protr: Protein Sequence Descriptor Calculation and Similarity Computation with R

Nan Xiao
Central South University

Qingsong Xu
Central South University

Dongsheng Cao
Central South University

Abstract

The **protr** package focus on offering a unique and comprehensive toolkit for protein sequence descriptor calculation and similarity computation. The descriptors included are extensively utilized in Bioinformatics and Chemogenomics research. The qualitative descriptors listed in **protr** include Amino Acid Composition (Amino Acid Composition/Dipeptide Composition/Tripeptide Composition) descriptor, Autocorrelation (Normalized Moreau-Broto Autocorrelation/Moran Autocorrelation/Geary Autocorrelation) descriptor, CTD (Composition/Transition/Distribution) descriptor, Conjoint Traid descriptor, Quasi-sequence Order (Sequence Order Coupling Number/Quasi-sequence Order Descriptors) descriptor and Pseudo Amino Acid Composition (Pseudo Amino Acid Composition/Amphiphilic Pseudo Amino Acid Composition) descriptor. The quantitative descriptors, for Proteochemometric (PCM) Modeling, includes the Generalized Scales-Based Descriptors derived by Principal Components Analysis, Generalized Scales-Based Descriptors derived by AA-Properties (AAindex), Generalized Scales-Based Descriptors derived by 20+ classes of 2D and 3D Molecular Descriptors (Topological, WHIM, VHSE, etc.), Generalized Scales-Based Descriptors derived by Factor Analysis, Generalized Scales-Based Descriptors derived by Multidimensional Scaling, and Generalized BLOSUM/PAM Matrix-Derived Descriptors. The **protr** package also integrates the functionality of parallellized similarity computation derived by protein sequence alignment and Gene Ontology (GO) semantic similarity measures between a list of protein sequences / GO terms / Entrez Gene IDs. **ProtrWeb**, the web service built on **protr**, is located at: `http://cbdd.csu.edu.cn:8080/protrweb/`. The **protr** package is developed by Computational Biology and Drug Design (CBDD) Group, Central South University.

Keywords: R, **protr**, protein sequence, amino acid, descriptor calculation, feature extraction, parallel computation, similarity, sequence alignment, Gene Ontology.

1. Introduction

The **protr** package (Xiao *et al.* 2013) implemented most of the state-of-the-art protein sequence descriptors with R. Several self-explanatory examples have been included to illustrate the benefits of using **protr**. Many more examples are available within the package.

The **protr** package is available from the Comprehensive R Archive Network (`http://CRAN.R-project.org/package=protr`). This vignette corresponds to **protr** version 0.2-0 and was typeset on 2014-01-25.

Generally, each type of the descriptors (features) could be extracted with a function named `extractX()` in the **protr** package, where `X` stands for the abbrevation of the descriptor name.

The descriptors and the function names implemented are listed below:

- Amino Acid Composition
  - `extractAAC()` - Amino Acid Composition
  - `extractDC()` - Dipeptide Composition
  - `extractTC()` - Tripeptide Composition
- Autocorrelation
  - `extractMoreauBroto()` - Normalized Moreau-Broto Autocorrelation
  - `extractMoran()` - Moran Autocorrelation
  - `extractGeary()` - Geary Autocorrelation
- CTD
  - `extractCTDC()` - Composition
  - `extractCTDT()` - Transition
  - `extractCTDD()` - Distribution
- Conjoint Triad
  - `extractCTriad()` - Conjoint Triad
- Quasi-sequence-order Descriptors
  - `extractSOCN()` - Sequence-order-coupling Number
  - `extractQSO()` - Quasi-sequence-order Descriptors
- Pseudo-Amino Acid Composition
  - `extractPAAC()` - Pseudo-Amino Acid Composition
  - `extractAPAAC()` - Amphiphilic Pseudo-Amino Acid Composition

The descriptors commonly used in Proteochemometric Modeling (PCM) implemented in **protr** include:

- `extractScales()` - Generalized Scales-Based Descriptors derived by Principal Components Analysis
  - `extractPropScales()` - Generalized Scales-Based Descriptors derived by AA-Properties (AAindex)
  - `extractDescScales()` - Generalized Scales-Based Descriptors derived by 20+ classes of 2D and 3D Molecular Descriptors (Topological, WHIM, VHSE, etc.)
- `extractFAScales()` - Generalized Scales-Based Descriptors derived by Factor Analysis
- `extractMDSScales()` - Generalized Scales-Based Descriptors derived by Multidimensional Scaling

- `extractBLOSUM()` - Generalized BLOSUM and PAM Matrix-Derived Descriptors

The **protr** package integrates the functionality of parallellized similarity computation derived by local or global protein sequence alignment between a list of protein sequences, the sequence alignment computation is provided by **Biostrings**, the corresponding functions listed in the **protr** package include:

- `twoSeqSim()` - Similarity calculation derived by sequence alignment between two protein sequences
- `parSeqSim()` - Parallelized pairwise similarity calculation with a list of protein sequences

The **protr** package also integrates the functionality of parallellized similarity computation derived by Gene Ontology (GO) semantic similarity measures between a list of GO terms / Entrez Gene IDs, the GO similarity computation is provided by **GOSemSim**, the corresponding functions listed in the **protr** package include:

- `twoGOSim()` - Similarity calculation derived by GO-terms semantic similarity measures between two GO terms / Entrez Gene IDs
- `parGOSim()` - Pairwise similarity calculation with a list of GO terms / Entrez Gene IDs

To use the `parSeqSim()` function, we suggest the users to install the packages **foreach** and **doMC/doParallel** first, according to their platforms. The **protr** package will automatically decide which backend to use if they are available, specifically, use **doParallel** under Microsoft Windows, and try to use **doMC** first under GNU Linux/OS X.

In the next sections, we'll introduce the descriptors and function usage in this order.

2. Qualitative Descriptors

A protein or peptide sequence with N amino acid residues could be generally represented as $\{\, R_1, R_2, \ldots, R_n \,\}$, where R_i represents the residue at the i-th position in the sequence. The labels i and j are used to index amino acid position in a sequence, and r, s, t are used to represent the amino acid type. The computed descriptors are roughly divided into 4 groups according to their known applications described in the literature.

A protein sequence could be divided equally into segments and the methods, described as follows for the global sequence, could be applied to each segment.

2.1. Amino Acid Composition (AAC)

The Amino Acid Composition (AAC) is the fraction of each amino acid type within a protein. The fractions of all 20 natural amino acids are calculated as:

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

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

As was described above, we could use the function `extractAAC()` to extract the descriptors (features) from protein sequences:

```
> require(protr)
> x = readFASTA(system.file('protseq/P00750.fasta', package = 'protr'))[[1]]
> extractAAC(x)

         A          R          N          D          C          E          Q
0.06405694 0.07117438 0.03914591 0.05160142 0.06761566 0.04804270 0.04804270
         G          H          I          L          K          M          F
0.08185053 0.03024911 0.03558719 0.07651246 0.03914591 0.01245552 0.03202847
         P          S          T          W          Y          V
0.05338078 0.08896797 0.04448399 0.02313167 0.04270463 0.04982206
```

Here with the function `readFASTA()` we loaded a single protein sequence (P00750, Tissue-type plasminogen activator) from a FASTA format file. Then extracted the AAC descriptors with `extractAAC()`. The result returned is a named vector, whose elements are tagged with the name of each amino acid.

2.2. Dipeptide Composition (DC)

The Dipeptide Composition (DC) gives 400 descriptors, defined as:

$$f(r, s) = \frac{N_{rs}}{N - 1} \quad r, s = 1, 2, \ldots, 20.$$

where N_{rs} is the number of dipeptide represented by amino acid type r and type s. Similar to `extractAAC()`, here we use `extractDC()` to compute the descriptors:

```
> dc = extractDC(x)
> head(dc, n = 30L)

         AA          RA          NA          DA          CA          EA
0.003565062 0.003565062 0.000000000 0.007130125 0.003565062 0.003565062
         QA          GA          HA          IA          LA          KA
0.007130125 0.007130125 0.001782531 0.003565062 0.001782531 0.001782531
         MA          FA          PA          SA          TA          WA
0.000000000 0.005347594 0.003565062 0.007130125 0.003565062 0.000000000
         YA          VA          AR          RR          NR          DR
0.000000000 0.000000000 0.003565062 0.007130125 0.005347594 0.001782531
         CR          ER          QR          GR          HR          IR
0.005347594 0.005347594 0.000000000 0.007130125 0.001782531 0.003565062
```

Here we only showed the first 30 elements of the result vector and omitted the rest of the result. The element names of the returned vector are self-explanatory as before.

2.3. Tripeptide Composition (TC)

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

$$f(r, s, t) = \frac{N_{rst}}{N - 2} \quad r, s, t = 1, 2, \ldots, 20$$

where N_{rst} is the number of tripeptides represented by amino acid type r, s and t. With function `extractTC()`, we could easily obtain the length-8000 descriptor, to save some space, here we also omitted the tedious outputs:

```
> tc = extractTC(x)
> head(tc, n = 36L)
```

```
        AAA         RAA         NAA         DAA         CAA         EAA
0.000000000 0.000000000 0.000000000 0.000000000 0.000000000 0.000000000
        QAA         GAA         HAA         IAA         LAA         KAA
0.001785714 0.000000000 0.000000000 0.000000000 0.000000000 0.000000000
        MAA         FAA         PAA         SAA         TAA         WAA
0.000000000 0.000000000 0.000000000 0.001785714 0.000000000 0.000000000
        YAA         VAA         ARA         RRA         NRA         DRA
0.000000000 0.000000000 0.000000000 0.000000000 0.000000000 0.000000000
        CRA         ERA         QRA         GRA         HRA         IRA
0.000000000 0.000000000 0.000000000 0.001785714 0.000000000 0.000000000
        LRA         KRA         MRA         FRA         PRA         SRA
0.000000000 0.000000000 0.000000000 0.000000000 0.000000000 0.000000000
```

2.4. Autocorrelation Descriptors

Autocorrelation descriptors are defined based on the distribution of amino acid properties along the sequence. The amino acid properties used here are various types of amino acids index (Retrieved from AAindex Database: `http://www.genome.jp/dbget/aaindex.html`, see Kawashima *et al.* (1999), Kawashima and Kanehisa (2000), and Kawashima *et al.* (2008), see Figure 1 for an illustrated example). Three types of autocorrelation descriptors are defined here and described below.

All the amino acid indices are centralized and standardized before the calculation, i.e.

$$P_r = \frac{P_r - \bar{P}}{\sigma}$$

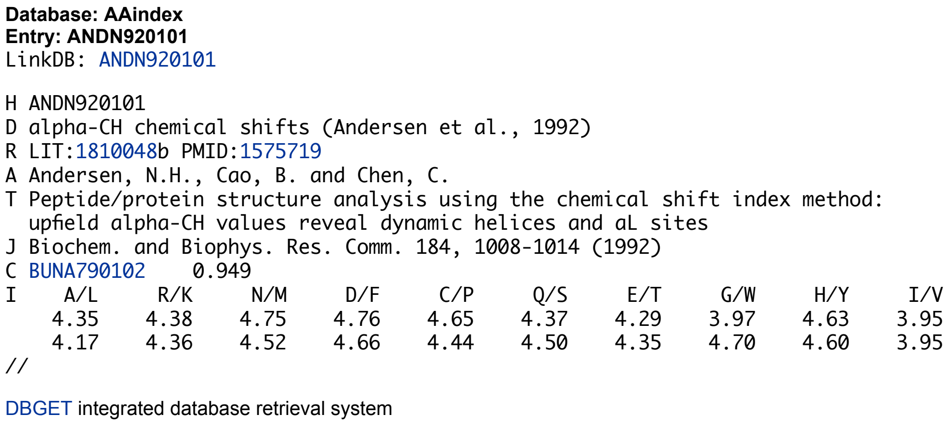
where $\bar{P}$ is the average of the property of the 20 amino acids:

$$\bar{P} = \frac{\sum_{r=1}^{20} P_r}{20} \quad \text{and} \quad \sigma = \sqrt{\frac{1}{2}\sum_{r=1}^{20}(P_r - \bar{P})^2}$$

Normalized Moreau-Broto Autocorrelation Descriptors

Moreau-Broto autocorrelation descriptors application to protein sequences could be defined as:

$$AC(d) = \sum_{i=1}^{N-d} P_i P_{i+d} \quad d = 1, 2, \ldots, \text{nlag}$$



Database: AAindex
Entry: ANDN920101
LinkDB: ANDN920101

```
H ANDN920101
D alpha-CH chemical shifts (Andersen et al., 1992)
R LIT:1810048b PMID:1575719
A Andersen, N.H., Cao, B. and Chen, C.
T Peptide/protein structure analysis using the chemical shift index method:
  upfield alpha-CH values reveal dynamic helices and aL sites
J Biochem. and Biophys. Res. Comm. 184, 1008-1014 (1992)
C BUNA790102    0.949
I    A/L     R/K     N/M     D/F     C/P     Q/S     E/T     G/W     H/Y     I/V
    4.35    4.38    4.75    4.76    4.65    4.37    4.29    3.97    4.63    3.95
    4.17    4.36    4.52    4.66    4.44    4.50    4.35    4.70    4.60    3.95
//
```

DBGET integrated database retrieval system

Figure 1: An illustrated example in the AAIndex database

where d is called the lag of the autocorrelation and P_i and P_{i+d} are the properties of the amino acids at position i and $i + d$, respectively. nlag is the maximum value of the lag.

The normalized Moreau-Broto autocorrelation descriptors are defined as:

$$ATS(d) = \frac{AC(d)}{N - d} \quad d = 1, 2, \ldots, \text{nlag}$$

The corresponding function for this descriptor is `extractMoreauBroto()`. A typical call could be:

```
> moreau = extractMoreauBroto(x)
> head(moreau, n = 36L)

 CIDH920105.lag1  CIDH920105.lag2  CIDH920105.lag3  CIDH920105.lag4
     0.081573213     -0.016064817     -0.015982990     -0.025739038
 CIDH920105.lag5  CIDH920105.lag6  CIDH920105.lag7  CIDH920105.lag8
     0.079058632     -0.042771564     -0.036320847      0.024087298
 CIDH920105.lag9 CIDH920105.lag10 CIDH920105.lag11 CIDH920105.lag12
    -0.005273958      0.052274763      0.082170073      0.005419919
CIDH920105.lag13 CIDH920105.lag14 CIDH920105.lag15 CIDH920105.lag16
     0.083292042      0.004810584      0.001872446     -0.001531495
CIDH920105.lag17 CIDH920105.lag18 CIDH920105.lag19 CIDH920105.lag20
    -0.011917230      0.071161551      0.033473197      0.026882737
CIDH920105.lag21 CIDH920105.lag22 CIDH920105.lag23 CIDH920105.lag24
     0.073075402      0.115272790      0.041517897     -0.027025993
CIDH920105.lag25 CIDH920105.lag26 CIDH920105.lag27 CIDH920105.lag28
     0.033477388     -0.003245255      0.078117010     -0.028177304
CIDH920105.lag29 CIDH920105.lag30  BHAR880101.lag1  BHAR880101.lag2
     0.046695832      0.020584423      0.052740185      0.030804784
 BHAR880101.lag3  BHAR880101.lag4  BHAR880101.lag5  BHAR880101.lag6
     0.037170476     -0.058993771      0.070641780     -0.089192490
```

The 8 default properties used here are:

- **AccNo. CIDH920105** — Normalized Average Hydrophobicity Scales
- **AccNo. BHAR880101** — Average Flexibility Indices
- **AccNo. CHAM820101** — Polarizability Parameter
- **AccNo. CHAM820102** — Free Energy of Solution in Water, kcal/mole
- **AccNo. CHOC760101** — Residue Accessible Surface Area in Tripeptide
- **AccNo. BIGC670101** — Residue Volume
- **AccNo. CHAM810101** — Steric Parameter
- **AccNo. DAYM780201** — Relative Mutability

Users could change the property names of AAindex database with the argument `props`. The AAindex data shipped with **protr** could be loaded by `data(AAindex)`, which has the detailed information of each property. With the argument `customprops` and `nlag`, users could specify their own properties and lag value to calculate with. For illustration, we could use:

```
> # Define 3 custom properties
> myprops = data.frame(AccNo = c("MyProp1", "MyProp2", "MyProp3"),
+                      A = c(0.62,  -0.5, 15),  R = c(-2.53,   3, 101),
+                      N = c(-0.78,  0.2, 58),  D = c(-0.9,    3, 59),
+                      C = c(0.29,    -1, 47),  E = c(-0.74,   3, 73),
+                      Q = c(-0.85,  0.2, 72),  G = c(0.48,    0, 1),
+                      H = c(-0.4,  -0.5, 82),  I = c(1.38, -1.8, 57),
+                      L = c(1.06,  -1.8, 57),  K = c(-1.5,    3, 73),
+                      M = c(0.64,  -1.3, 75),  F = c(1.19, -2.5, 91),
+                      P = c(0.12,     0, 42),  S = c(-0.18, 0.3, 31),
+                      T = c(-0.05, -0.4, 45),  W = c(0.81, -3.4, 130),
+                      Y = c(0.26,  -2.3, 107), V = c(1.08, -1.5, 43))
> # Use 4 properties in the AAindex database, and 3 cutomized properties
> moreau2 = extractMoreauBroto(x, customprops = myprops,
+                              props = c('CIDH920105', 'BHAR880101',
+                                        'CHAM820101', 'CHAM820102',
+                                        'MyProp1', 'MyProp2', 'MyProp3'))
> head(moreau2, n = 36L)

 CIDH920105.lag1  CIDH920105.lag2  CIDH920105.lag3  CIDH920105.lag4
     0.081573213     -0.016064817     -0.015982990     -0.025739038
 CIDH920105.lag5  CIDH920105.lag6  CIDH920105.lag7  CIDH920105.lag8
     0.079058632     -0.042771564     -0.036320847      0.024087298
 CIDH920105.lag9 CIDH920105.lag10 CIDH920105.lag11 CIDH920105.lag12
    -0.005273958      0.052274763      0.082170073      0.005419919
CIDH920105.lag13 CIDH920105.lag14 CIDH920105.lag15 CIDH920105.lag16
     0.083292042      0.004810584      0.001872446     -0.001531495
CIDH920105.lag17 CIDH920105.lag18 CIDH920105.lag19 CIDH920105.lag20
```

```
   -0.011917230       0.071161551       0.033473197       0.026882737
CIDH920105.lag21 CIDH920105.lag22 CIDH920105.lag23 CIDH920105.lag24
    0.073075402       0.115272790       0.041517897      -0.027025993
CIDH920105.lag25 CIDH920105.lag26 CIDH920105.lag27 CIDH920105.lag28
    0.033477388      -0.003245255       0.078117010      -0.028177304
CIDH920105.lag29 CIDH920105.lag30  BHAR880101.lag1  BHAR880101.lag2
    0.046695832       0.020584423       0.052740185       0.030804784
 BHAR880101.lag3  BHAR880101.lag4  BHAR880101.lag5  BHAR880101.lag6
    0.037170476      -0.058993771       0.070641780      -0.089192490
```

About the standard input format of `props` and `customprops`, see `?extractMoreauBroto` for details.

Moran Autocorrelation Descriptors

Moran autocorrelation descriptors application to protein sequence may be defined as:

$$I(d) = \frac{\frac{1}{N-d}\sum_{i=1}^{N-d}(P_i - \bar{P}')(P_{i+d} - \bar{P}')}{\frac{1}{N}\sum_{i=1}^{N}(P_i - \bar{P}')^2} \quad d = 1, 2, \ldots, 30$$

where d and P_i and P_{i+d} are defined in the same way as in the first place, and $\bar{P}'$ is the considered property P along the sequence, i.e.,

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

d, P, P_i and P_{i+d}, nlag have the same meaning as above.

With `extractMoran()`, which has exactly the same arguments with `extractMoreauBroto()`, we could compute the Moran autocorrelation descriptors (only output the first 36 elements of the result):

```
> # Use the 3 custom properties defined before
> # and 4 properties in the AAindex database
> moran = extractMoran(x, customprops = myprops,
+                      props = c('CIDH920105', 'BHAR880101',
+                                'CHAM820101', 'CHAM820102',
+                                'MyProp1', 'MyProp2', 'MyProp3'))
> head(moran, n = 36L)
```

```
 CIDH920105.lag1  CIDH920105.lag2  CIDH920105.lag3  CIDH920105.lag4
     0.062895724      -0.044827681      -0.045065117      -0.055955678
 CIDH920105.lag5  CIDH920105.lag6  CIDH920105.lag7  CIDH920105.lag8
     0.060586377      -0.074128412      -0.067308852      -0.001293384
 CIDH920105.lag9 CIDH920105.lag10 CIDH920105.lag11 CIDH920105.lag12
    -0.033747588       0.029392193       0.061789800      -0.023368437
CIDH920105.lag13 CIDH920105.lag14 CIDH920105.lag15 CIDH920105.lag16
```

```
      0.062769417      -0.024912264      -0.028298043      -0.031584063
CIDH920105.lag17 CIDH920105.lag18 CIDH920105.lag19 CIDH920105.lag20
     -0.043466730       0.047830694       0.005883901      -0.001769769
CIDH920105.lag21 CIDH920105.lag22 CIDH920105.lag23 CIDH920105.lag24
      0.049334048       0.096427969       0.015147594      -0.060092509
CIDH920105.lag25 CIDH920105.lag26 CIDH920105.lag27 CIDH920105.lag28
      0.007549152      -0.033987885       0.056307675      -0.061844453
CIDH920105.lag29 CIDH920105.lag30  BHAR880101.lag1  BHAR880101.lag2
      0.021484780      -0.008461776       0.014229951      -0.009142419
 BHAR880101.lag3  BHAR880101.lag4  BHAR880101.lag5  BHAR880101.lag6
     -0.003272262      -0.109613332       0.033346233      -0.141538598
```

Geary Autocorrelation Descriptors

Geary autocorrelation descriptors for protein sequence could be defined as:

$$C(d) = \frac{\frac{1}{2(N-d)} \sum_{i=1}^{N-d} (P_i - P_{i+d})^2}{\frac{1}{N-1} \sum_{i=1}^{N} (P_i - \bar{P}')^2} \quad d = 1, 2, \ldots, 30$$

where d, P, P_i and P_{i+d}, nlag have the same meaning as above.
For each amino acid index, there will be $3 \times$ nlag autocorrelation descriptors. The usage of `extractGeary()` is exactly the same with `extractMoreauBroto()` and `extractMoran()`:

```
> # Use the 3 custom properties defined before
> # and 4 properties in the AAindex database
> geary = extractGeary(x, customprops = myprops,
+                      props = c('CIDH920105', 'BHAR880101',
+                                'CHAM820101', 'CHAM820102',
+                                'MyProp1', 'MyProp2', 'MyProp3'))
> head(geary, n = 36L)
```

```
 CIDH920105.lag1  CIDH920105.lag2  CIDH920105.lag3  CIDH920105.lag4
       0.9361830        1.0442920        1.0452843        1.0563467
 CIDH920105.lag5  CIDH920105.lag6  CIDH920105.lag7  CIDH920105.lag8
       0.9406031        1.0765517        1.0675786        0.9991363
 CIDH920105.lag9 CIDH920105.lag10 CIDH920105.lag11 CIDH920105.lag12
       1.0316555        0.9684585        0.9353130        1.0201990
CIDH920105.lag13 CIDH920105.lag14 CIDH920105.lag15 CIDH920105.lag16
       0.9340933        1.0207373        1.0251486        1.0290464
CIDH920105.lag17 CIDH920105.lag18 CIDH920105.lag19 CIDH920105.lag20
       1.0414375        0.9494403        0.9905987        0.9987183
CIDH920105.lag21 CIDH920105.lag22 CIDH920105.lag23 CIDH920105.lag24
       0.9472542        0.9010009        0.9828848        1.0574098
CIDH920105.lag25 CIDH920105.lag26 CIDH920105.lag27 CIDH920105.lag28
       0.9897955        1.0290018        0.9400066        1.0584150
```

```
CIDH920105.lag29 CIDH920105.lag30  BHAR880101.lag1  BHAR880101.lag2
       0.9762904        1.0029734        0.9818711        1.0051730
 BHAR880101.lag3  BHAR880101.lag4  BHAR880101.lag5  BHAR880101.lag6
       0.9967069        1.1012905        0.9595859        1.1337056
```

2.5. Composition / Transition / Distribution

These descriptors are developed and described by Dubchak *et al.* (1995) and Dubchak *et al.* (1999).

Sequence	M	T	E	I	T	A	S	M	V	K	E	L	R	E	A	T	G	T	G	A
Sequence Index	1				5					10					15					20
Transformation	3	2	1	3	2	2	2	3	3	1	1	3	1	1	2	2	2	2	2	2
Index for 1			1							2	3		4	5						
Index for 2		1			2	3	4								5	6	7	8	9	10
Index for 3	1			2				3	4			5								
1/2 Transitions			|												|					
1/3 Transitions				|					|		|	|							
2/3 Transitions		|			|			|											

Figure 2: The sequence of a hypothetic protein indicating the construction of composition, transition and distribution descriptors of a protein. Sequence index indicates the position of an amino acid in the sequence. The index for each type of amino acids in the sequence ('1', '2' or '3') indicates the position of the first, second, third, ... of that type of amino acid. 1/2 transition indicates the position of '12' or '21' pairs in the sequence (1/3 and 2/3 are defined in the same way.).

Step 1: Sequence Encoding

The amino acids are divided in three classes according to its attribute and each amino acid is encoded by one of the indices 1, 2, 3 according to which class it belonged. The attributes used here include hydrophobicity, normalized van der Waals volume polarity, and polarizability, as in the references. The corresponding division is in the table 1.

For example, for a given sequence "MTEITAAMVKELRESTGAGA", it will be encoded as "32132223311311222222" according to its hydrophobicity division.

Step 2: Compute Composition, Transition and Distribution Descriptors

Three descriptors, *Composition* (C), *Transition* (T), and *Distribution* (D) were calculated for a given attribute as follows.

Composition

It is the global percent for each encoded class in the sequence. In the above example using hydrophobicity division, the numbers for encoded classes "1", "2", "3" are 5, 10, 5 respectively, so the compositions for them are $5/20 = 25\%$, $10/20 = 10\%$, and $5/20 = 25\%$ respectively, where 20 is the length of the protein sequence. Composition can be defined as

Table 1: Amino acid attributes and the division of the amino acids into three groups for each attribute

	Group 1	**Group 2**	**Group 3**
Hydrophobicity	Polar R, K, E, D, Q, N	Neutral G, A, S, T, P, H, Y	Hydrophobicity C, L, V, I, M, F, W
Normalized van der Waals Volume	0-2.78 G, A, S, T, P, D, C	2.95-4.0 N, V, E, Q, I, L	4.03-8.08 M, H, K, F, R, Y, W
Polarity	4.9-6.2 L, I, F, W, C, M, V, Y	8.0-9.2 P, A, T, G, S	10.4-13.0 H, Q, R, K, N, E, D
Polarizability	0-1.08 G, A, S, D, T	0.128-0.186 C, P, N, V, E, Q, I, L	0.219-0.409 K, M, H, F, R, Y, W
Charge	Positive K, R	Neutral A, N, C, Q, G, H, I, L, M, F, P, S, T, W, Y, V	Negative D, E
Secondary Structure	Helix E, A, L, M, Q, K, R, H	Strand V, I, Y, C, W, F, T	Coil G, N, P, S, D
Solvent Accessibility	Buried A, L, F, C, G, I, V, W	Exposed R, K, Q, E, N, D	Intermediate M, S, P, T, H, Y

$$C_r = \frac{n_r}{n} \quad r = 1, 2, 3$$

where n_r is the number of amino acid type r in the encoded sequence and N is the length of the sequence. An example for `extractCTDC()` could be:

```
> extractCTDC(x)

  prop1.G1   prop1.G2   prop1.G3   prop2.G1   prop2.G2   prop2.G3   prop3.G1
0.29715302 0.40569395 0.29715302 0.45195730 0.29715302 0.25088968 0.33985765
  prop3.G2   prop3.G3   prop4.G1   prop4.G2   prop4.G3   prop5.G1   prop5.G2
0.33274021 0.32740214 0.33096085 0.41814947 0.25088968 0.11032028 0.79003559
  prop5.G3   prop6.G1   prop6.G2   prop6.G3   prop7.G1   prop7.G2   prop7.G3
0.09964413 0.38967972 0.29537367 0.31494662 0.43060498 0.29715302 0.27224199
```

The result shows the elements whose names are `PropertyNumber.GroupNumber` in the returned vector.

Transition

A transition from class 1 to 2 is the percent frequency with which 1 is followed by 2 or 2 is followed by 1 in the encoded sequence. Transition descriptor can be calculated as

$$T_{rs} = \frac{n_{rs} + n_{sr}}{N - 1} \quad rs = \text{`12'}, \text{`13'}, \text{`23'}$$

where n_{rs}, n_{sr} is the numbers of dipeptide encoded as "rs" and "sr" respectively in the sequence and N is the length of the sequence. An example for `extractCTDT()` could be:

```
> extractCTDT(x)

prop1.Tr1221 prop1.Tr1331 prop1.Tr2332 prop2.Tr1221 prop2.Tr1331 prop2.Tr2332
  0.27094474   0.16042781   0.23351159   0.26737968   0.22638146   0.17112299
prop3.Tr1221 prop3.Tr1331 prop3.Tr2332 prop4.Tr1221 prop4.Tr1331 prop4.Tr2332
  0.21033868   0.20499109   0.23707665   0.27272727   0.15151515   0.24598930
prop5.Tr1221 prop5.Tr1331 prop5.Tr2332 prop6.Tr1221 prop6.Tr1331 prop6.Tr2332
  0.18181818   0.02139037   0.15686275   0.21925134   0.22816399   0.15864528
prop7.Tr1221 prop7.Tr1331 prop7.Tr2332
  0.25133690   0.21568627   0.18003565
```

Distribution

The "distribution" descriptor describes the distribution of each attribute in the sequence.

There are five "distribution" descriptors for each attribute and they are the position percents in the whole sequence for the first residue, 25% residues, 50% residues, 75% residues and 100% residues, respectively, for a specified encoded class. For example, there are 10 residues encoded as "2" in the above example, the positions for the first residue "2", the 2th residue "2" (25%*10=2), the 5th "2" residue (50%*10=5), the 7th "2" (75%*10=7) and the 10th residue "2" (100%*10) in the encoded sequence are 2, 5, 15, 17, 20 respectively, so the distribution descriptors for "2" are: 10.0 (2/20*100), 25.0 (5/20*100), 75.0 (15/20*100), 85.0 (17/20*100) , 100.0 (20/20*100), respectively.

Finally, an example for `extractCTDD()` could be:

```
> extractCTDD(x)

  prop1.G1.residue0  prop1.G1.residue25  prop1.G1.residue50  prop1.G1.residue75
          0.3558719          23.1316726          50.1779359          73.8434164
prop1.G1.residue100   prop1.G2.residue0  prop1.G2.residue25  prop1.G2.residue50
         99.8220641           0.5338078          27.4021352          47.3309609
 prop1.G2.residue75 prop1.G2.residue100   prop1.G3.residue0  prop1.G3.residue25
         75.2669039         100.0000000           0.1779359          19.5729537
 prop1.G3.residue50  prop1.G3.residue75 prop1.G3.residue100   prop2.G1.residue0
         51.7793594          75.6227758          99.6441281           0.3558719
 prop2.G1.residue25  prop2.G1.residue50  prop2.G1.residue75 prop2.G1.residue100
         25.6227758          48.0427046          75.4448399         100.0000000
  prop2.G2.residue0  prop2.G2.residue25  prop2.G2.residue50  prop2.G2.residue75
          1.4234875          23.3096085          54.4483986          76.3345196
prop2.G2.residue100   prop2.G3.residue0  prop2.G3.residue25  prop2.G3.residue50
         99.4661922           0.1779359          22.7758007          48.9323843
 prop2.G3.residue75 prop2.G3.residue100   prop3.G1.residue0  prop3.G1.residue25
         69.5729537          99.8220641           0.1779359          20.9964413
 prop3.G1.residue50  prop3.G1.residue75 prop3.G1.residue100   prop3.G2.residue0
         50.8896797          74.5551601          99.6441281           0.5338078
 prop3.G2.residue25  prop3.G2.residue50  prop3.G2.residue75 prop3.G2.residue100
```

```
        26.5124555          46.2633452          75.4448399         100.0000000
 prop3.G3.residue0  prop3.G3.residue25  prop3.G3.residue50  prop3.G3.residue75
         0.3558719          24.1992883          50.5338078          73.8434164
prop3.G3.residue100   prop4.G1.residue0  prop4.G1.residue25  prop4.G1.residue50
        99.8220641           0.3558719          26.5124555          48.3985765
prop4.G1.residue75 prop4.G1.residue100   prop4.G2.residue0  prop4.G2.residue25
        76.1565836          99.2882562           1.4234875          21.5302491
prop4.G2.residue50  prop4.G2.residue75 prop4.G2.residue100   prop4.G3.residue0
        51.4234875          75.8007117         100.0000000           0.1779359
prop4.G3.residue25  prop4.G3.residue50  prop4.G3.residue75 prop4.G3.residue100
        22.7758007          48.9323843          69.5729537          99.8220641
 prop5.G1.residue0  prop5.G1.residue25  prop5.G1.residue50  prop5.G1.residue75
         0.8896797          20.8185053          48.9323843          69.5729537
prop5.G1.residue100   prop5.G2.residue0  prop5.G2.residue25  prop5.G2.residue50
        99.8220641           0.1779359          24.9110320          49.1103203
prop5.G2.residue75 prop5.G2.residue100   prop5.G3.residue0  prop5.G3.residue25
        75.2669039         100.0000000           0.3558719          26.1565836
prop5.G3.residue50  prop5.G3.residue75 prop5.G3.residue100   prop6.G1.residue0
        64.2348754          77.4021352          99.2882562           0.1779359
prop6.G1.residue25  prop6.G1.residue50  prop6.G1.residue75 prop6.G1.residue100
        22.9537367          50.8896797          74.3772242          99.8220641
 prop6.G2.residue0  prop6.G2.residue25  prop6.G2.residue50  prop6.G2.residue75
         1.6014235          21.5302491          49.2882562          70.8185053
prop6.G2.residue100   prop6.G3.residue0  prop6.G3.residue25  prop6.G3.residue50
        98.9323843           0.3558719          29.0035587          48.2206406
prop6.G3.residue75 prop6.G3.residue100   prop7.G1.residue0  prop7.G1.residue25
        77.4021352         100.0000000           0.5338078          23.4875445
prop7.G1.residue50  prop7.G1.residue75 prop7.G1.residue100   prop7.G2.residue0
        50.0000000          74.5551601          98.9323843           0.3558719
prop7.G2.residue25  prop7.G2.residue50  prop7.G2.residue75 prop7.G2.residue100
        23.1316726          50.1779359          73.8434164          99.8220641
 prop7.G3.residue0  prop7.G3.residue25  prop7.G3.residue50  prop7.G3.residue75
         0.1779359          27.2241993          48.0427046          75.4448399
prop7.G3.residue100
       100.0000000
```

2.6. Conjoint Triad Descriptors

Conjoint triad descriptors are proposed by Shen *et al.* (2007). These conjoint triad descriptors abstracts the features of protein pairs based on the classification of amino acids. In this approach, each protein sequence is represented by a vector space consisting of descriptors of amino acids. To reduce the dimensions of vector space, the 20 amino acids were clustered into several classes according to their dipoles and volumes of the side chains. The conjoint triad descriptors are calculated as follows:

Step 1: Classification of Amino Acids

Electrostatic and hydrophobic interactions dominate protein-protein interactions. These two kinds of interactions may be reflected by the dipoles and volumes of the side chains of amino acids, respectively. Accordingly, these two parameters were calculated, respectively, by using the density-functional theory method B3LYP/6-31G and molecular modeling approach. Based on the dipoles and volumes of the side chains, the 20 amino acids could be clustered into seven classes (See Table 2). Amino acids within the same class likely involve synonymous mutations because of their similar characteristics.

Table 2: Classification of amino acids based on dipoles and volumes of the side chains

No.	Dipole Scale[1]	Volume Scale[2]	Class
1	$-$	$-$	Ala, Gly, Val
2	$-$	$+$	Ile, Leu, Phe, Pro
3	$+$	$+$	Tyr, Met, Thr, Ser
4	$++$	$+$	His, Asn, Gln, Tpr
5	$+++$	$+$	Arg, Lys
6	$+'+'+'$	$+$	Asp, Glu
7	$+$[3]	$+$	Cys

Step 2: Conjoint Triad Calculation

The conjoint triad descriptors considered the properties of one amino acid and its vicinal amino acids and regarded any three continuous amino acids as a unit. Thus, the triads can be differentiated according to the classes of amino acids, i.e., triads composed by three amino acids belonging to the same classes, such as ART and VKS, could be treated identically. To conveniently represent a protein, we first use a binary space $(\mathbf{V}, \mathbf{F})$ to represent a protein sequence. Here, $\mathbf{V}$ is the vector space of the sequence features, and each feature v_i represents a sort of triad type; $\mathbf{F}$ is the frequency vector corresponding to $\mathbf{V}$, and the value of the i-th dimension of $\mathbf{F}(f_i)$ is the frequency of type v_i appearing in the protein sequence. For the amino acids that have been catogorized into seven classes, the size of $\mathbf{V}$ should be $7 \times 7 \times 7$; thus $i = 1, 2, \ldots, 343$. The detailed description for ($\mathbf{V}$, $\mathbf{F}$) is illustrated in Figure 3.

Clearly, each protein correlates to the length (number of amino acids) of protein. In general, a long protein would have a large value of f_i, which complicates the comparison between two heterogeneous proteins. Thus, we defined a new parameter, d_i, by normalizing f_i with the following equation:

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

The numerical value of d_i of each protein ranges from 0 to 1, which thereby enables the comparison between proteins. Accordingly, we obtain another vector space (designated $\mathbf{D}$) consisting of d_i to represent protein.

To compute conjoint triads of protein sequences, we could simply use:

[1]Dipole Scale (Debye): $-$, Dipole < 1.0; $+$, $1.0 <$ Dipole < 2.0; $++$, $2.0 <$ Dipole < 3.0; $+++$, Dipole > 3.0; $+'+'+'$, Dipole > 3.0 with opposite orientation.

[2]Volume Scale (Å^3): $-$, Volume < 50; $+$, Volume > 50.

[3]Cys is separated from class 3 because of its ability to form disulfide bonds.

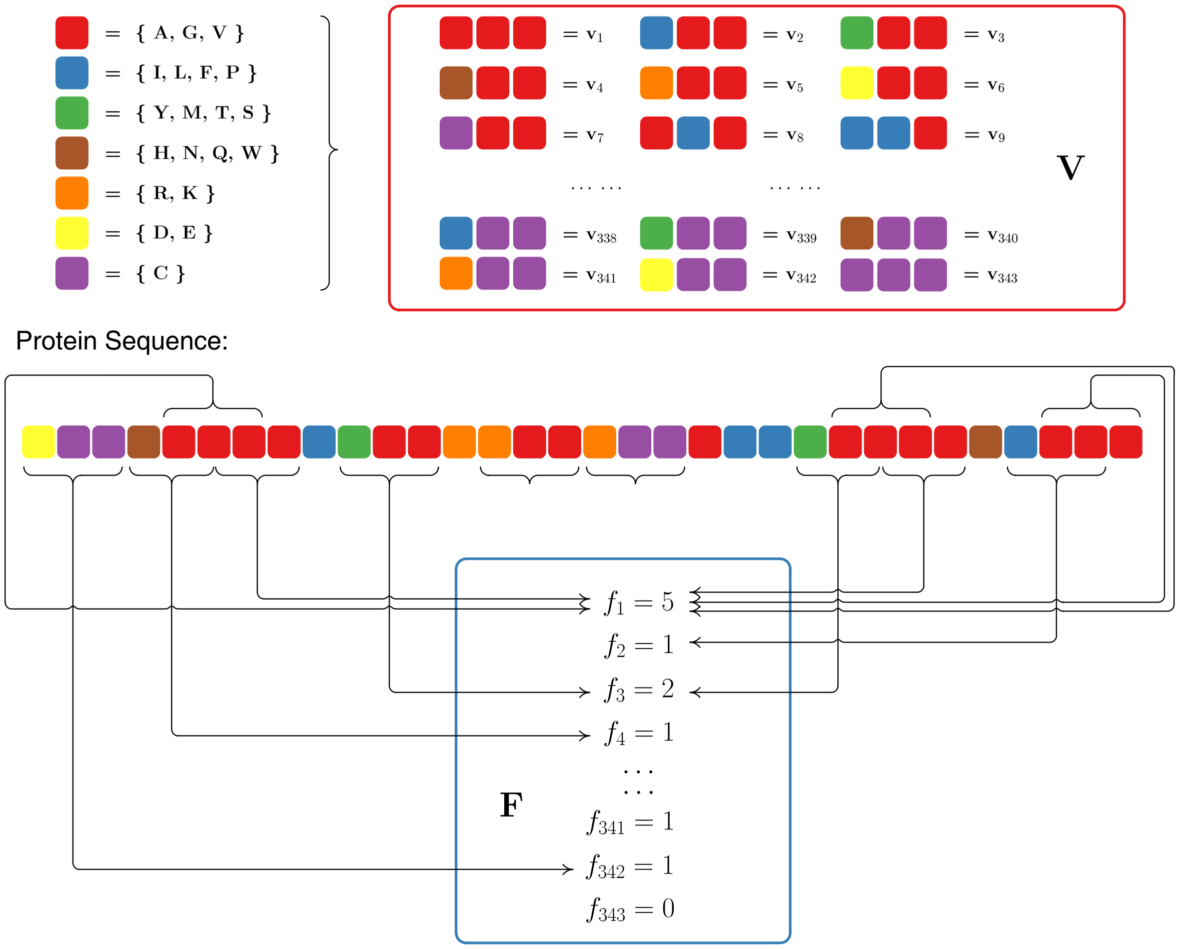


Figure 3: Schematic diagram for constructing the vector space $(\mathbf{V}, \mathbf{F})$ of protein sequence. $\mathbf{V}$ is the vector space of the sequence features; each feature (v_i) represents a triad composed of three consecutive amino acids; $\mathbf{F}$ is the frequency vector corresponding to $\mathbf{V}$, and the value of the i-th dimension of $\mathbf{F}(f_i)$ is the frequency that v_i triad appeared in the protein sequence.

```
> ctriad = extractCTriad(x)
> head(ctriad, n = 65L)

VS111 VS211 VS311 VS411 VS511 VS611 VS711 VS121 VS221 VS321 VS421 VS521 VS621
  0.1   0.3   0.6   0.2   0.4   0.0   0.3   1.0   0.6   0.5   0.0   0.2   0.3
VS721 VS131 VS231 VS331 VS431 VS531 VS631 VS731 VS141 VS241 VS341 VS441 VS541
  0.0   0.2   0.4   0.5   0.2   0.3   0.3   0.1   0.3   0.3   0.2   0.2   0.0
VS641 VS741 VS151 VS251 VS351 VS451 VS551 VS651 VS751 VS161 VS261 VS361 VS461
  0.1   0.2   0.2   0.2   0.5   0.1   0.2   0.0   0.0   0.1   0.4   0.2   0.3
VS561 VS661 VS761 VS171 VS271 VS371 VS471 VS571 VS671 VS771 VS112 VS212 VS312
  0.2   0.0   0.1   0.1   0.3   0.1   0.0   0.1   0.0   0.1   0.8   0.4   0.4
VS412 VS512 VS612 VS712 VS122 VS222 VS322 VS422 VS522 VS622 VS722 VS132 VS232
  0.6   0.1   0.5   0.2   0.8   0.5   0.2   0.3   0.2   0.0   0.2   0.1   0.3
```

by which we only outputted the first 65 of total 343 dimension to save space.

2.7. Quasi-sequence-order Descriptors

The quasi-sequence-order descriptors are proposed by Chou (2000). They are derived from the distance matrix between the 20 amino acids.

Sequence-order-coupling Number

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

$$\tau_d = \sum_{i=1}^{N-d} (d_{i,i+d})^2 \quad d = 1, 2, \ldots, \text{maxlag}$$

where $d_{i,i+d}$ is the distance between the two amino acids at position i and $i + d$.

Note: maxlag is the maximum lag and the length of the protein must be not less than maxlag.

The function `extractSOCN(x)` is used for computing the sequence-order-coupling numbers:

```
> extractSOCN(x)

 Schneider.lag1  Schneider.lag2  Schneider.lag3  Schneider.lag4  Schneider.lag5
       204.2036        199.8708        206.8102        197.4828        193.3366
 Schneider.lag6  Schneider.lag7  Schneider.lag8  Schneider.lag9 Schneider.lag10
       208.1936        195.5476        200.9789        196.7110        193.9931
Schneider.lag11 Schneider.lag12 Schneider.lag13 Schneider.lag14 Schneider.lag15
       199.7031        204.9389        187.0140        198.4702        205.4526
Schneider.lag16 Schneider.lag17 Schneider.lag18 Schneider.lag19 Schneider.lag20
       193.1274        187.3529        190.4949        202.8853        198.5299
Schneider.lag21 Schneider.lag22 Schneider.lag23 Schneider.lag24 Schneider.lag25
       191.1013        185.0074        189.9857        202.7113        201.6267
Schneider.lag26 Schneider.lag27 Schneider.lag28 Schneider.lag29 Schneider.lag30
```

```
       194.5770        185.9939        204.1297        191.1629        183.9073
 Grantham.lag1   Grantham.lag2   Grantham.lag3   Grantham.lag4   Grantham.lag5
  6674686.0000    6761609.0000    7138892.0000    6748261.0000    6291229.0000
 Grantham.lag6   Grantham.lag7   Grantham.lag8   Grantham.lag9  Grantham.lag10
  6839853.0000    6594164.0000    6556148.0000    6620183.0000    6770614.0000
Grantham.lag11  Grantham.lag12  Grantham.lag13  Grantham.lag14  Grantham.lag15
  6495689.0000    6865537.0000    6297267.0000    6498247.0000    6615566.0000
Grantham.lag16  Grantham.lag17  Grantham.lag18  Grantham.lag19  Grantham.lag20
  6572680.0000    6569081.0000    6173947.0000    6570829.0000    6471308.0000
Grantham.lag21  Grantham.lag22  Grantham.lag23  Grantham.lag24  Grantham.lag25
  6461649.0000    5939432.0000    6532121.0000    6652472.0000    6480660.0000
Grantham.lag26  Grantham.lag27  Grantham.lag28  Grantham.lag29  Grantham.lag30
  6382281.0000    6276521.0000    6537634.0000    6442991.0000    6350157.0000
```

Users could also specify the maximum lag value with the `nlag` argument.

Note: In addition to Schneider-Wrede physicochemical distance matrix (Schneider and Wrede 1994) used by Kuo-Chen Chou, another chemical distance matrix by Grantham (1974) is also used here. So the descriptors dimension will be `nlag * 2`. The quasi-sequence-order descriptors described next also utilized the two matrices.

Quasi-sequence-order Descriptors

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

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

where f_r is the normalized occurrence for amino acid type i and w is a weighting factor ($w = 0.1$). These are the first 20 quasi-sequence-order descriptors. The other 30 quasi-sequence-order are defined as:

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

An minimal example for `extractQSO()` could be:

```
> extractQSO(x)

Schneider.Xr.A  Schneider.Xr.R  Schneider.Xr.N  Schneider.Xr.D  Schneider.Xr.C
  6.096218e-02    6.773576e-02    3.725467e-02    4.910842e-02    6.434897e-02
Schneider.Xr.E  Schneider.Xr.Q  Schneider.Xr.G  Schneider.Xr.H  Schneider.Xr.I
  4.572164e-02    4.572164e-02    7.789612e-02    2.878770e-02    3.386788e-02
Schneider.Xr.L  Schneider.Xr.K  Schneider.Xr.M  Schneider.Xr.F  Schneider.Xr.P
  7.281594e-02    3.725467e-02    1.185376e-02    3.048109e-02    5.080182e-02
Schneider.Xr.S  Schneider.Xr.T  Schneider.Xr.W  Schneider.Xr.Y  Schneider.Xr.V
  8.466970e-02    4.233485e-02    2.201412e-02    4.064145e-02    4.741503e-02
```

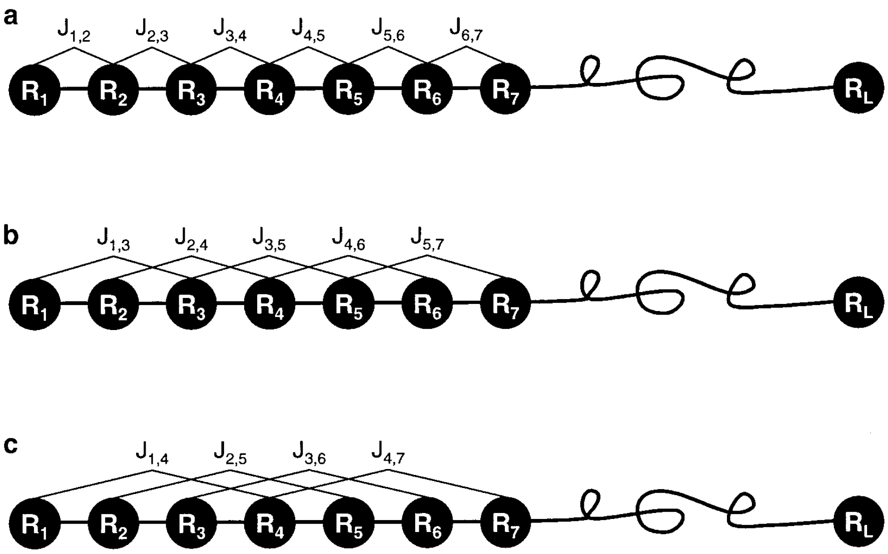


Figure 4: A schematic drawing to show (a) the 1st-rank, (b) the 2nd-rank, and (3) the 3rd-rank sequence-order-coupling mode along a protein sequence. (a) Reflects the coupling mode between all the most contiguous residues, (b) that between all the 2nd most contiguous residues, and (c) that between all the 3rd most contiguous residues. This figure is from Chou (2000).

```
   Grantham.Xr.A    Grantham.Xr.R    Grantham.Xr.N    Grantham.Xr.D    Grantham.Xr.C
    1.835033e-06     2.038926e-06     1.121409e-06     1.478221e-06     1.936980e-06
   Grantham.Xr.E    Grantham.Xr.Q    Grantham.Xr.G    Grantham.Xr.H    Grantham.Xr.I
    1.376275e-06     1.376275e-06     2.344765e-06     8.665435e-07     1.019463e-06
   Grantham.Xr.L    Grantham.Xr.K    Grantham.Xr.M    Grantham.Xr.F    Grantham.Xr.P
    2.191845e-06     1.121409e-06     3.568120e-07     9.175167e-07     1.529194e-06
   Grantham.Xr.S    Grantham.Xr.T    Grantham.Xr.W    Grantham.Xr.Y    Grantham.Xr.V
    2.548657e-06     1.274329e-06     6.626509e-07     1.223356e-06     1.427248e-06
  Schneider.Xd.1   Schneider.Xd.2   Schneider.Xd.3   Schneider.Xd.4   Schneider.Xd.5
    3.457972e-02     3.384600e-02     3.502111e-02     3.344162e-02     3.273951e-02
  Schneider.Xd.6   Schneider.Xd.7   Schneider.Xd.8   Schneider.Xd.9  Schneider.Xd.10
    3.525537e-02     3.311390e-02     3.403364e-02     3.331093e-02     3.285068e-02
 Schneider.Xd.11  Schneider.Xd.12  Schneider.Xd.13  Schneider.Xd.14  Schneider.Xd.15
    3.381760e-02     3.470422e-02     3.166883e-02     3.360882e-02     3.479121e-02
 Schneider.Xd.16  Schneider.Xd.17  Schneider.Xd.18  Schneider.Xd.19  Schneider.Xd.20
    3.270408e-02     3.172623e-02     3.225829e-02     3.435647e-02     3.361893e-02
 Schneider.Xd.21  Schneider.Xd.22  Schneider.Xd.23  Schneider.Xd.24  Schneider.Xd.25
    3.236099e-02     3.132904e-02     3.217206e-02     3.432701e-02     3.414334e-02
 Schneider.Xd.26  Schneider.Xd.27  Schneider.Xd.28  Schneider.Xd.29  Schneider.Xd.30
    3.294954e-02     3.149609e-02     3.456720e-02     3.237140e-02     3.114275e-02
   Grantham.Xd.1    Grantham.Xd.2    Grantham.Xd.3    Grantham.Xd.4    Grantham.Xd.5
    3.402298e-02     3.446605e-02     3.638918e-02     3.439801e-02     3.206838e-02
   Grantham.Xd.6    Grantham.Xd.7    Grantham.Xd.8    Grantham.Xd.9   Grantham.Xd.10
    3.486488e-02     3.361253e-02     3.341875e-02     3.374516e-02     3.451195e-02
```

```
Grantham.Xd.11  Grantham.Xd.12  Grantham.Xd.13  Grantham.Xd.14  Grantham.Xd.15
  3.311057e-02    3.499580e-02    3.209915e-02    3.312361e-02    3.372162e-02
Grantham.Xd.16  Grantham.Xd.17  Grantham.Xd.18  Grantham.Xd.19  Grantham.Xd.20
  3.350302e-02    3.348467e-02    3.147055e-02    3.349358e-02    3.298629e-02
Grantham.Xd.21  Grantham.Xd.22  Grantham.Xd.23  Grantham.Xd.24  Grantham.Xd.25
  3.293706e-02    3.027516e-02    3.329628e-02    3.390974e-02    3.303396e-02
Grantham.Xd.26  Grantham.Xd.27  Grantham.Xd.28  Grantham.Xd.29  Grantham.Xd.30
  3.253250e-02    3.199340e-02    3.332438e-02    3.284195e-02    3.236875e-02
```

where users could also specify the maximum lag with argument `nlag` and the weighting factor with argument `w`.

2.8. Pseudo-Amino Acid Composition (PAAC)

This groups of descriptors are proposed in Chou (2001). PAAC descriptors (`http://www.csbio.sjtu.edu.cn/bioinf/PseAAC/type1.htm`) are also called the *type 1 pseudo-amino acid composition*. Let $H_1^o(i)$, $H_2^o(i)$, $M^o(i)$ $(i = 1, 2, 3, \dots, 20)$ 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 following qualities by a standard conversion:

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

$H_2^o(i)$ and $M^o(i)$ are normalized as $H_2(i)$ and $M(i)$ in the same way.

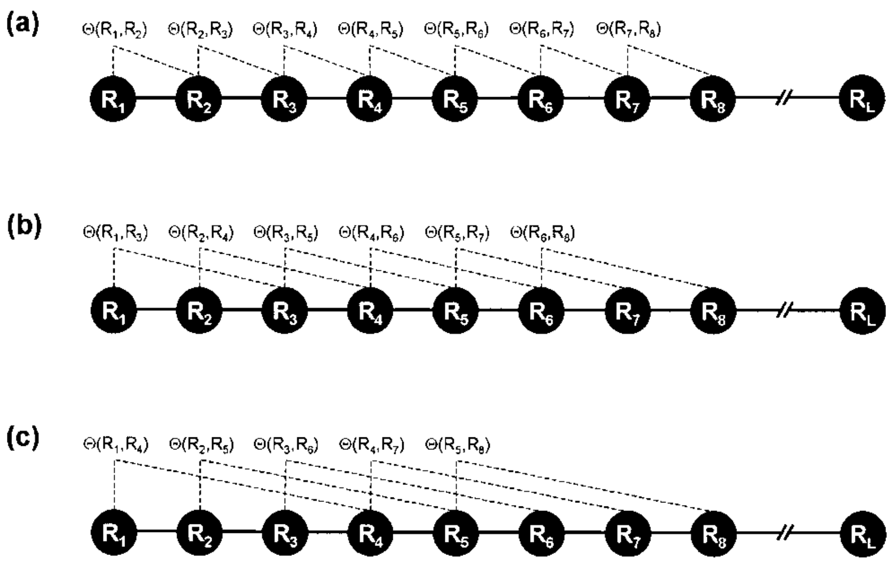


Figure 5: A schematic drawing to show (a) the first-tier, (b) the second-tier, and (3) the third-tiersequence order correlation mode along a protein sequence. Panel (a) reflects the correlation mode between all the most contiguous residues, panel (b) that between all the second-most contiguous residues, and panel (c) that between all the third-most contiguous residues. This figure is from Chou (2001).

Then, a correlation function could be defines as

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

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

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

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:

$$\begin{aligned}
\theta_1 &= \frac{1}{N-1}\sum_{i=1}^{N-1}\Theta(R_i, R_{i+1}) \\
\theta_2 &= \frac{1}{N-2}\sum_{i=1}^{N-2}\Theta(R_i, R_{i+2}) \\
\theta_3 &= \frac{1}{N-3}\sum_{i=1}^{N-3}\Theta(R_i, R_{i+3}) \\
&\dots \\
\theta_\lambda &= \frac{1}{N-\lambda}\sum_{i=1}^{N-\lambda}\Theta(R_i, R_{i+\lambda})
\end{aligned}$$

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

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

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

where w is the weighting factor for the sequence-order effect and is set as $w = 0.05$ in **protr** as suggested by Kuo-Chen Chou.

With `extractPAAC()`, we could compute the PAAC descriptors:

```
> extractPAAC(x)
```

```
         Xc1.A          Xc1.R          Xc1.N          Xc1.D          Xc1.C
    9.07025432    10.07806035     5.54293319     7.30659376     9.57415734
         Xc1.E          Xc1.Q          Xc1.G          Xc1.H          Xc1.I
    6.80269074     6.80269074    11.58976941     4.28317565     5.03903018
         Xc1.L          Xc1.K          Xc1.M          Xc1.F          Xc1.P
   10.83391488     5.54293319     1.76366056     4.53512716     7.55854527
         Xc1.S          Xc1.T          Xc1.W          Xc1.Y          Xc1.V
   12.59757544     6.29878772     3.27536961     6.04683621     7.05464225
  Xc2.lambda.1   Xc2.lambda.2   Xc2.lambda.3   Xc2.lambda.4   Xc2.lambda.5
    0.02514092     0.02500357     0.02527773     0.02553159     0.02445265
  Xc2.lambda.6   Xc2.lambda.7   Xc2.lambda.8   Xc2.lambda.9  Xc2.lambda.10
    0.02561910     0.02486131     0.02506656     0.02553952     0.02437663
 Xc2.lambda.11  Xc2.lambda.12  Xc2.lambda.13  Xc2.lambda.14  Xc2.lambda.15
    0.02491262     0.02533803     0.02351915     0.02479912     0.02548431
 Xc2.lambda.16  Xc2.lambda.17  Xc2.lambda.18  Xc2.lambda.19  Xc2.lambda.20
    0.02478210     0.02513770     0.02457224     0.02543046     0.02500889
 Xc2.lambda.21  Xc2.lambda.22  Xc2.lambda.23  Xc2.lambda.24  Xc2.lambda.25
    0.02476967     0.02342389     0.02431684     0.02610300     0.02626722
 Xc2.lambda.26  Xc2.lambda.27  Xc2.lambda.28  Xc2.lambda.29  Xc2.lambda.30
    0.02457082     0.02343049     0.02588823     0.02490463     0.02451951
```

The `extractPAAC()` fucntion also provides the `props` and `customprops` arguments, which is similar to the functions for Moreau-Broto/Moran/Geary autocorrelation descriptors. For minor differences, see `?extracPAAC`. Users could specify the lambda parameter and the weighting factor with arguments `lambda` and `w`.

Note: In the work of Kuo-Chen Chou, the definition for "normalized occurrence frequency" was not given. In this work, we define it as the occurrence frequency of amino acid in the sequence normalized to 100% and hence our calculated values are not the same as values by them.

2.9. Amphiphilic Pseudo-Amino Acid Composition (APAAC)

Amphiphilic Pseudo-Amino Acid Composition (APAAC, `http://www.csbio.sjtu.edu.cn/bioinf/PseAAC/type2.htm`) was proposed in Chou (2001). APAAC is also recognized as the *type 2 pseudo-amino acid composition*. The definitions of these qualities are similar to the PAAC descriptors. From $H_1(i)$ and $H_2(j)$ defined before, the hydrophobicity and hydrophilicity correlation functions are defined respectively as:

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

From these qualities, sequence order factors can be defines as:

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

Then a set of descriptors called *Amphiphilic Pseudo-Amino Acid Composition* (*APAAC*) are defined as:

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

where w is the weighting factor and is taken as $w = 0.5$ in **protr** as in the work of Chou KC. A minimal example for `extracAPAAC()` is:

```
> extractAPAAC(x)

         Pc1.A          Pc1.R          Pc1.N
  3.537412e+01   3.930458e+01   2.161752e+01
         Pc1.D          Pc1.C          Pc1.E
  2.849582e+01   3.733935e+01   2.653059e+01
         Pc1.Q          Pc1.G          Pc1.H
  2.653059e+01   4.520027e+01   1.670445e+01
         Pc1.I          Pc1.L          Pc1.K
  1.965229e+01   4.225242e+01   2.161752e+01
         Pc1.M          Pc1.F          Pc1.P
  6.878302e+00   1.768706e+01   2.947844e+01
         Pc1.S          Pc1.T          Pc1.W
```

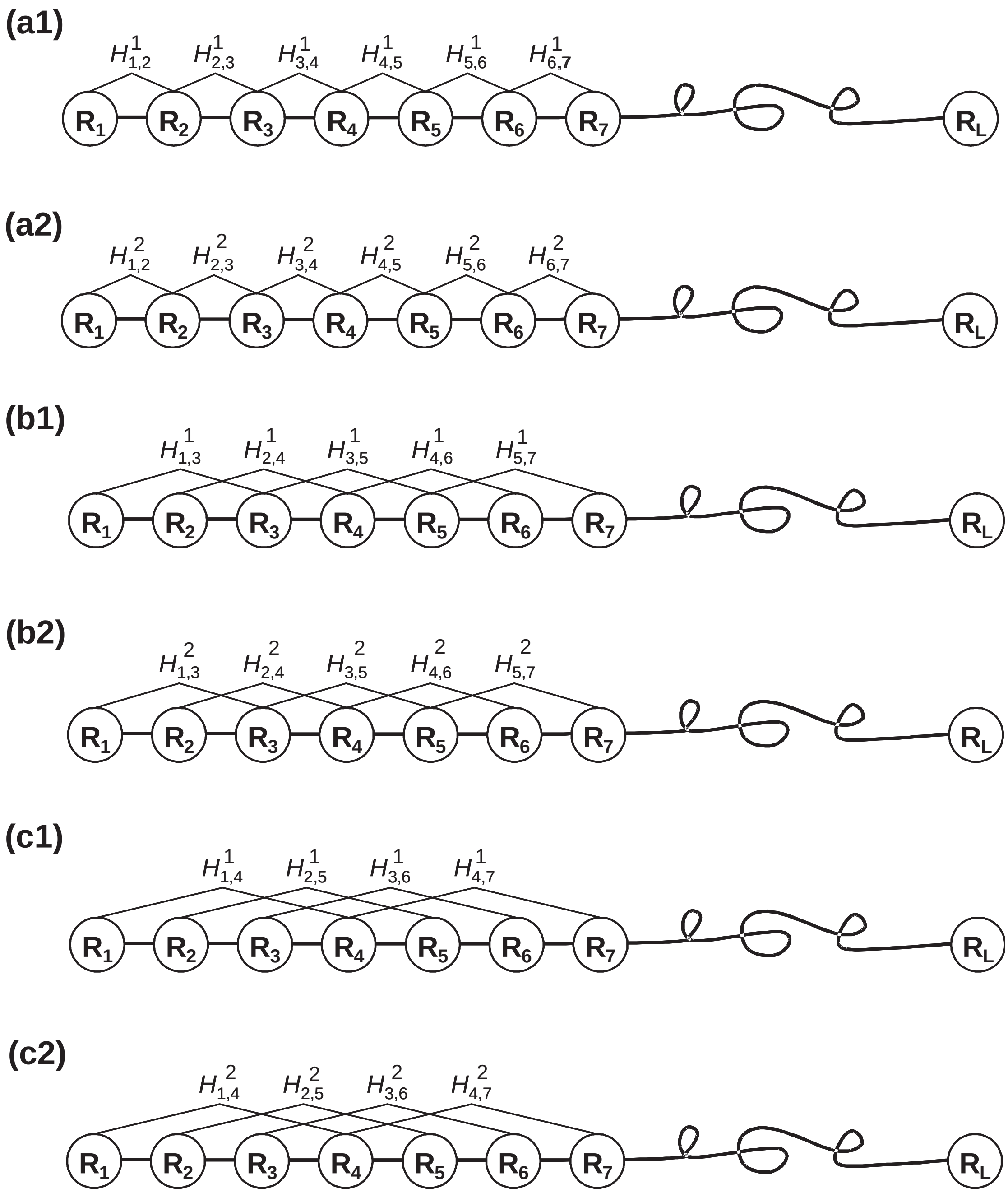


Figure 6: A schematic diagram to show (**a1/a2**) the first-rank, (**b1/b2**) the second-rank and (**c1/c2**) the third-rank sequence-order-coupling mode along a protein sequence through a hydrophobicity/hydrophilicity correlation function, where $H^1_{i,j}$ and $H^2_{i,j}$ are given by Equation (3). Panel (a1/a2) reflects the coupling mode between all the most contiguous residues, panel (b1/b2) that between all the second-most contiguous residues and panel (c1/c2) that between all the third-most contiguous residues. This figure is from Chou (2005).

```
          4.913073e+01            2.456536e+01            1.277399e+01
                 Pc1.Y                   Pc1.V  Pc2.Hydrophobicity.1
          2.358275e+01            2.751321e+01            2.196320e-04
 Pc2.Hydrophilicity.1  Pc2.Hydrophobicity.2  Pc2.Hydrophilicity.2
          1.025766e-03           -3.088876e-04           -1.834385e-04
 Pc2.Hydrophobicity.3  Pc2.Hydrophilicity.3  Pc2.Hydrophobicity.4
          1.174146e-03            7.400156e-04           -1.105715e-03
 Pc2.Hydrophilicity.4  Pc2.Hydrophobicity.5  Pc2.Hydrophilicity.5
         -4.493680e-04            1.766358e-03            1.471212e-03
 Pc2.Hydrophobicity.6  Pc2.Hydrophilicity.6  Pc2.Hydrophobicity.7
         -1.441572e-03           -4.913600e-03           -1.678053e-05
 Pc2.Hydrophilicity.7  Pc2.Hydrophobicity.8  Pc2.Hydrophilicity.8
          7.312356e-04           -1.885399e-03           -1.928708e-03
 Pc2.Hydrophobicity.9  Pc2.Hydrophilicity.9 Pc2.Hydrophobicity.10
         -2.931177e-03           -1.555660e-03            2.916597e-03
Pc2.Hydrophilicity.10 Pc2.Hydrophobicity.11 Pc2.Hydrophilicity.11
          3.602591e-03            1.055082e-04            8.697920e-04
Pc2.Hydrophobicity.12 Pc2.Hydrophilicity.12 Pc2.Hydrophobicity.13
         -9.276413e-04           -2.001384e-03            1.705044e-03
Pc2.Hydrophilicity.13 Pc2.Hydrophobicity.14 Pc2.Hydrophilicity.14
          4.364007e-03            7.883453e-04           -9.441693e-04
Pc2.Hydrophobicity.15 Pc2.Hydrophilicity.15 Pc2.Hydrophobicity.16
         -3.133437e-04           -3.599332e-03            3.689079e-05
Pc2.Hydrophilicity.16 Pc2.Hydrophobicity.17 Pc2.Hydrophilicity.17
          2.483867e-03            4.832798e-04            2.465788e-03
Pc2.Hydrophobicity.18 Pc2.Hydrophilicity.18 Pc2.Hydrophobicity.19
         -3.142728e-04            2.021961e-03            6.421283e-05
Pc2.Hydrophilicity.19 Pc2.Hydrophobicity.20 Pc2.Hydrophilicity.20
         -8.896690e-04           -2.986886e-04            9.304039e-04
Pc2.Hydrophobicity.21 Pc2.Hydrophilicity.21 Pc2.Hydrophobicity.22
         -6.777458e-04            1.646818e-03            3.193506e-03
Pc2.Hydrophilicity.22 Pc2.Hydrophobicity.23 Pc2.Hydrophilicity.23
          3.270656e-03            2.533569e-03            2.478252e-03
Pc2.Hydrophobicity.24 Pc2.Hydrophilicity.24 Pc2.Hydrophobicity.25
         -2.489106e-03           -1.031008e-03           -3.992322e-03
Pc2.Hydrophilicity.25 Pc2.Hydrophobicity.26 Pc2.Hydrophilicity.26
         -2.596060e-03            8.690771e-04           -1.221378e-03
Pc2.Hydrophobicity.27 Pc2.Hydrophilicity.27 Pc2.Hydrophobicity.28
          5.208649e-03            4.617400e-03           -1.088584e-03
Pc2.Hydrophilicity.28 Pc2.Hydrophobicity.29 Pc2.Hydrophilicity.29
         -2.512263e-03            1.387641e-03            2.060890e-03
Pc2.Hydrophobicity.30 Pc2.Hydrophilicity.30
          3.177340e-04            1.451909e-03
```

This function has the same arguments as `extractPAAC()`.

3. Quantitative Descriptors

Proteochemometric (PCM) modeling utilizes statistical modeling techniques to model ligand-target interaction space. The below descriptors implemented in **protr** are commonly used in Proteochemometric modeling.

- Generalized Scales-Based Descriptors derived by Principal Components Analysis
  - Generalized Scales-Based Descriptors derived by AA-Properties (AAindex)
  - Generalized Scales-Based Descriptors derived by 20+ classes of 2D and 3D Molecular Descriptors (Topological, WHIM, VHSE, etc.)
- Generalized Scales-Based Descriptors derived by Factor Analysis
- Generalized Scales-Based Descriptors derived by Multidimensional Scaling
- Generalized BLOSUM and PAM Matrix-Derived Descriptors

Note that each of the generalized scales-based descriptor functions are freely to combine with the more than 20 classes of 2D and 3D molecular descriptors to construct highly customized scales-based descriptors. Of course, these functions are designed to be flexible enough that users could provide totally self-defined property matrices to construct scales-based descriptors.

For example, to compute the "topological scales" derived by PCA (using the first 5 principal components), one could use `extractDescScales()`:

```
> x = readFASTA(system.file('protseq/P00750.fasta', package = 'protr'))[[1]]
> descscales = extractDescScales(x, propmat = 'AATopo',
+                               index = c(37:41, 43:47),
+                               pc = 5, lag = 7, silent = FALSE)

Summary of the first 5 principal components:
                            PC1      PC2       PC3       PC4        PC5
Standard deviation     2.581537 1.754133 0.4621854 0.1918666 0.08972087
Proportion of Variance 0.666430 0.307700 0.0213600 0.0036800 0.00080000
Cumulative Proportion  0.666430 0.974130 0.9954900 0.9991700 0.99998000
```

the argument `propmat` involkes the `AATopo` dataset shipped with **protr** package, and the argument `index` selects the 37 to 41 and 43 to 47 columns (molecular descriptors) in the `AATopo` dataset to use, the `lag` parameter was set for the Auto Cross Covariance (ACC) for generating scales-based descriptors of the same length. At last, we printed the summary of the first 5 principal components (standard deviation, proportion of variance, cumulative proportion of variance).

The result is a length 175 named vector, which is consistent with the descriptors before:

```
> length(descscales)

[1] 175
```

```
> head(descscales, 15)

    scl1.lag1     scl2.lag1     scl3.lag1     scl4.lag1     scl5.lag1 
-2.645644e-01 -1.717847e-02  1.975438e-02 -7.930659e-05 -3.710597e-05 
    scl1.lag2     scl2.lag2     scl3.lag2     scl4.lag2     scl5.lag2 
 3.548612e-01  1.343712e-01  5.699395e-03 -5.489472e-04 -6.364577e-05 
    scl1.lag3     scl2.lag3     scl3.lag3     scl4.lag3     scl5.lag3 
 2.011431e-02 -9.211136e-02 -1.461755e-03  6.747801e-04  2.386782e-04 
```

For another example, to compute the descriptors derived by BLOSUM62 matrix and use the first 5 scales, one could use:

```
> x = readFASTA(system.file('protseq/P00750.fasta', package = 'protr'))[[1]]
> blosum = extractBLOSUM(x, submat = 'AABLOSUM62',
+                        k = 5, lag = 7, scale = TRUE, silent = FALSE)

Relative importance of all the possible 20 scales: 
 [1]  1.204960e+01  7.982007e+00  6.254364e+00  4.533706e+00  4.326286e+00
 [6]  3.850579e+00  3.752197e+00  3.538207e+00  3.139155e+00  2.546405e+00
[11]  2.373286e+00  1.666259e+00  1.553126e+00  1.263685e+00  1.024699e+00
[16]  9.630187e-01  9.225759e-01  7.221636e-01  1.020085e-01 -4.714220e-16
```

The result is a length 175 named vector:

```
> length(blosum)

[1] 175

> head(blosum, 15)

    scl1.lag1     scl2.lag1     scl3.lag1     scl4.lag1     scl5.lag1 
 0.0042370555 -0.0021502057  0.0005993291  0.0006456375  0.0014849592 
    scl1.lag2     scl2.lag2     scl3.lag2     scl4.lag2     scl5.lag2 
-0.0014919096  0.0032873726  0.0011734162 -0.0021758536 -0.0018127568 
    scl1.lag3     scl2.lag3     scl3.lag3     scl4.lag3     scl5.lag3 
-0.0029413528  0.0001494193  0.0003298806 -0.0017877430 -0.0051044133 
```

4. Parallelized Similarity Calculation by Sequence Alignment

Similarity computation derived by local or global protein sequence alignment between a list of protein sequences is great need in the protein related research and applications. However, this sort of pairwise similarity computation often computationally intensive, especially when there exists many protein sequences. Luckily, this process is also embarassingly parallel, the **protr** package integrates the functionality of parallellized similarity computation derived by local or global protein sequence alignment between a list of protein sequences.

The function `twoSeqSim()` calculates the alignment result between two protein sequences, and the function `parSeqSim()` calculates the pairwise similarity calculation with a list of protein sequences in parallel:

```
> s1 = readFASTA(system.file('protseq/P00750.fasta', package = 'protr'))[[1]]
> s2 = readFASTA(system.file('protseq/P08218.fasta', package = 'protr'))[[1]]
> s3 = readFASTA(system.file('protseq/P10323.fasta', package = 'protr'))[[1]]
> s4 = readFASTA(system.file('protseq/P20160.fasta', package = 'protr'))[[1]]
> s5 = readFASTA(system.file('protseq/Q9NZP8.fasta', package = 'protr'))[[1]]
> plist   = list(s1, s2, s3, s4, s5)
> psimmat = parSeqSim(plist, cores = 4, type = 'local', submat = 'BLOSUM62')
> print(psimmat)

           [,1]       [,2]       [,3]       [,4]       [,5]
[1,] 1.00000000 0.11825938 0.10236985 0.04921696 0.03943488
[2,] 0.11825938 1.00000000 0.18858241 0.12124217 0.06391103
[3,] 0.10236985 0.18858241 1.00000000 0.05819984 0.06175942
[4,] 0.04921696 0.12124217 0.05819984 1.00000000 0.05714638
[5,] 0.03943488 0.06391103 0.06175942 0.05714638 1.00000000
```

Users should install the packages **foreach** and **doMC**/**doParallel** before using `parSeqSim()`, according to their operation system. The **protr** package will automatically decide which backend to use.

5. Similarity Calculation by GO Semantic Similarity

The **protr** package also integrates the functionality of similarity computation derived by Gene Ontology (GO) semantic similarity measures between a list of GO terms / Entrez Gene IDs.

The function `twoGOSim()` calculates the similarity derived by GO-terms semantic similarity measures between two GO terms / Entrez Gene IDs, and the function `parGOSim()` calculates the pairwise similarity with a list of GO terms / Entrez Gene IDs:

```
# by GO Terms
> go1 = c('GO:0005215', 'GO:0005488', 'GO:0005515',
+         'GO:0005625', 'GO:0005802', 'GO:0005905')  # AP4B1
> go2 = c('GO:0005515', 'GO:0005634', 'GO:0005681',
+         'GO:0008380', 'GO:0031202')                # BCAS2
> go3 = c('GO:0003735', 'GO:0005622', 'GO:0005840',
+         'GO:0006412')                              # PDE4DIP
> glist = list(go1, go2, go3)
> gsimmat1 = parGOSim(glist, type = 'go', ont = 'CC')
> print(gsimmat1)

      [,1]  [,2]  [,3]
[1,] 1.000 0.077 0.055
[2,] 0.077 1.000 0.220
[3,] 0.055 0.220 1.000

# by Entrez gene id
> genelist = list(c('150', '151', '152', '1814', '1815', '1816'))
```

```
> gsimmat2 = parGOSim(genelist, type = 'gene')
> print(gsimmat2)

       150   151   152  1814  1815  1816
150  0.689 0.335 0.487 0.133 0.169 0.160
151  0.335 0.605 0.441 0.171 0.198 0.274
152  0.487 0.441 0.591 0.151 0.178 0.198
1814 0.133 0.171 0.151 0.512 0.401 0.411
1815 0.169 0.198 0.178 0.401 0.619 0.481
1816 0.160 0.274 0.198 0.411 0.481 0.819
```

6. ProtrWeb

The web service built on **protr**, namely **ProtrWeb**, is located at:

http://cbdd.csu.edu.cn:8080/protrweb/

ProtrWeb (Figure 7) does not require any knowledge of programming for the users, it is a user-friendly and one-click-to-go online platform for computing the protein descriptors presented in the **protr** package.

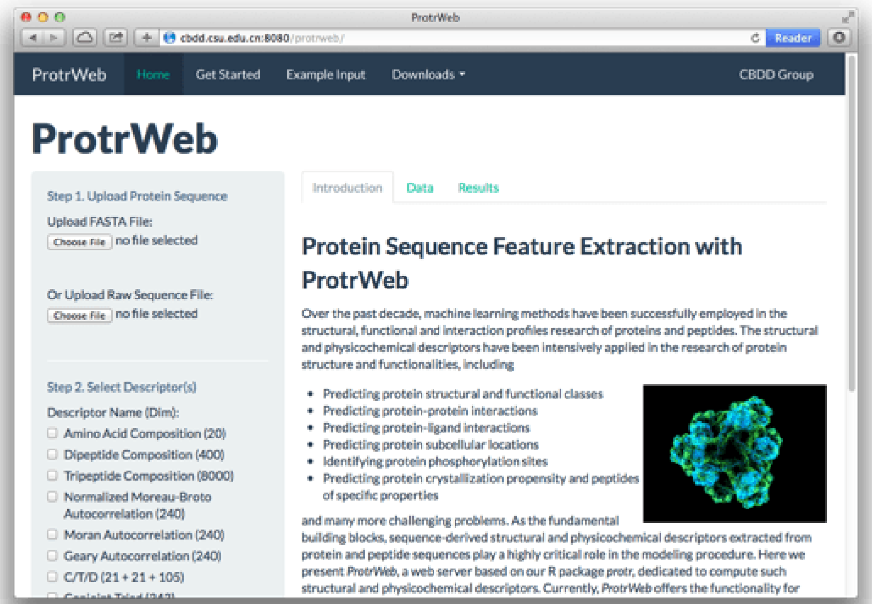


Figure 7: A Screenshot of **ProtrWeb**

A step-by-step instruction on how to use **ProtrWeb** could be found at:

http://cbdd.csu.edu.cn:8080/protrweb/intro.html

7. Miscellaneous Tools

In this section, we will briefly introduce some useful tools provided by the **protr** package.

7.1. Retrieve Protein Sequences from UniProt

This function `getUniProt()` gets protein sequences from uniprot.org by protein ID(s). The input `ID` is a character vector specifying the protein ID(s). The returned sequences are stored in a list:

```
> ids = c('P00750', 'P00751', 'P00752')
> prots = getUniProt(ids)
> print(prots)

[[1]]
[1] "MDAMKRGLCCVLLLCGAVFVSPSQEIHARFRRGARSYQVICRDEKTQMIYQQHQSWLRPVLRSNRVEYCWCN
SGRAQCHSVPVKSCSEPRCFNGGTCQQALYFSDFVCQCPEGFAGKCCEIDTRATCYEDQGISYRGTWSTAESGAECT
NWNSSALAQKPYSGRRPDAIRLGLGNHNYCRNPDRDSKPWCYVFKAGKYSSEFCSTPACSEGNSDCYFGNGSAYRGT
HSLTESGASCLPWNSMILIGKVYTAQNPSAQALGLGKHNYCRNPDGDAKPWCHVLKNRRLTWEYCDVPSCSTCGLRQ
YSQPQFRIKGGLFADIASHPWQAAIFAKHRRSPGERFLCGGILISSCWILSAAHCFQERFPPHHLTVILGRTYRVVP
GEEEQKFEVEKYIVHKEFDDDTYDNDIALLQLKSDSSRCAQESSVVRTVCLPPADLQLPDWTECELSGYGKHEALSP
FYSERLKEAHVRLYPSSRCTSQHLLNRTVTDNMLCAGDTRSGGPQANLHDACQGDSGGPLVCLNDGRMTLVGIISWG
LGCGQKDVPGVYTKVTNYLDWIRDNMRP"

[[2]]
[1] "MGSNLSPQLCLMPFILGLLSGGVTTTPWSLARPQGSCSLEGVEIKGGSFRLLQEGQALEYVCPSGFYPYPVQ
TRTCRSTGSWSTLKTQDQKTVRKAECRAIHCPRPHDFENGEYWPRSPYYNVSDEISFHCYDGYTLRGSANRTCQVNG
RWSGQTAICDNGAGYCSNPGIPIGTRKVGSQYRLEDSVTYHCSRGLTLRGSQRRTCQEGGSWSGTEPSCQDSFMYDT
PQEVAEAFLSSLTETIEGVDAEDGHGPGEQQKRKIVLDPSGSMNIYLVLDGSDSIGASNFTGAKKCLVNLIEKVASY
GVKPRYGLVTYATYPKIWVKVSEADSSNADWVTKQLNEINYEDHKLKSGTNTKKALQAVYSMMSWPDDVPPEGWNRT
RHVIILMTDGLHNMGGDPITVIDEIRDLLYIGKDRKNPREDYLDVYVFGVGPLVNQVNINALASKKDNEQHVFKVKD
MENLEDVFYQMIDESQSLSLCGMVWEHRKGTDYHKQPWQAKISVIRPSKGHESCMGAVVSEYFVLTAAHCFTVDDKE
HSIKVSVGGEKRDLEIEVVLFHPNYNINGKKEAGIPEFYDYDVALIKLKNKLKYGQTIRPICLPCTEGTTRALRLPP
TTTCQQQKEELLPAQDIKALFVSEEEKKLTRKEVYIKNGDKKGSCERDAQYAPGYDKVKDISEVVTPRFLCTGGVSP
YADPNTCRGDSGGPLIVHKRSRFIQVGVISWGVVDVCKNQKRQKQVPAHARDFHINLFQVLPWLKEKLQDEDLGFL"

[[3]]
[1] "APPIQSRIIGGRECEKNSHPWQVAIYHYSSFQCGGVLVNPKWVLTAAHCKNDNYEVWLGRHNLFENENTAQF
FGVTADFPHPGFNLSLLKXHTKADGKDYSHDLMLLRLQSPAKITDAVKVLELPTQEPELGSTCEASGWGSIEPGPDB
FEFPDEIQCVQLTLLQNTFCABAHPBKVTESMLCAGYLPGGKDTCMGDSGGPLICNGMWQGITSWGHTPCGSANKPS
IYTKLIFYLDWINDTITENP"
```

7.2. Read FASTA Format files

The `readFASTA()` function provides a convenient way to read protein sequences stored in FASTA format files. See `?readFASTA` for details. The returned sequences are stored in a named list, whose components are named with the protein sequences' names.

7.3. Read PDB Format files

The Protein Data Bank (pdb) file format is a textual file format describing the three dimensional structures of protein. The `readPDB()` function provides the functionality to read protein sequences stored in PDB format files. See `?readPDB` for details.

7.4. Sanity Check of the Amino Acid Types

The `protcheck()` function checks if the protein sequence's amino acid types are in the 20 default types, which returns a `TRUE` if all the amino acids in the sequence belongs to the 20 default types:

```
> x = readFASTA(system.file('protseq/P00750.fasta', package = 'protr'))[[1]]
> # A real sequence
> protcheck(x)

[1] TRUE

> # An artificial sequence
> protcheck(paste(x, 'Z', sep = ''))

[1] FALSE
```

7.5. Protein Sequence Segmentation

The `protseg()` function extracts the segmentations from the protein sequence. Users could specify a sequence `x`, and a character `aa`, one of the 20 amino acid types, and a positive integer `k`, which controls the window size (half of the window).

This function returns a named list, each component contains one of the segmentations (a character string), names of the list components are the positions of the specified amino acid in the sequence. See the example below:

```
> protseg(x, aa = 'M', k = 5)

$`48`
[1] "DEKTQMIYQQH"

$`242`
[1] "LPWNSMILIGK"

$`490`
[1] "TVTDNMLCAGD"

$`525`
[1] "LNDGRMTLVGI"
```

7.6. Auto Cross Covariance (ACC) Computation

Auto Cross Covariance (ACC) is extensively used in the scales-based descriptors computation, this approach calculates the auto covariance and auto cross covariance for generating scale-based descriptors of the same length. Users could write their own scales-based descriptor functions with the help of `acc()` function in the **protr** package.

7.7. Pre-computed 2D and 3D Descriptor Sets for the 20 Amino Acids

The **protr** package ships with more than 20 pre-computed 2D and 3D descriptor sets for the 20 amino acids to use with the generalized scales-based descriptors, see `data(package = 'protr')` for all the datasets included in the **protr** package.

7.8. BLOSUM and PAM Matrices for the 20 Amino Acids

The BLOSUM and PAM matrices for the 20 amino acids could be used to calculate BLOSUM and PAM matrix-derived descriptors with function `extractBLOSUM()`, the datasets are named in `AABLOSUM45`, `AABLOSUM50`, `AABLOSUM62`, `AABLOSUM80`, `AABLOSUM100`, `AAPAM30`, `AAPAM40`, `AAPAM70`, `AAPAM120`, and `AAPAM250`.

7.9. Meta Information of the 20 Amino Acids

As the reference, the `AAMetaInfo` dataset includes the meta information of the 20 amino acids used for the 2D and 3D descriptor calculation in the **protr** package. This dataset include each amino acid's name, one-letter representation, three-letter representation, SMILE representation, PubChem CID and PubChem link. See `data(AAMetaInfo)` for details.

8. Summary

The summary of the qualitative descriptors in the **protr** package is listed in table 3.

Table 3: List of qualitative descriptors in **protr**

Descriptor Group	Descriptor Name	Descriptor Dimension	Function Name
Amino Acid Composition	Amino Acid Composition	20	`extractAAC()`
	Dipeptide Composition	400	`extractDC()`
	Tripeptide Composition	8000	`extractTC()`
Autocorrelation	Normalized Moreau-Broto Autocorrelation	240[1]	`extractMoreauBroto()`
	Moran Autocorrelation	240[1]	`extractMoran()`
	Geary Autocorrelation	240[1]	`extractGeary()`
CTD	Composition	21	`extractCTDC()`
	Transition	21	`extractCTDT()`
	Distribution	105	`extractCTDD()`
Conjoint Triad	Conjoint Triad	343	`extractCTriad()`
Quasi-Sequence-Order	Sequence-Order-Coupling Number	60[2]	`extractSOCN()`
	Quasi-Sequence-Order Descriptors	100[2]	`extractQSO()`
Pseudo-Amino Acid Composition	Pseudo-Amino Acid Composition	50[3]	`extractPAAC()`
	Amphiphilic Pseudo-Amino Acid Composition	80[4]	`extractAPAAC()`

The summary of the quantitative (scales-based) descriptors in the **protr** package is listed in table 4.

Table 4: List of quantitative descriptors in **protr**

Derived by	Descriptor Class	Function Name
Principal Components Analysis	Generalized Scales-Based Descriptors derived by Principal Components Analysis	`extractScales()`
	Generalized Scales-Based Descriptors derived by Amino Acid Properties (AAindex)	`extractPropScales()`
	Generalized Scales-Based Descriptors derived by 2D and 3D Molecular Descriptors (Topological, WHIM, VHSE, etc.)	`extractDescScales()`
Factor Analysis	Generalized Scales-Based Descriptors derived by Factor Analysis	`extractFAScales()`
Multidimensional Scaling	Generalized Scales-Based Descriptors derived by Multidimensional Scaling	`extractMDSScales()`
Substitution Matrix	Generalized BLOSUM and PAM Matrix-Derived Descriptors	`extractBLOSUM()`

The summary of the amino acid descriptor sets used by scales-based descriptors provided in the **protr** package is listed in table 5. Note that the non-informative descriptors (like the descriptors have only one value across all the 20 amino acids) in these datasets have already been filtered out.

In this article, we discussed the functionality of the **protr** package, which is trying to offer a comprehensive and unique toolkit for protein sequence descriptor calculation and similarity computation.

Acknowledgments

We would like to thank the Computational Biology and Drug Design (CBDD) Group (`http://cbdd.csu.edu.cn/`) of Central South University for their inspiring workshops and their support for the development of the **protr** package.

[1]The number depends on the choice of the number of properties of amino acids and the choice of the maximum values of the `lag`. The default is use 8 types of properties and `lag` $= 30$.

[2]The number depends on the maximum value of `lag`. By default `lag` $= 30$. And two distance matrices were used, so the descriptor dimension is $30 \times 2 = 60$ and $(20 + 30) \times 2 = 100$.

[3]The number depends on the choice of the number of the set of amino acid properties and the choice of the λ value. The default is use 3 types of properties proposed by Kuo-Chen Chou and $\lambda = 30$.

[4]The number depends on the choice of the λ vlaue. The default is that $\lambda = 30$.

Table 5: List of the pre-calculated descriptor sets of the 20 amino acids in **protr**

Dataset Name	Descriptor Set Name	Dimensionality	Calculated by
`AA2DACOR`	2D Autocorrelations Descriptors	92	Dragon
`AA3DMoRSE`	3D-MoRSE Descriptors	160	Dragon
`AAACF`	Atom-Centred Fragments Descriptors	6	Dragon
`AABurden`	Burden Eigenvalues Descriptors	62	Dragon
`AAConn`	Connectivity Indices Descriptors	33	Dragon
`AAConst`	Constitutional Descriptors	23	Dragon
`AAEdgeAdj`	Edge Adjacency Indices Descriptors	97	Dragon
`AAEigIdx`	Eigenvalue-Based Indices Descriptors	44	Dragon
`AAFGC`	Functional Group Counts Descriptors	5	Dragon
`AAGeom`	Geometrical Descriptors	41	Dragon
`AAGETAWAY`	GETAWAY Descriptors	194	Dragon
`AAInfo`	Information Indices Descriptors	47	Dragon
`AAMolProp`	Molecular Properties Descriptors	12	Dragon
`AARandic`	Randic Molecular Profiles Descriptors	41	Dragon
`AARDF`	RDF Descriptors	82	Dragon
`AATopo`	Topological Descriptors	78	Dragon
`AATopoChg`	Topological Charge Indices Descriptors	15	Dragon
`AAWalk`	Walk and Path Counts Descriptors	40	Dragon
`AAWHIM`	WHIM Descriptors	99	Dragon
`AACPSA`	CPSA Descriptors	41	Accelrys Discovery Studio
`AADescAll`	All the 2D Descriptors Calculated by Dragon	1171	Dragon
`AAMOE2D`	All the 2D Descriptors Calculated by MOE	148	MOE
`AAMOE3D`	All the 3D Descriptors Calculated by MOE	143	MOE

References

Atchley WR, Zhao J, Fernandes AD, Drüke T (2005). "Solving the protein sequence metric problem." *Proceedings of the National Academy of Sciences of the United States of America*, **102**(18), 6395–6400.

Bhasin M, Raghava GPS (2004). "Classification of Nuclear Receptors Based on Amino Acid Composition and Dipeptide Composition." *Journal of Biological Chemistry*, **279**(22), 23262–6.

Chou KC (2000). "Prediction of Protein Subcellar Locations by Incorporating Quasi-Sequence-Order Effect." *Biochemical and Biophysical Research Communications*, **278**, 477–483.

Chou KC (2001). "Prediction of Protein Cellular Attributes Using Pseudo-Amino Acid Composition." *PROTEINS: Structure, Function, and Genetics*, **43**, 246–255.

Chou KC (2005). "Using Amphiphilic Pseudo Amino Acid Composition to Predict Enzyme Subfamily Classes." *Bioinformatics*, **21**, 10–19.

Chou KC, Cai YD (2004). "Prediction of Protein Sub-cellular Locations by GO-FunD-PseAA Predictor." *Biochemical and Biophysical Research Communications*, **320**, 1236–1239.

Damborsky J (1998). "Quantitative Structure-function and Structure-stability Relationships of Purposely Modified Proteins." *Protein Engineering*, **11**, 21–30.

Dubchak I, Muchink I, Holbrook SR, Kim SH (1995). "Prediction of Protein Folding Class Using Global Description of Amino Acid Sequence." *Proceedings of the National Academy of Sciences*, **92**, 8700–8704.

Dubchak I, Muchink I, Mayor C, Dralyuk I, Kim SH (1999). "Recognition of a Protein Fold in the Context of the SCOP Classification." *Proteins: Structure, Function and Genetics*, **35**, 401–407.

Georgiev AG (2009). "Interpretable numerical descriptors of amino acid space." *Journal of Computational Biology*, **16**(5), 703–723.

Grantham R (1974). "Amino Acid Difference Formula to Help Explain Protein Evolution." *Science*, **185**, 862–864.

Hellberg S, Sjoestroem M, Skagerberg B, Wold S (1987). "Peptide quantitative structure-activity relationships, a multivariate approach." *Journal of medicinal chemistry*, **30**(7), 1126–1135.

Hopp-Woods (1981). "Prediction of Protein Antigenic Determinants from Amino Acid Sequences." *Proceedings of the National Academy of Sciences*, **78**, 3824–3828.

Kawashima S, Kanehisa M (2000). "AAindex: Amino Acid Index Database." *Nucleic Acids Research*, **28**, 374.

Kawashima S, Ogata H, Kanehisa M (1999). "AAindex: Amino Acid Index Database." *Nucleic Acids Research*, **27**, 368–369.

Kawashima S, Pokarowski P, Pokarowska M, Kolinski A, Katayama T, Kanehisa M (2008). "AAindex: Amino Acid Index Database (Progress Report)." *Nucleic Acids Research*, **36**, D202–D205.

Li Z, Lin H, Han Y, Jiang L, Chen X, Chen Y (2006). "PROFEAT: A Web Server for Computing Structural and Physicochemical Features of Proteins and Peptides from Amino Acid Sequence." *Nucleic Acids Research*, **34**, 32–37.

Mei H, Liao ZH, Zhou Y, Li SZ (2005). "A new set of amino acid descriptors and its application in peptide QSARs." *Peptide Science*, **80**(6), 775–786.

Pages H, Aboyoun P, Gentleman R, DebRoy S (2013). *Biostrings: String objects representing biological sequences, and matching algorithms.* R package version 2.30.1.

Rao H, Zhu F, Yang G, Li Z, Chen Y (2011). "Update of PROFEAT: A Web Server for Computing Structural and Physicochemical Features of Proteins and Peptides from Amino Acid Sequence." *Nucleic Acids Research*, **39**, 385–390.

Sandberg M, Eriksson L, Jonsson J, Sjöström M, Wold S (1998). "New chemical descriptors relevant for the design of biologically active peptides. A multivariate characterization of 87 amino acids." *Journal of medicinal chemistry*, **41**(14), 2481–2491.

Schneider G, Wrede P (1994). "The Rational Design of Amino Acid Sequences by Artificial Neural Networks and Simulated Molecular Evolution: Do Novo Design of an Idealized Leader Cleavage Site." *Biophysical Journal*, **66**, 335–344.

Shen J, Zhang J, Luo X, Zhu W, Yu K, Chen K, Li Y, Jiang H (2007). "Predicting Protein-protein Interactions Based Only on Sequences Information." *Proceedings of the National Academy of Sciences*, **104**, 4337–4341.

Sjöström M, Rännar S, Wieslander Å (1995). "Polypeptide sequence property relationships in Escherichia coli based on auto cross covariances." *Chemometrics and intelligent laboratory systems*, **29**(2), 295–305.

Tian F, Zhou P, Li Z (2007). "T-scale as a novel vector of topological descriptors for amino acids and its application in QSARs of peptides." *Journal of molecular structure*, **830**(1), 106–115.

van Westen GJ, Swier RF, Cortes-Ciriano I, Wegner JK, Overington JP, IJzerman AP, van Vlijmen HW, Bender A (2013a). "Benchmarking of protein descriptor sets in proteochemometric modeling (part 2): modeling performance of 13 amino acid descriptor sets." *Journal of cheminformatics*, **5**(1), 42.

van Westen GJ, Swier RF, Wegner JK, IJzerman AP, van Vlijmen HW, Bender A (2013b). "Benchmarking of protein descriptor sets in proteochemometric modeling (part 1): comparative study of 13 amino acid descriptor sets." *Journal of cheminformatics*, **5**(1), 41.

van Westen GJ, van den Hoven OO, van der Pijl R, Mulder-Krieger T, de Vries H, Wegner JK, IJzerman AP, van Vlijmen HW, Bender A (2012). "Identifying novel adenosine receptor ligands by simultaneous proteochemometric modeling of rat and human bioactivity data." *Journal of Medicinal Chemistry*, **55**(16), 7010–7020.

van Westen GJ, Wegner JK, Geluykens P, Kwanten L, Vereycken I, Peeters A, IJzerman AP, van Vlijmen HW, Bender A (2011). "Which compound to select in lead optimization? Prospectively validated proteochemometric models guide preclinical development." *PloS one*, **6**(11), e27518.

Venkatarajan MS, Braun W (2001). "New quantitative descriptors of amino acids based on multidimensional scaling of a large number of physical–chemical properties." *Molecular modeling annual*, **7**(12), 445–453.

Wikberg JE, Lapinsh M, Prusis P (2004). "Proteochemometrics: a tool for modeling the molecular interaction space." *Chemogenomics in drug discovery*, pp. 289–309.

Xiao N, Xu Q, Cao D (2013). *protr: Protein Sequence Feature Extraction with R.* R package version 0.2-0, URL `http://CRAN.R-project.org/package=protr`.

Yu G, Li F, Qin Y, Bo X, Wu Y, Wang S (2010). "GOSemSim: an R package for measuring semantic similarity among GO terms and gene products." *Bioinformatics*, **26**(7), 976–978.

Zaliani A, Gancia E (1999). "MS-WHIM scores for amino acids: a new 3D-description for peptide QSAR and QSPR studies." *Journal of chemical information and computer sciences*, **39**(3), 525–533.

Affiliation:

Nan Xiao
School of Mathematics and Statistics
Central South University
Changsha, Hunan, P. R. China
E-mail: `road2stat@gmail.com`
URL: `http://www.road2stat.com/`

Qingsong Xu
School of Mathematics and Statistics
Central South University
Changsha, Hunan, P. R. China
E-mail: `dasongxu@gmail.com`

Dongsheng Cao
School of Pharmaceutical Sciences
Central South University
Changsha, Hunan, P. R. China
E-mail: `oriental-cds@163.com`
URL: `http://cbdd.csu.edu.cn/`