\lambda-3}\sum_{i=1}^{L-\lambda-3} J_{i,i+\lambda}^{\Lambda-1} \\ \theta_{\lambda\Lambda} = \dfrac{1}{L-\lambda-3}\sum_{i=1}^{L-\lambda-3} J_{i,i+\lambda}^{\Lambda} \end{cases}$$

where the correlation function is defined:

$$\begin{cases} J_{i,i+m}^{\zeta} = P_u(R_iR_{i+1})P_u(R_{i+m}R_{i+m+1}R_{i+m+2}) \\ \zeta = 1,2,\dots,\Lambda; m = 1,2,\dots,\lambda; i = 1,2,\dots,L-\lambda-3 \end{cases},$$

where μ is the number of physicochemical indices. $P_u(R_iR_{i+1}R_{i+2})$ is the numerical value of the u-th (u=1, 2, …, μ) physicochemical index of the dinucleotide $R_iR_{i+1}R_{i+2}$ at position i and $P_u(R_jR_{j+1}R_{j+2})$ represents the corresponding value of the dinucleotide $R_jR_{j+1}R_{j+2}$ at position j.

Parameter(s):

- *Lambda value: the highest counted rank of the correlation along the nucleotide sequence, default is 2.*
- *Weight value: weight factor, ranged from 0 to 1, default is 0.1.*
- *Tri-DNA physicochemical indices: the names of used physicochemical trinucleotides indices.*

11. Commonly Used Feature Descriptors and Parameters for Protein or Peptide Sequences

Amino Acid Composition (AAC)

The Amino Acid Composition (AAC) encoding (2) calculates the frequency of each amino acid type in a protein or peptide sequence.

Enhanced Amino Acid Composition (EAAC)

The Enhanced Amino Acid Composition (EAAC) feature calculates the AAC based on the sequence window of fixed length that continuously slides from the N- to C-terminus of each peptide and can be usually applied to encode the peptides with an equal length.

Parameters:

- *Sliding window size:* the length of the sliding window, default is 5.

Enhanced GAAC (EGAAC)

The Enhanced GAAC (EGAAC) is also for the first time proposed in this work. It calculates GAAC in windows of fixed length continuously sliding from the N- to C-terminal of each peptide and is usually applied to peptides with an equal length.

Parameters:

- *Sliding window size:* the length of the sliding window, default is 5.

Composition of k-spaced Amino Acid Pairs (CKSAAP)

The CKSAAP feature encoding calculates the frequency of amino acid pairs separated by any *k* residues (*k* = 0, 1, 2, … , 5. The default maximum value of *k* is 5) (5,6,84,85).

Parameters:

- *Gap value: the length of k-spaced amino acids, default is 3.*

Composition of k-Spaced Amino Acid Group Pairs (CKSAAGP)

The Composition of *k*-Spaced Amino Acid Group Pairs (CKSAAGP) is a variation of the CKSAAP descriptor, which is our own proposal. It calculates the frequency of amino acid group pairs separated by any *k* residues.

Parameters:

- *Gap value: the length of k-spaced amino acids, default is 3.*

Di-Peptide Composition (DPC)

The Dipeptide Composition (7) gives 400 descriptors. It is defined as:

$$D(r,s)=\frac{N_{rs}}{N-1}, \qquad r,s\in\{A,C,D,\dots Y\}$$

where N_{rs} is the number of dipeptides represented by amino acid types r and s.

Grouped Di-Peptide Composition (GDPC)

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:

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

where N_{rs} is the number of tripeptides represented by amino acid type groups *r* and *s*, *N* is the length of a protein or peptide sequence.

Tri-Peptide Composition (TPC)

The Tripeptide Composition (TPC) (2) gives 8000 descriptors, defined as:

$$f(r,s,t)=\frac{N_{rst}}{N-2}, \quad r,s,t\in\{A,C,D,...,Y\}$$

where N_{rst} is the number of tripeptides represented by amino acid types *r*, *s* and *t.*

Gouped Tri-Peptide Composition (GTPC)

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 tripeptides represented by amino acid type groups *r*, *s* and *t*. $\underline{N}$ is the length of a protein or peptide sequence.

Dipeptide Deviation from Expected Mean (DDE)

The Dipeptide Deviation from Expected Mean feature vector (7) is constructed by computing three parameters, i.e. dipeptide composition (D_c), theoretical mean (T_m), and theoretical variance (T_v). The above three parameters and the DDE are computed as follows. $D_c(r,s)$, the dipeptide composition measure for the dipeptide '*rs'*, is given as

$$D_c(r,s)=\frac{N_{rs}}{N-1}, \qquad r,s\in\{A,C,D,\dots Y\}$$

where N_{rs} is the number of dipeptides represented by amino acid types *r* and *s* and *N* is the length of the protein or peptide. $T_m(r,s)$, the theoretical mean, is given by:

$$T_m(r,s)=\frac{C_r}{C_N}\times\frac{C_s}{C_N}$$

where C_r is the number of codons that code for the first amino acid and C_s is the number of codons that code for the second amino acid in the given dipeptide '*rs*'. C_N is the total number of possible codons, excluding the three stop codons (i.e., 61). T_v (*r,s*), the theoretical variance of the dipeptide '*rs*', is given by:

$$T_v(r,s)=\frac{T_m(r,s)(1-T_m(r,s))}{N-1}$$

Finally, *DDE(r,s)* is calculated as:

$$DDE(r,s) = \frac{D_c(r,s) - T_m(r,s)}{\sqrt{T_v(r,s)}}$$

Binary

In the Binary encoding (31,86), each amino acid is represented by a 20-dimensional binary vector, e.g.

A is encoded by (10000000000000000000), C is encoded by (01000000000000000000), …, Y is encoded by (00000000000000000001), respectively. This encoding scheme is often used to encode peptides with an equal length.

Binary_6bit

In this descriptor, the 6-letter exchange group $\{e_1, e_2, e_3, e_4, e_5, e_6\}$ is adopted to represent a protein sequence (16,32), where $e_1 \in \{H, R, K\}$, $e_2 \in \{D, E, N, D\}$, $e_3 \in \{C\}$, $e_4 \in \{S, T, P, A, G\}$, $e_5 \in \{M, I, L, V\}$, $e_6 \in \{F, Y, W\}$. Exchange groups represent conservative replacements through evolution. These exchange groups are effectively equivalence classes of amino acids and are derived from PAM. For example, the protein sequence PVKTNVK can be represented as $e_4e_5e_1e_4e_2e_5e_1$. Then, each group is represented by a 6-dimensional binary vector, e.g. e_1 is encoded by (100000), e_2 is encoded by (010000), …, e_6 is encoded by (000001).

Binary_5bit_type 1

Like binary_6bit descriptor, the 5-letter amino acid group $\{e_1, e_2, e_3, e_4, e_5\}$ is adopted to represent a protein sequence, and each group is represented by a 5-dimensional binary vector (16,33). $e_1 \in \{G, A, V, L, M, I\}$, $e_2 \in \{F, Y, W\}$, $e_3 \in \{K, R, H\}$, $e_4 \in \{D, E\}$, $e_5 \in \{S, T, C, P, N, Q\}$. Then, each group is represented by a 5-dimensional binary vector, e.g. e_1 is encoded by (10000), e_2 is encoded by (01000), …, e_5 is encoded by (00001).

Binary_5bit_type 2

For this descriptor, it is based on all the possible ways that ones and zeros can be combined in a five bit unit. There are 32 possible ways to represent 20 amino acids. When the representations with no or all ones and those with 1 or 4 ones are removed there are exactly twenty representations. And A is encoded by (00011), C (00101), D (00110), E (00111), F(01001), G (01010), H (01011), I (01100), K (01101), L (01110), M (10001), N (10010), P (10011), Q (10100), R (10101), S (10110), T (11000), V (11001), W (11010), Y (11100).

Binary_3bit_type 1-7

For this descriptor, the 3-letter amino acid group $\{e_1, e_2, e_3\}$ is adopted to represent a protein sequence, and each group is represented by a 3-dimensional binary vector (77). Then, each group is represented by a 5-dimensional binary vector, e.g. e_1 is encoded by (100), e_2 is encoded by (010), e_3 is encoded by (001). The division of the amino acids based on physicochemical properties (PRAM900101) in **Table 12**. The difference of the type 1 to type 7 subtypes is the different division of amino acids. The division of amino acids for type 2 to 7 is based on “Normalized van der Waals volume”, “Polarity”, “Polarizability”, “Charge”, “Secondary structure” and “Solvent accessibility” in **Table 12**.

Table 12. Amino acid physicochemical attributes and the division of the amino acids into three groups according to each attribute.

Attribute	Division		
Hydrophobicity_PRAM900101	Polar: RKEDQN	Neutral: GASTPHY	Hydrophobicity: CLVIMFW
Hydrophobicity_ARGP820101	Polar: QSTNGDE	Neutral: RAHCKMV	Hydrophobicity: LYPFIW
Hydrophobicity_ZIMJ680101	Polar: QNGSWTDERA	Neutral: HMCKV	Hydrophobicity: LPFYI
Hydrophobicity_PONP930101	Polar: KPDESNQT	Neutral: GRHA	Hydrophobicity: YMFWLCVI
Hydrophobicity_CASG920101	Polar: KDEQPSRNTG	Neutral: AHYMLV	Hydrophobicity: FIWC
Hydrophobicity_ENGD860101	Polar: RDKENQHYP	Neutral :SGTAW	Hydrophobicity: CVLIMF
Hydrophobicity_FASG890101	Polar: KERSQD	Neutral: NTPG	Hydrophobicity: AYHWVMFLIC
Normalized van der Waals volume	Volume range: 0-2.78 GASTPD	Volume range: 2.95-94.0 NVEQIL	Volume range: 4.03-8.08 MHKFRYW
Polarity	Polarity value: 4.9-6.2 LIFWCMVY	Polarity value: 8.0-9.2 PATGS	Polarity value: 10.4-13.0 HQRKNED
Polarizability	Polarizability value: 0-1.08 GASDT	Polarizability value: 0.128-120.186 GPNVEQIL	Polarizability value: 0.219-0.409 KMHFRYW
Charge	Positive: KR	Neutral: ANCQGHILMFPSTWYV	Negative: DE
Secondary structure	Helix: EALMQKRH	Strand: VIYCWFT	Coil: GNPSD
Solvent accessibility	Buried: ALFCGIVW	Exposed: PKQEND	Intermediate: MPSTHY

AESNN3 (Learn from alignments)

For this descriptor, each amino acid type is described using a three-dimensional vector. Values are taken from the three hidden units from the neural network trained on structure alignments (16,34). The values are listed in **Table 13**.

Table 13. AESNN3 values learning from alignments.

Amino acids	AESNN3 values		
A	-0.99	-0.61	0.00
R	0.28	-0.99	-0.22
N	0.77	-0.24	0.59
D	0.74	-0.72	-0.35
C	0.34	0.88	0.35
Q	0.12	-0.99	-0.99
E	0.59	-0.55	-0.99
G	-0.79	-0.99	0.10
H	0.08	-0.71	0.68
I	-0.77	0.67	-0.37
L	-0.92	0.31	-0.99
K	-0.63	0.25	0.50
M	-0.80	0.44	-0.71
F	0.87	0.65	-0.53
P	-0.99	-0.99	-0.99
S	0.99	0.40	0.37
T	0.42	0.21	0.97
W	-0.13	0.77	-0.90
Y	0.59	0.33	-0.99
V	-0.99	0.27	-0.52

Moran

The autocorrelation descriptors are defined based on the distribution of amino acid properties along the sequence (17,19,20). The amino acid properties used here are different types of amino acids index, which is retrieved from the AAindex Database (80) available at http://www.genome.jp/dbget/aaindex.html/. All the amino acid indices are centralized and standardized prior to the calculation:

$$P_r = \frac{P_r - \overline{P}}{\sigma},$$

where $\overline{P}$ is the average of the properties of the 20 amino acids and σ is the standard deviation of the properties of the 20 amino acids. $\overline{P}$ and σ can be calculated as follows:

$$\overline{P} = \frac{\sum_{r=1}^{20} P_r}{20}, \quad \sigma = \sqrt{\frac{1}{20}\sum_{r=1}^{20}(P_r - \overline{P})^2}.$$

The Moran autocorrelation descriptors (17,18) can thus be defined as:

$$I(d)=\frac{\frac{1}{N-d}\sum_{i=1}^{N-d}(P_i-\overline{P}')(P_{i+d}-\overline{P}')}{\frac{1}{N}\sum_{i=1}^{N}(P_i-\overline{P}')^2}, \qquad d=1,2,3...,nlag,$$

where d is the lag of the autocorrelation, $nlag$ is the maximum value of the lag, P_i and P_{i+d} are the properties of the amino acids at positions i and $i + d$, respectively. $\overline{P}'$ is the average of the considered property P over the entire sequence of length N and is calculated as:

$$\overline{P}'=\frac{\sum_{i=1}^{N}P_i}{N}.$$

The Moran descriptor has been successfully applied to membrane protein type prediction (17) and protein secondary structural content prediction (18).

Parameters:

- *Physicochemical properties for proteins: the names of used physicochemical amino acids indices.*

Geary

The Geary autocorrelation descriptors for a protein or peptide sequence are defined as:

$$C(d)=\frac{\frac{1}{2(N-d)}\sum_{i=1}^{N-d}(P_i-P_{i+d})^2}{\frac{1}{N-1}\sum_{i=1}^{N}(P_i-\overline{P}')^2}, \qquad d=1,2,...,nlag,$$

where d, P, P_i and P_{i+d}, $nlag$ have the same definitions as described above. The Geary descriptor has been successfully applied to population structure inferring (19).

Parameters:

- *Physicochemical properties for proteins: the names of used physicochemical amino acids indices.*

NMBroto (Normalized moreau-broto autocorrelation)

The Moreau-Broto autocorrelation descriptors are defined as follows:

$$AC(d) = \sum_{i=1}^{N-d} P_i \times P_{i+d}, \qquad d = 1, 2, ..., nlag.$$

The normalized Moreau-Broto autocorrelation descriptors are thus defined as:

$$ATS(d) = \frac{AC(d)}{N-d}, \qquad d = 1, 2, ..., nlag.$$

The NMBroto descriptor has been successfully applied to protein helix content prediction (20).

Parameters:

- *Physicochemical properties for proteins: the names of used physicochemical amino acids indices.*

Composition/Transition/Distribution (CTD)

The Composition, Transition and Distribution (CTD) features represent the amino acid distribution patterns of a specific structural or physicochemical property in a protein or peptide sequence (8-12). 13 types of physicochemical properties have been previously used for computing these features (**Table 12**). These include hydrophobicity, normalized Van der Waals Volume, polarity, polarizability, charge, secondary structures and solvent accessibility. These descriptors are calculated according to the following procedures: (i) The sequence of amino acids is transformed into a sequence of certain structural or physicochemical properties of residues; (ii) Twenty amino acids are divided into three groups for each of the seven different physicochemical attributes based on the main clusters of the amino acid indices of Tomii and Kanehisa (87). The groups of amino acids are listed in **Table 12**. The Composition/Transition/Distribution descriptors has been successfully applied to protein folding class prediction (10,11), enzyme family classification (9), RNA-binding protein prediction (12), protein structural prediction (87) and anti-cancer peptide prediction (77).

CTDC

Taking the hydrophobicity attribute as an example, all amino acids are divided into three groups: polar, neutral and hydrophobic (**Table 12**). The Composition descriptor consists of three values: the global compositions (percentage) of polar, neutral and hydrophobic residues of the protein. An illustrated example of this encoding scheme is provided in the following **Figure 15**. The Composition descriptor can be calculated as follows:

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

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

CTDT

The Transition descriptor T also consists of three values (10,11): A transition from the polar group to the neutral group is the percentage frequency with which a polar residue is followed by a neutral residue or a neutral residue by a polar residue. Transitions between the neutral group and the hydrophobic group and those between the hydrophobic group and the polar group are defined in a similar way. The transition descriptor can then be calculated as:

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

where $N(r,s)$ and $N(s,r)$ are the numbers of dipeptides encoded as "*rs*" and "*sr*" respectively in the sequence, while N is the length of the sequence. An illustrated example of this encoding scheme is provided in the following **Figure 15.**

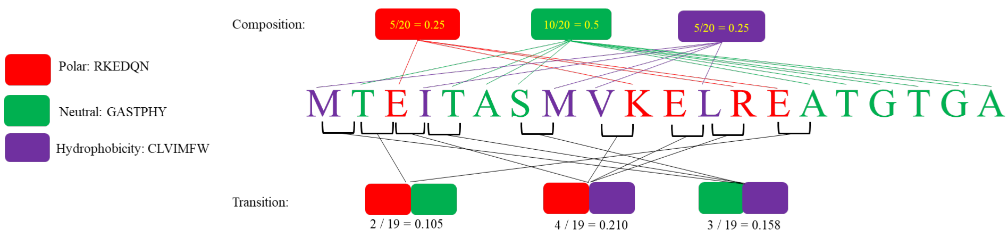

Figure 15. An example of the calculation of composition and transition descriptors. This example uses the hydrophobicity attribute.

CTDD

The Distribution descriptor consists of five values for each of the three groups (polar, neutral and hydrophobic) (10,11), namely the corresponding fraction of the entire sequence, where the first residue of a given group is located, and where 25, 50, 75 and 100% of occurrences are contained.

For example, we start with the first residue up to and including the residue that marks 25/50/75/100% of occurrences for residues of any given group and then we simply divide the position of this residue by the length of the entire sequence.

CTriad (Conjoint triad)

The Conjoint Triad descriptor (CTriad) considers the properties of one amino acid and its vicinal amino acids by regarding any three continuous amino acids as a single unit (13). First, the protein sequence is represented by a binary space (*V, F*), where *V* denotes the vector space of the sequence features, and each feature (V_i) represents a sort of triad type; *F* is the number vector corresponding to *V*, where f_i, the value of the *i*-th dimension of *F*, is the number of type V_i appearing in the protein sequence. For the amino acids that have been catalogued into seven classes, the size of *V* should be equal to 7 x 7 x 7=343. Accordingly, i = 1, 2, 3, …, 343. An illustrated example of this encoding scheme is provided in the following **Figure 16**. In principle, the longer a protein sequence, the higher the probability to have larger values of f_i, confounding the comparison of proteins with different lengths. Thus, we define a new parameter, d_i, by normalizing f_i with the following equation:

$$d_i = \frac{f_i - \min\{f_1, f_2, ..., f_{343}\}}{\max\{f_1, f_2, ..., f_{343}\}}.$$

The CTriad descriptors has been successfully applied to protein-protein interaction prediction (13).

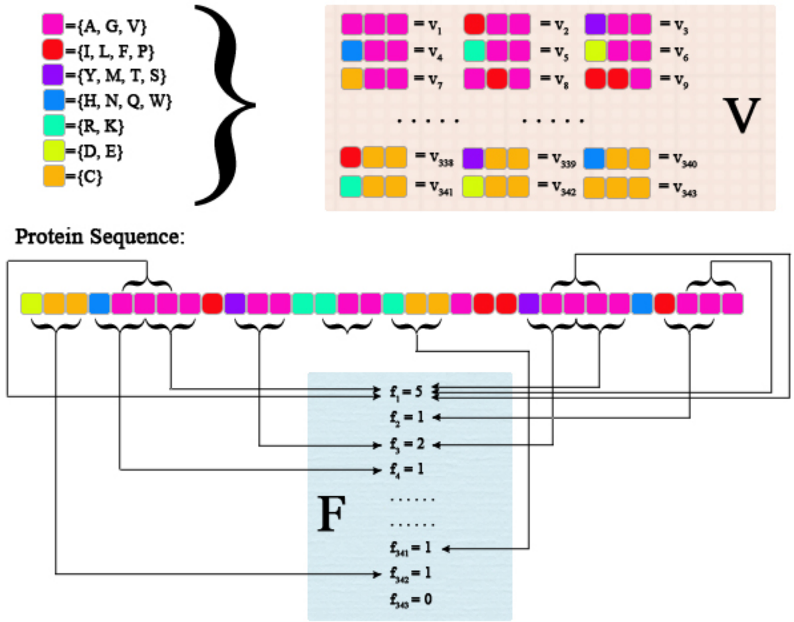

Figure 16. Schematic diagram for constructing the vector space (*V, F*) of a given protein sequence. *V* is the vector space of the sequence features; each feature (V_i) represents a triad composed of three consecutive amino acids; *F* is the number vector corresponding to *V*, and the value of the *i*-th entry of *F*, denoted f_i, is the number of occurrences that the triad associated with V_i appearing in the protein sequence. The figure was adapted from the Supplementary Figure in (13).

KSCTriad (Conjoint k-spaced Triad)

The *k*-Spaced Conjoint Triad (KSCTriad) 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). An illustrated example of this encoding scheme is provided in **Figure 17**.

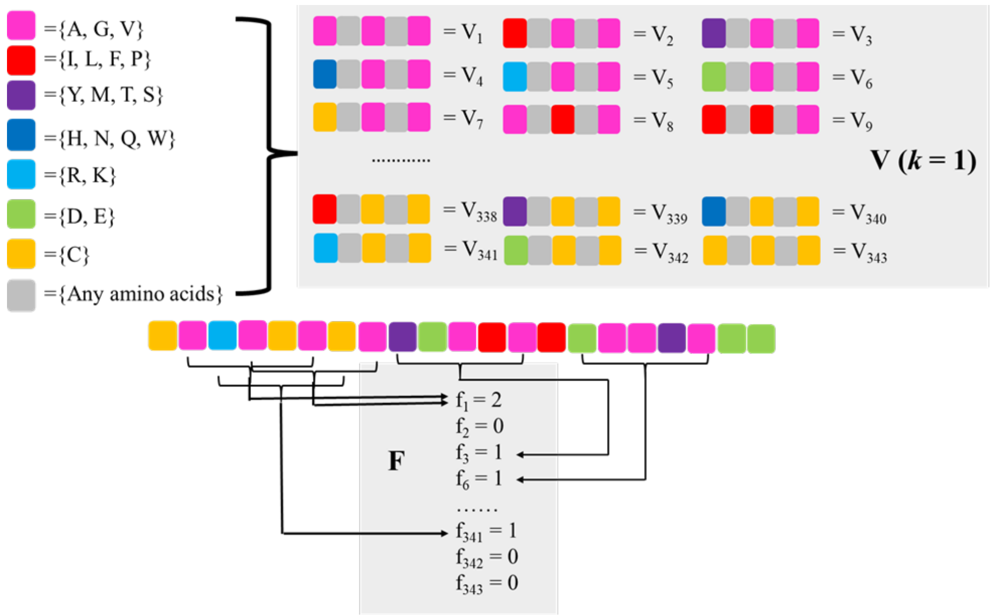

Figure 17. A schematic diagram for constructing the vector space (V, F) of protein sequence (k=1).

Parameters:

- *Gap value: the length of k-spaced amino acids, default is 3.*

SOCNumber (Sequence-Order-Coupling Number)

The d-th rank sequence-order-coupling number is defined as:

$$\tau_d = \sum_{i=1}^{N-d} (d_{i,i+d})^2, \qquad d = 1,2,3,\ldots,nlag\,,$$

where $d_{i,i+d}$ is the entry in a given distance matrix describing a distance between the two amino acids at position i and $i + d$, *nlag* denotes the maximum value of the lag (default value: 30) and N is the length of a protein or peptide sequence. As distance matrix both the Schneider-Wrede physicochemical distance matrix (26) used by Kuo-Chen Chou, and the chemical distance matrix by Grantham (88) are used. Accordingly, the descriptor dimension will be *nlag* x 2. The quasi-sequence-order descriptors described next also utilizes the two matrices. An illustrated example of this encoding scheme is provided in the following **Figure 18**.

Note: the length of the protein must be not less than the maximum value of *nlag*.

Parameter(s):

- *Lag value: the maximum value of the lag, default value is 3.*

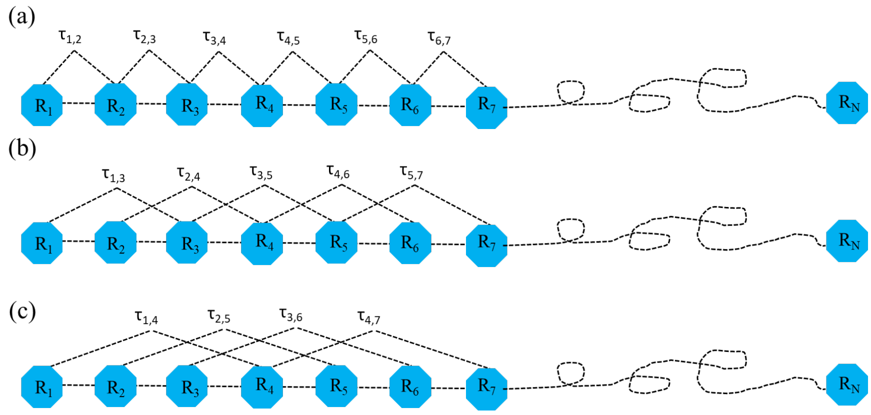

Figure 18. A schematic drawing to show (a) the 1st-rank, (b) the 2nd-rank, and (3) the 3rd-rank sequence-order-coupling mode along a protein sequence. (a) reflects the coupling mode between all the most adjacent residues, (b) shows the coupling between the adjacent plus one residue, and (c) shows the coupling between the adjacent plus two residues. This figure is adapted from (24).

QSOrder (Quasi-sequence-order)

For each amino acid type, a quasi-sequence-order descriptor can be defined as:

$$X_r = \frac{f_r}{\sum_{r=1}^{20} f_r + w \sum_{d=1}^{nlag} \tau_d}, \qquad r = 1, 2, \ldots, 20$$

where f_r is the normalized occurrence of amino acid type r and w is a weighting factor (w = 0.1), *nlag* and τ_d have the same definitions as described above. These are the first 20 quasi-sequence-order descriptors. The other 30 quasi-sequence-order descriptors are defined as:

$$X_d = \frac{w\tau_d - 20}{\sum_{r=1}^{20} f_r + w \sum_{d=1}^{nlag} \tau_d}, \qquad d = 21, 22, \ldots, 20 + nlag\ .$$

The SOCNumber and QSOrder descriptors have been successfully applied to protein subcellular location prediction (25,26).

Parameter(s):

- *Lag value: the maximum value of the lag, default value is 3.*

- *Weight factor: the weight factor value, range from 0 to 1, and default is 0.05.*

PAAC (Pseudo-Amino Acid Composition)

This group of descriptors has been proposed in (27,28). Let $H_1^o(i)$, $H_2^o(i)$, $M^o(i)$ for $i = 1, 2, 3, \ldots$ 20 be the original hydrophobicity values, the original hydrophilicity values and the original side chain masses of the 20 natural amino acids, respectively. They are converted to the following quantities by a standard conversion:

$$H_1(i) = \frac{H_1^o(i) - \frac{1}{20}\sum_{i=1}^{20} H_1^o(i)}{\sqrt{\frac{\sum_{i=1}^{20}[H_1^o(i) - \frac{1}{20}\sum_{i=1}^{20} H_1^o(i)]^2}{20}}},$$

where $H_2^o(i)$ and $M^o(i)$ are normalized as $H_2(i)$ and $M(i)$ in the same manner. An example of the correlation function is provided in the following **Figure 19**.

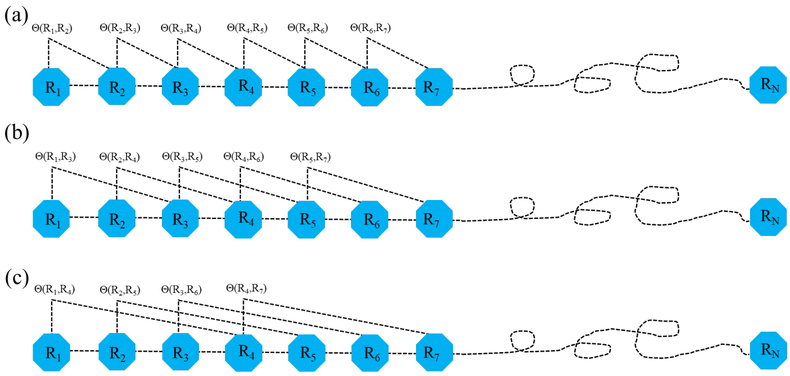

Figure 19. A schematic illustration showing (a) the first-tier, (b) the second-tier, and (3) the third-tier sequence order correlation mode along a protein sequence. (a) reflects the coupling mode between all the most adjacent residues, (b) shows the coupling between the adjacent plus one residue, and (c) shows the coupling between the adjacent plus two residues. This figure is adapted from (27) for illustration purposes.

Next, a correlation function can be defined as:

$$\Theta(R_i, R_j) = \frac{1}{3}\{[H_1(R_i) - H_1(R_j)]^2 + [H_2(R_i) - H_2(R_j)]^2 + [M(R_i) - M(R_j)]^2\}.$$

This correlation function is actually an averaged value for the three amino acid properties: hydrophobicity value, hydrophilicity value and side chain mass. Therefore, we can extend this definition of correlation function for one amino acid property or for a set of *n* amino acid properties. For one amino acid property, the correlation can be defined as:

$$\Theta(R_i, R_j) = [H_1(R_i) - H_1(R_j)]^2 ,$$

where $H(R_i)$ is the amino acid property of amino acid R_i after standardization.

For a set of *n* amino acid properties, it can be defined as:

$$\Theta(R_i, R_j) = \frac{1}{n}\sum_{n=1}^{n}[H_k(R_i) - H_k(R_j)]^2 ,$$

where $H_k(R_i)$ is the *k*-th property in the amino acid property set for amino acid R_i.

A set of descriptors called sequence order-correlated factors are defined as:

$$\theta_1 = \frac{1}{N-1}\sum_{i=1}^{N-1}\Theta(R_i, R_{i+1}) ,$$

$$\theta_2 = \frac{1}{N-2}\sum_{i=1}^{N-2}\Theta(R_i, R_{i+2}) ,$$

$$\theta_3 = \frac{1}{N-3}\sum_{i=1}^{N-3}\Theta(R_i, R_{i+3}) ,$$

$$\ldots,$$

$$\theta_\lambda = \frac{1}{N-\lambda}\sum_{i=1}^{N-\lambda}\Theta(R_i, R_{i+\lambda}) ,$$

where λ ($\lambda < N$) is an integer parameter to be chosen. Let f_i be the normalized occurrence frequency of amino acid *i* in the protein sequence. Then, a set of 20 + λ descriptors called the pseudo-amino acid composition for a protein sequence can be defines as:

$$X_c = \frac{f_c}{\sum_{r=1}^{20} f_r + w\sum_{j=1}^{\lambda}\theta_j}, \qquad (1 < c < 20) ,$$

$$X_c = \frac{w\theta_{c-20}}{\sum_{r=1}^{20} f_r + w\sum_{j=1}^{\lambda}\theta_j}, \qquad (21 < c < 20 + \lambda) ,$$

where *w* is the weighting factor for the sequence-order effect and is set to $w = 0.05$ as suggested by

Chou *et al*. (27).

Parameter(s):

- *Lambda value: integer, should be small than sequence length, default is 2.*
- *Weight value: weight factor, ranged from 0 to 1, default is 0.05.*

APAAC (Amphiphilic Pseudo-Amino Acid Composition)

Amphiphilic Pseudo-Amino Acid Composition (APAAC) was proposed in (27,28). The definition of this set of features is similar to the PAAC descriptors. Using $H_1(i)$ and $H_2(j)$ as previously defined, the hydrophobicity and hydrophilicity correlation functions are defined as:

$$H_{i,j}^1 = H_1(i)H_1(j)$$
$$H_{i,j}^2 = H_2(i)H_2(j),$$

respectively. An illustrated example of the correlation functions is provided in the following **Figure 20**. Thus, sequence order factors can be defined as:

$$\tau_1 = \frac{1}{N-1}\sum_{i=1}^{N-1} H_{i,i+1}^1$$
$$\tau_2 = \frac{1}{N-1}\sum_{i=1}^{N-1} H_{i,i+1}^2$$
$$\tau_3 = \frac{1}{N-2}\sum_{i=1}^{N-2} H_{i,i+2}^1$$
$$\tau_4 = \frac{1}{N-2}\sum_{i=1}^{N-2} H_{i,i+2}^2$$
$$\ldots$$
$$\tau_{2\lambda-1} = \frac{1}{N-\lambda}\sum_{i=1}^{N-\lambda} H_{i,i+\lambda}^1$$
$$\tau_{2\lambda} = \frac{1}{N-\lambda}\sum_{i=1}^{N-\lambda} H_{i,i+\lambda}^2$$

Then, Amphiphilic Pseudo-Amino Acid Composition (APAAC) is defined as:

$$P_c = \frac{f_c}{\sum_{r=1}^{20} f_r + w\sum_{j=1}^{2\lambda}\tau_j}, \qquad (1 < c < 20)$$
$$P_c = \frac{\omega\tau_u}{\sum_{r=1}^{20} f_r + w\sum_{j=1}^{2\lambda}\tau_j}, \qquad (21 < u < 20 + 2\lambda)$$

where *w* is the weighting factor. In *iLearnPlus* this factor is set to *w* = 0.5 as described in Chou's work (27). The PAAC and APAAC have been successfully applied to protein cellular attributes prediction (27) and enzyme subfamily classes prediction (28).

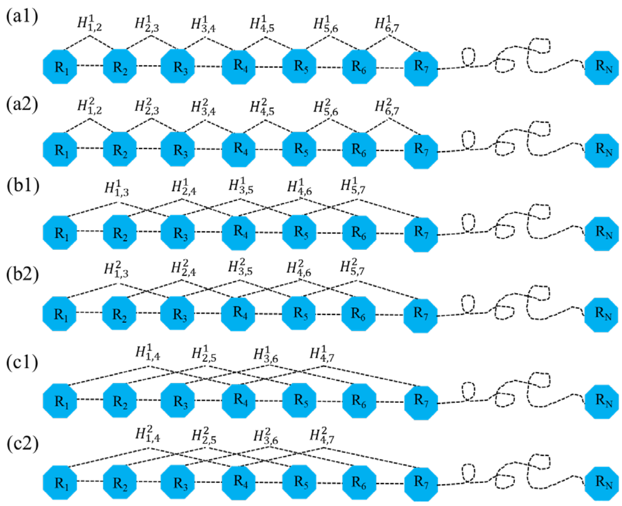

Figure 20. A schematic diagram to show (a1/a2) the first-rank, (b1/b2) the second-rank and (c1/c2) the third-rank sequence-order-coupling mode along a protein sequence through a hydrophobicity/hydrophilicity correlation function, where $H^1_{i,j}$ and $H^2_{i,j}$ are given by the aforementioned equation. Panels (a1/a2) reflects the coupling mode between the most adjacent residues, panels (b1/b2) shows the coupling between the adjacent plus one residue, and panels (c1/c2) shows the coupling between the adjacent plus two residues. This figure is adapted from (28) for illustration purposes.

Parameter(s):

- *Lambda value: integer, should be small than sequence length, default is 2.*
- *Weight value: weight factor, ranged from 0 to 1, default is 0.05.*

AAindex

Physicochemical properties of amino acids are the most intuitive features for representing biochemical reactions and have been extensively applied in bioinformatics research. The amino acid indices (AAindex) database (80) collects many published indices representing physicochemical properties of amino acids. For each physicochemical property, there is a set of 20 numerical values for all amino acids. Currently, 544 physicochemical properties can be retrieved from the AAindex database. After removing physicochemical properties with value 'NA' for any of the amino acids, 531 physicochemical properties were left. In contrast to the residue-based encoding methods of amino acid identity and evolutionary information, a vector of 531 mean values is used to represent a sample for various window sizes. The AAINDEX descriptor (35) can be applied to encode peptides of equal length.

Parameters:

- *Physicochemical properties for proteins: the names of used physicochemical amino acids indices.*

BLOSUM62

In this descriptor, the BLOSUM62 matrix is employed to represent the protein primary sequence information as the basic feature set. A matrix comprising of $m \times n$ elements is used to represent each residue in a training dataset, where n denotes the peptide length and $m = 20$, which elements comprise 20 amino acids. Each row in the BLOSUM62 matrix is adopted to encode one of 20 amino acids. The BLOSUM62 descriptor can be applied to encode peptides of equal length. The BLOSUM62 descriptor has been successfully applied to ubiquitination site prediction (36).

ZScale

For this descriptor, each amino acid is characterized by five physicochemical descriptor variables (cf. **Table 14**), which were developed by Sandberg *et al.* in 1998 (89). The ZSCALE descriptor can be applied to encode peptides with equal length. The descriptor has been successfully applied to sumoylation site prediction (37).

Table 14. Z-scales for the 20 amino acids.

Amino acid	Z1	Z2	Z3	Z4	Z5	Amino Acid	Z1	Z2	Z3	Z4	Z5
A	0.24	-2.32	0.60	-0.14	1.30	M	-2.85	-0.22	0.47	1.94	-0.98
C	0.84	-1.67	3.71	0.18	-2.65	N	3.05	1.60	1.04	-1.15	1.61
D	3.98	0.93	1.93	-2.46	0.75	P	-1.66	0.27	1.84	0.70	2.00
E	3.11	0.26	-0.11	-3.04	-0.25	Q	1.75	0.50	-1.44	-1.34	0.66
F	-4.22	1.94	1.06	0.54	-0.62	R	3.52	2.50	-3.50	1.99	-0.17
G	2.05	4.06	0.36	-0.82	-0.38	S	2.39	-1.07	1.15	-1.39	0.67
H	2.47	1.95	0.26	3.90	0.09	T	0.75	-2.18	-1.12	-1.46	-0.40
I	-3.89	-1.73	-1.71	-0.84	0.26	V	-2.59	-2.64	-1.54	-0.85	-0.02
K	2.29	0.89	-2.49	1.49	0.31	W	-4.36	3.94	0.59	3.44	-1.59
L	-4.28	-1.30	-1.49	-0.72	0.84	Y	-2.54	2.44	0.43	0.04	-1.47

OPF_10bit

For this descriptor, the amino acids are classified into 10 groups based their physicochemical properties (**Table 15**). Note that different groups might overlap, since a specific amino acid type may have two or more physicochemical properties. To reflect the correlation of different properties, a 10-bit vector were calculated to represent each amino acid of the N-terminus of peptide. Similarly, the position of the bit of this 10-bit vector is set to 1, if the amino acid belongs to a corresponding group and 0 otherwise. The OPF_10bit descriptor has been successfully applied to anti-cancer peptides prediction (77).

Table 15. Details of the division of the standard amino acid alphabet based on ten physicochemical properties.

Rank	Physicochemical properties	Amino acid group
1	Aromatic	{F, Y, W, H}
2	Negative	{D, E}
3	Positive	{K, H, R}
4	Polar	{N, Q, S, D, E, C, T, K, R, H, Y, W}
5	Hydrophobic	{A, G, C, T, I, V, L, K, H, F, Y, W, M}
6	Aliphatic	{I, V, L}
7	Tiny	{A, S, G, C}
8	Charged	{K, H, R, D, E}
9	Small	{P, N, D, T, C, A, G, S, V}
10	Proline	{P}

OPF_7bit type 1

Similar to OPF_10bit descriptor, for this descriptor, the amino acids are classified into 7 groups. There are three subtypes of OPF_7bit descriptor (i.e. type 1, type 2 and type 3), due to different division of the amino acids. The difference of the type 1 to type 3 subtypes is the different division of amino acids. The division of amino acids for type 1 to 3 is listed in **Table 16**.

ASDC (Adaptive skip dinucleotide composition)

The adaptive skip dipeptide composition is a modified dipeptide composition, which sufficiently considers the correlation information present not only between adjacent residues but also between intervening residues (77). For given a sequence, the feature vector for ASDC is represented by:

$$ASDC = (f_{v1}, f_{v1}, \dots, f_{v400}),$$

where f_{vi} is calculated by

$$f_{vi} = \frac{\sum_{g=1}^{L-1} O_i^g}{\sum_{i=1}^{400} \sum_{g=1}^{L-1} O_i^g},$$

where f_{vi} denotes the occurrence frequency of all possible dipeptide with $\leq L$-1 intervening nucleotides. The ASDC descriptor has been successfully applied to anti-cancer peptide prediction (77) and cell-penetrating peptide prediction (78).

Table 16. Details of the division of the standard amino acid alphabet based on seven physicochemical properties.

Rank	Physicochemical properties	Type 1	Type 2	Type 3
1	Hydrophobicity	{A, C, F, G, H, I, L, M, N, P, Q, S, T, V, W, Y}	{D, E}	{K, R}
2	Normalized Van der Waals volume	{C, F, I, L, M, V, W}	{A, G, H, P, S, T, Y}	{D, E, K, N, Q, R}
3	Polarity	{A, C, D, G, P, S, T}	{E, I, L, N, Q, V}	{F, H, K, M, R, W, Y}
4	Polarizibility	{C, F, I, L, M, V, W, Y}	{A, G, P, S, T}	{D, E, H, K, N, Q, R}
5	Charge	{A, D, G, S, T}	{C, E, I, L, N, P, Q, V}	{F, H, K, M, R, W, Y}
6	Secondary structures	{D, G, N, P, S}	{A, E, H, K, L, M, Q, R}	{C, F, I, T, V, W, Y}
7	Solvent accessibility	{A, C, F, G, I, L, V, W}	{H, M, P, S, T, Y}	{D, E, K, N, R, Q}

DistancePair (PseAAC of distance-pair and reduced alphabet)

The descriptor incorporates the amino acid distance pair coupling information and the amino acid reduced alphabet profile into the general pseudo amino acid composition vector. For the reduced alphabet profile, they are cp(13), cp(14), and cp(15) as defined below:

cp(13) = {MF; IL;V;A;C;WYQHP;G;T; S;N;RK;D; E}

cp(14) = {EIMV; L;F;WY;G; P;C;A; S; T;N;HRKQ; E;D}

sp(15) = {P;G; E;K;R;Q;D; S;N; T;H;C; I;V;W;YF;A; L;M}

where the single letters without a semicolon (;) to separate them mean belonging to a same cluster. The DistancePair descriptor has been successfully applied to DNA-binding protein identification (16).

Parameter(s):

- *Maximum distance: the maximum distance value, default is 0.*
- *Reduced alphabet scheme: i.e. cp(13), cp(14), cp(15) or cp(20).*

PseKRAAC (pseudo K-tuple reduced amino acids composition)

Previous studies indicate that certain residues are similar in their physicochemical features, and can be clustered into groups because they play similar structural or functional roles in proteins (90). By implementing reduced amino acid alphabets, the protein complexity can be significantly simplified, which reduces information redundancy and decreases the risk of overfitting. The Pseudo K-tuple Reduced Amino Acids Composition (PseKRAAC) descriptor (29) includes two different feature types for protein sequence analysis: *g-gap* and λ-correlation PseKRAAC (27).

The *g-gap* PseKRAAC is used to represent a protein sequence with a vector containing RAAC^K components, where g represents the gap between each K-tuple peptides (21,49,91,92). A *g-gap* of n reflects the sequence-order information for all K-tuple peptides with the starting residues separated by n residues. An illustrated example of this encoding scheme (K = 2) is provided in the following **Figure 21A**.

The λ-correlation PseKRAAC is used to represent a protein sequence with a vector containing RAAC^K components, where λ is an integer that represents the correlation tier and is less than N-K, where N is the sequence length. The n-th-tier correlation factor ($\lambda = n$) reflects the sequence-order correlation between the n-th nearest residues. An illustrated example of this encoding scheme (K = 2) is provided in the following **Figure 21B**.

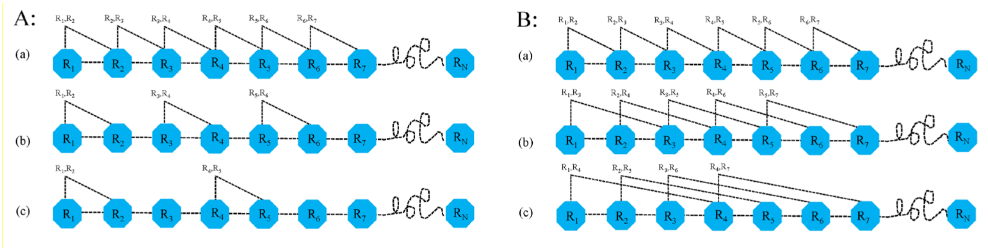

Figure 21. A schematic diagram showing: (A) *g-gap* definition of dipeptide, and (B) λ-correlation definition of dipeptide A: (a) *g-gap* of 0 reflects the sequence-order information between all adjacent dipeptides, i.e. separated by zero residues, (b) *g-gap* of 1 reflects the sequence-order information for all dipeptides with the starting residues separated by one residue, and (c) *g-gap* of 2 reflects the sequence-order information for all dipeptides with the starting residues separated by two residues; B: (a) the first-tier correlation factor reflects the sequence-order correlation between the nearest residues along a protein chain, (b) the second-tier correlation factor reflects the sequence-order correlation between the second nearest residues, (c) the third-tier correlation factor reflects the sequence-order correlation between the 3rd nearest residues, and so forth. The figure is adapted from (29).

The 16 types of reduced amino acid alphabets with different clustering approaches can be used to generate different versions of pseudo reduced amino acid compositions (PseRAACs) (**Table17**).

Table 17. A list of 16 types of reduced amino acid alphabets for proteins (29).

Type	Description	Cluster	Reference
1	RedPSSM	2-19	(93)
2	BLOSUM 62 matrix	2-6, 8, 15	(94)
3	PAM matrix (3A) and WAG matrix (3B)	2-19	(95)
4	Protein Blocks	5,8,9,11,13	(96)
5	BLOSUM50 matrix	3,4,8,10,15	(96)
6	Multiple cluster	4,5A,5B,5C	(97)
7	Metric multi-dimensional scaling	2-19	(98)
8	Grantham Distance Matrix	2-19	(99)
9	Grantham Distance Matrix	2-19	(99)
10	BLOSUM matrix for SWISS-PROT	2-19	(100)
11	BLOSUM matrix for SWISS-PROT	2-19	(100)
12	BLOSUM matrix for DAPS	2-18	(101)
13	Coarse-graining substitution matrices	4,12,17	(102)
14	Alphabet Simplifer	2-19	(103)
15	MJ matrix	2-16	(104)
16	BLOSUM50 matrix	2-16	(104)

Parameter(s):

- *RAAC subtype model: RAAC subtype model, i.e. g-gap or lambda-correlation.*
- *Gap value: the gap value for between two amino acids.*
- *Lambda value: the lambda value in lambda-correlation model.*
- *K-tuple: k-tuple value.*
- *RAAC cluster: the RAAC cluster type for each type of feature descriptor.*

12. Commonly Used Feature Descriptors and Parameters for Ligands

Basak

The feature descriptor calculates some commonly used basak information index based on its topological structure, and 21 molecular connectivity can be obtained for this feature descriptor.

Burden

The feature descriptor calculates 64 burden eigvenvalue descriptors.

Phamacophore

The feature descriptor calculate potential pharmacophore point descriptors definitions as describes in Pharmacophores and Pharmacophore Searches 2006 (Eds. T. Langer and R.D. Hoffmann), Chapter 3: Alignment-free Pharmacophore Patterns - A Correlattion-vector Approach.

Constitution

The molecular constitution descriptors characterize composition of chemical elements and chemical bonds, path length, hydrogen bond-acceptor, and donator in the constitution module.

Topology

The topological descriptors, which are calculated directly from the ligand structure, quantify key topological aspects including molecular connectivity and valence connectivity for different path-orders, cycle, or cluster size.

Connectivity

The feature descriptor calculates 44 molecular connectivity indices based on its topological structure.

Kappa

The feature descriptor calculates 7 descriptors of Kier and Hall's kappa indices based on its topological structure.

Esate

The feature descriptor calculates the estate fingerprints and values based on Kier and Hall's paper.

Autocorrelation-moran

The feature descriptor calculates 32 moran autocorrelation descriptors.

Autocorrelation-geary

The feature descriptor calculates 32 geary autocorrelation descriptors based on its topological structure.

Autocorrelation-broto

The feature descriptor calculates 32 Moreau-Broto autocorrelation descriptors.

Molecular properties

The feature descriptor calculates Molecular physical/chemical properties based on some special type of approaches, including: LogP; LogP2; MR; TPSA, UI and Hy.

Charge

The feature descriptor calculates Charge descriptors based on Gasteiger/Marseli partial charges.

Moe-type

The MOE-type descriptors are computed from the connection table information based on atomic contributions to Van der Waals surface area, LogP, molar refractivity, partial charge, and E-state value.

Fingerprints

Molecular fingerprints are string representations of chemical structures, which consist of bins, each bin being a substructure descriptor associated with a specific molecular feature. 3 types of molecular fingerprints are provided, including E-state fingerprints, MACCS fingerprints, and Morgan fingerprints.

13. Commonly Used Feature Descriptors and Parameters for Protein Structure

AAC type 1 and 2

Amino Acids Content descriptor calculate the frequency of each amino acid type in the microenvironments of a target site. The microenvironments of the target site are defined by a three-dimensional position and a radius defining the neighborhood. Shells are formed around each target site. And the frequency of each amino acid type is calculated for each shell (AAC_type1) and for cumulative shells (AAC_type2). **Figure 22 s**hows an example. The solid dot represents the target site, while the cycles denote other residues. The microenvironment of the target site is specified as a three-dimensional position and a radius defining the neighborhood. And shells are formed around the site (The yellow part is the first shell, while the green part form the second shell, and the blue part is the third part). For AAC_type1 feature descriptor, the frequency of amino acids in the first shell (i.e. residue #1), the second shell (i.e. residue #2, #3 and #4) and the third shell (i.e. residue #5-9) will be calculated, respectively. For AAC_type2 descriptor, at first the frequency of amino acids in the first shell (i.e. residue #1) is calculated. Then, the frequency of amino acids in the first and second shells (i.e. residue #1-4) will be calculated. Finally, the frequency of amino acids in all the three shells (i.e. residue #1-9) will be calculated.

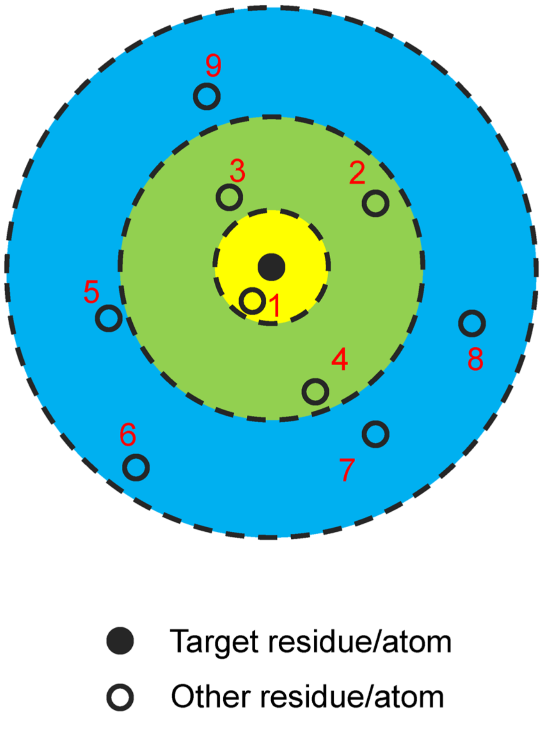

Figure 22. An example of feature extraction for protein structure "AAC_type1/2" descriptors.

Parameter(s):

- *Shell from: the start radius (i.e. the radius of first shell), default is 3.*
- *Shell to: the maximum radius of the shell, default is 20.*
- *Step: the interval between two adjacent shells, default is 3.*

GAAC type 1 and 2

In the GAAC encoding, the 20 amino acid types are further categorized into five classes according to their physicochemical properties, e.g. hydrophobicity, charge and molecular size (105). The five classes include the aliphatic group (*g1*: GAVLMI), aromatic group (*g2*: FYW), positive charge group (*g3*: KRH), negative charged group (*g4*: DE) and uncharged group (*g5*: STCPNQ). And the frequency of each amino acid group is calculated for each shell (GAAC_type1) and for cumulative shells (GAAC_type2).

Parameter(s):

- *Shell from: the start radius (i.e. the radius of first shell), default is 3.*
- *Shell to: the maximum radius of the shell, default is 20.*
- *Step: the interval between two adjacent shells, default is 3.*

SS3 and SS8

The "secondary structure" feature group encodes multiple features based on secondary structural elements around a target residue. For feature sets in this group, "SS3" considers three types of secondary structural elements (i.e. helix, β-strand, and β-turns and -loops(106)), while "SS8" considers eight types of secondary structural elements (i.e. α-helix, isolated β-bridge residue, strand, 3-10 helix, Π-helix, turn, bend and other(106)). The type1 features calculate the frequency of each type SSE in each shell (i.e. SS3_type1 and SS8_type1) while type2 features quantify the frequency of each SSE type in cumulative shells (i.e. SS3_type2 and SS8_type2)

Parameter(s):

- *Shell from: the start radius (i.e. the radius of first shell), default is 3.*
- *Shell to: the maximum radius of the shell, default is 20.*
- *Step: the interval between two adjacent shells, default is 3.*

HSE_CA and HSE_CB

HSE calculates the half sphere exposure and residue depth as descriptors for each residue in a given structure. Half sphere exposure (HSE) is a 2D measure of solvent exposure which counts the number of Cα atoms around a residue in the direction of its side chain and in the opposite direction (within a radius of 13 Å)(107). HSE compliments the residue depth measure(108), which is calculated as an average distance of a residue's atoms from the solvent accessible surface(109). HSE comes in two flavors: HSEα (HSE_CA) and HSEβ (HSE_CB). The former only uses the Cα atom positions, while the latter uses the Cα and Cβ atom positions.

Residue depth

The residue depth descriptor is the average distance of a residue's atoms from the solvent accessible surface.

AC_type1 and AC_type2

The "atom composition" feature group includes two types of encoding schemes that are computed at the atomic level. For the feature sets in this group, the target atom is specified as a three-dimensional position and a radius defining its neighborhood, and shells are formed around each target atom (**Figure 22**). Then, frequency of each atom type is calculated in each shell (i.e. AC_type1) and in cumulative shells (i.e. AC_type2).

Parameter(s):

- *Shell from: the start radius (i.e. the radius of first shell), default is 1.*
- *Shell to: the maximum radius of the shell, default is 10.*
- *Step: the interval between two adjacent shells, default is 1.*

Network-based index

The "network-based index" feature set encodes residues in the context of a network that represents placement of residues in the space defined by the protein structure. These features quantify the degree, degree centrality, betweenness, clustering coefficient, closeness and centrality values.

14. References

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