protr: **R** package for generating various numerical representation schemes of protein sequence

Nan Xiao, Qing-Song Xu, Dong-Sheng Cao

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COMPUTATIONAL BIOLOGY &
DRUG DESIGN GROUP
CENTRAL SOUTH UNIV., CHINA

Contents

Abstract

The **protr** package offers a unique and comprehensive toolkit for generating various numerical representation schemes of protein sequence. The descriptors included are extensively utilized in Bioinformatics and Chemogenomics research. The commonly used descriptors listed in **protr** include amino acid composition, autocorrelation, CTD, conjoint traid, quasi-sequence order, pseudo amino acid composition, and profile-based descriptors derived by Position-Specific Scoring Matrix (PSSM). The descriptors for proteochemometric (PCM) modeling, includes the scales-based descriptors derived by principal components analysis, factor analysis, multidimensional scaling, amino acid properties (AAindex), 20+ classes of 2D and 3D molecular descriptors (Topological, WHIM, VHSE, etc.), and BLOSUM/PAM matrix-derived descriptors. The **protr** package also integrates the function of parallelized similarity computation derived by pairwise protein sequence alignment and Gene Ontology (GO) semantic similarity measures. **ProtrWeb**, the web server built on **protr**, is located at: http://cbdd.csu.edu.cn:8080/protrweb/.

Keywords: protein sequence, amino acid, descriptor, structural similarity, functional similarity, sequence alignment, Gene Ontology

1. The Full Workflow Using protr

Here we use the subcellular localization dataset of human proteins presented in the study of Chou and Shen (2008) to demonstrate the full workflow when using protr.

The complete dataset includes 3134 protein sequences (2750 different proteins), classified into 14 human subcellular locations. We select two classes of proteins as our benchmark dataset. Class 1 contains 325 *extracell* proteins, and class 2 includes 307 *mitochondrion* proteins.

First, we load the **protr** package, then read the protein sequences stored in two separated FASTA files with `readFASTA()`:

```
require(protr)
```

```
# load FASTA files
extracell = readFASTA(system.file('protseq/extracell.fasta',
                                  package = 'protr'))
mitonchon = readFASTA(system.file('protseq/mitochondrion.fasta',
                                  package = 'protr'))
```

To read protein sequences stored in PDB format files, use `readPDB()` instead. The loaded sequences will be stored as two lists in R, and each component in the list is a character string representing one protein sequence. In this case, there are 325 *extracell* protein sequences and 306 *mitonchon* protein sequences:

```
length(extracell)
```

```
## [1] 325
```

```
length(mitonchon)
```

```
## [1] 306
```

To assure that the protein sequences only have the twenty standard amino acid types which is required for the descriptor computation, we use the `protcheck()` function in **protr** to do the amino acid type sanity checking and remove the *non-standard* sequences:

```
extracell = extracell[(sapply(extracell, protcheck))]
mitonchon = mitonchon[(sapply(mitonchon, protcheck))]

length(extracell)
```

```
## [1] 323
```

```
length(mitonchon)
```

```
## [1] 304
```

Two protein sequences were removed from each class. For the remaining sequences, we calculate the Type II PseAAC descriptor, i.e., the amphiphilic pseudo amino acid composition (APAAC) descriptor (Chou 2005) and make class labels for classification modeling.

```
# calculate APAAC descriptors
x1 = t(sapply(extracell, extractAPAAC))
x2 = t(sapply(mitonchon, extractAPAAC))
x  = rbind(x1, x2)

# make class labels
labels = as.factor(c(rep(0, length(extracell)), rep(1, length(mitonchon))))
```

In **protr**, the functions of commonly used descriptors for protein sequences and proteochemometric (PCM) modeling descriptors are named after `extract...()`.

Next, we will split the data into a 75% training set and a 25% test set.

```
# split training and test set
set.seed(1001)
tr.idx = c(sample(1:nrow(x1), round(nrow(x1) * 0.75)),
           sample(nrow(x1) + 1:nrow(x2), round(nrow(x2) * 0.75)))
te.idx = setdiff(1:nrow(x), tr.idx)
x.tr   = x[tr.idx, ]
x.te   = x[te.idx, ]
y.tr   = labels[tr.idx]
y.te   = labels[te.idx]
```

We will train a random forest classification model on the training set with 5-fold cross-validation, using the **randomForest** package.

```
require(randomForest)
rf.fit = randomForest(x.tr, y.tr, cv.fold = 5)
print(rf.fit)
```

The training result is:

```
## Call:
##  randomForest(x = x.tr, y = y.tr, cv.fold = 5)
##                Type of random forest: classification
##                      Number of trees: 500
## No. of variables tried at each split: 8
##
##          OOB estimate of  error rate: 25.11%
## Confusion matrix:
##     0   1 class.error
## 0 196  46   0.1900826
## 1  72 156   0.3157895
```

With the model trained on the training set, we predict on the test set and plot the ROC curve with the **pROC** package, as is shown in figure 1.

```
# predict on test set
rf.pred = predict(rf.fit, newdata = x.te, type = 'prob')[, 1]

# plot ROC curve
require(pROC)
plot.roc(y.te, rf.pred, col = '#0080ff', grid = TRUE, print.auc = TRUE)
```

The area under the ROC curve (AUC) is:

```
## Call:
## plot.roc.default(x = y.te, predictor = rf.pred, col = "#0080ff",
##                  grid = TRUE, print.auc = TRUE)
##
## Data: rf.pred in 81 controls (y.te 0) > 76 cases (y.te 1).
## Area under the curve: 0.8697
```

2. Package Overview

The **protr** package (Xiao *et al.* 2014) implemented most of the state-of-the-art protein sequence descriptors with R. The **protr** package is freely available from the Comprehensive R Archive Network (http://CRAN.R-project.org/package=protr). This vignette corresponds to **protr** version 0.5-1 and was typeset on 2014-12-24.

Generally, each type of the descriptors (features) could be calculated 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:
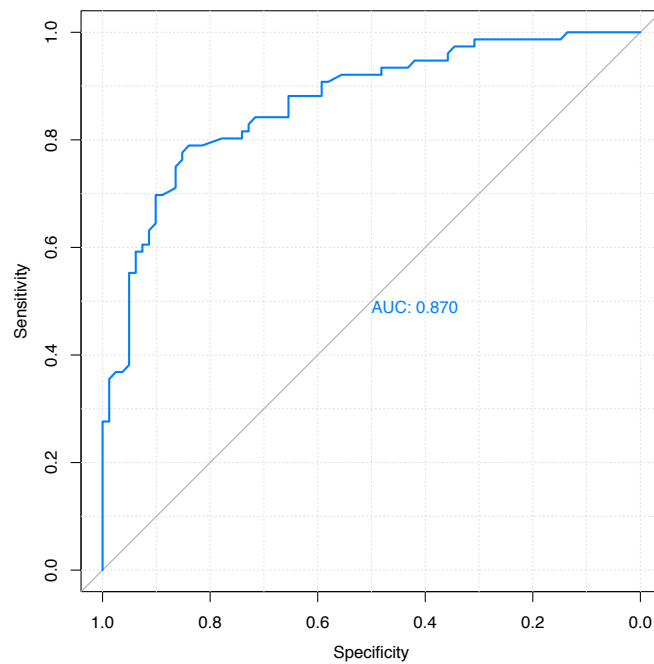
Figure 1: ROC curve for the test set of protein subcellular localization data

- 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 descriptors

  - `extractCTriad()` - Conjoint triad descriptors

- 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

- Profile-based descriptors

  - – `extractPSSM()`
  - – `extractPSSMAcc()`
  - – `extractPSSMFeature()`

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

- `extractScales()` and `extractScalesGap()` - Scales-based descriptors derived by Principal Components Analysis

  - – `extractProtFP()` and `extractProtFPGap()` - Scales-based descriptors derived by amino acid properties from AAindex (a.k.a. Protein Fingerprint)
  - – `extractDescScales()` - Scales-based descriptors derived by 20+ classes of 2D and 3D molecular descriptors (Topological, WHIM, VHSE, etc.)

- `extractFAScales()` - Scales-based descriptors derived by Factor Analysis

- `extractMDSScales()` - Scales-based descriptors derived by Multidimensional Scaling

- `extractBLOSUM()` - BLOSUM and PAM matrix-derived descriptors

The **protr** package integrates the function of parallelized similarity score 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 function of parallelized similarity score 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 **doParallel** first, in order to make the parallelized pairwise similarity computation available.

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

3. Commonly Used Descriptors

Disclaimer. Users of the **protr** package need to intelligently evaluate the underlying details of the descriptors provided, instead of using protr with their data blindly, especially for the descriptor types with more flexibility. It would be wise for the users to use some negative and positive control comparisons where relevant to help guide interpretation of the results.

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.

3.1. 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.

3.2. 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.

3.3. 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
```

3.4. 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 2 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:

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

```
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 2: An illustrated example in the AAIndex database

Normalized Moreau-Broto Autocorrelation Descriptors

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

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

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
```

3.5. Composition / Transition / Distribution

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

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

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 3: 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.).

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

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

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

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

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

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			

3.6. 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 us-

ing 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 4.

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:

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

---

[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.

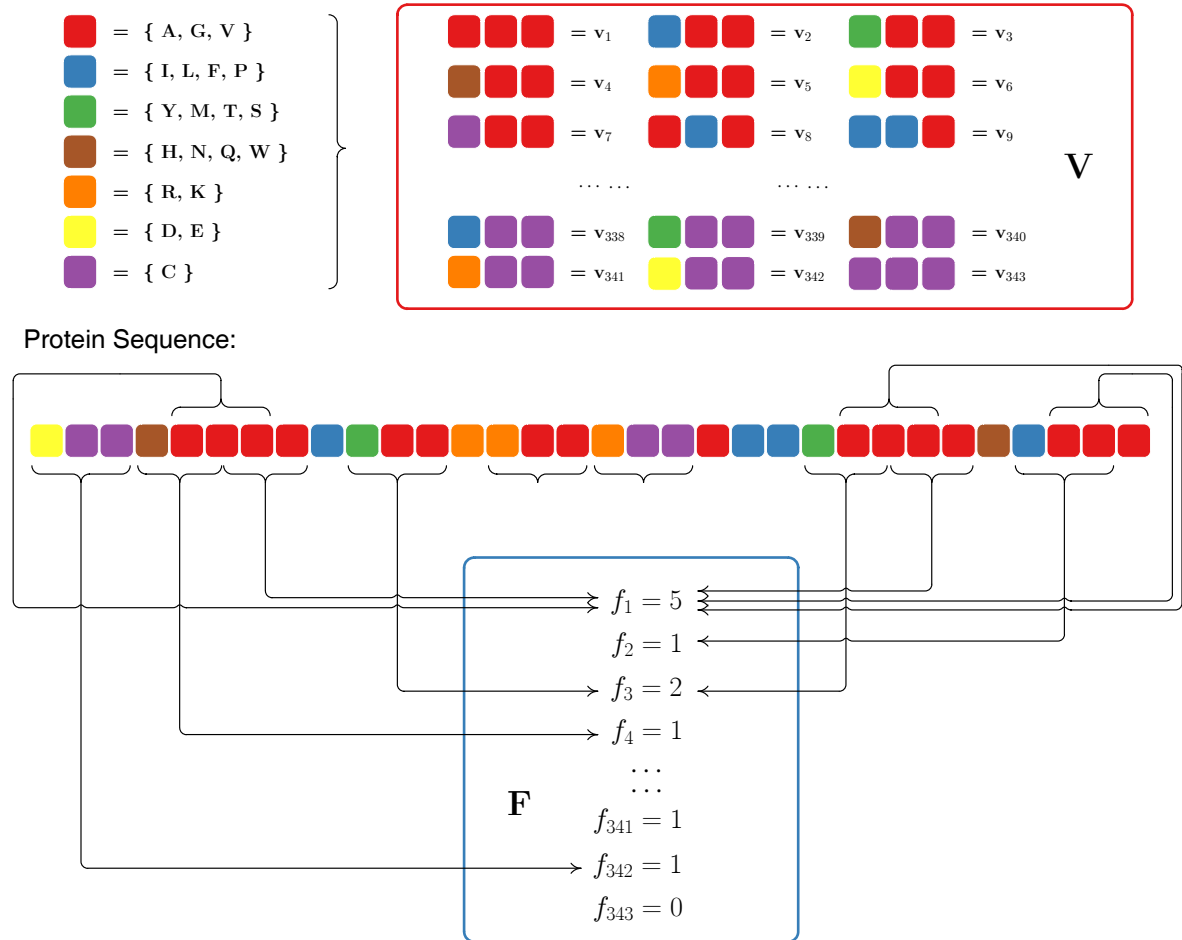[3]Cys is separated from class 3 because of its ability to form disulfide bonds.

Figure 4: 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.

```
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.

3.7. 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:

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

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:

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

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

```
> extractQSO(x)
```

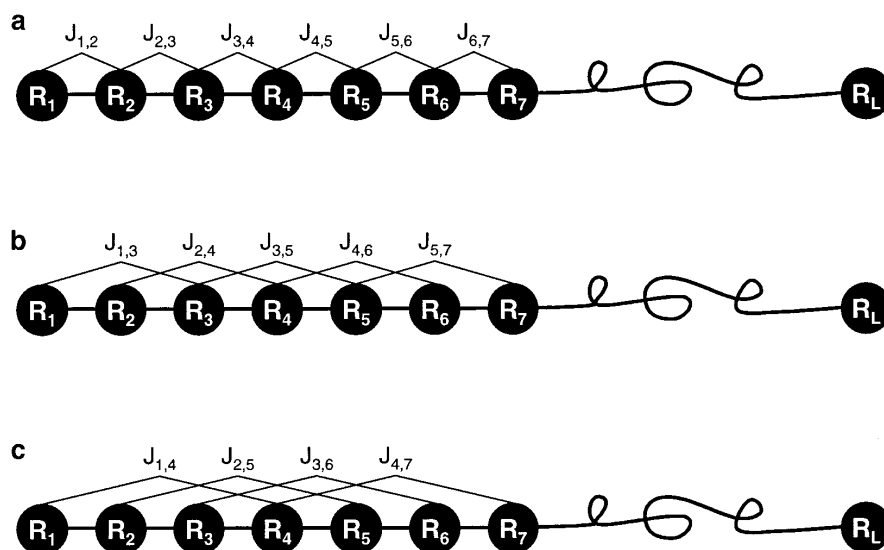| Schneider.Xr.A	Schneider.Xr.R	Schneider.Xr.N	Schneider.Xr.D	Schneider.Xr.C
6.096218e-02	6.773576e-02	3.725467e-02	4.910842e-02	6.434897e-02
Schneider.Xr.E	Schneider.Xr.Q	Schneider.Xr.G	Schneider.Xr.H	Schneider.Xr.I
4.572164e-02	4.572164e-02	7.789612e-02	2.878770e-02	3.386788e-02
Schneider.Xr.L	Schneider.Xr.K	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
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

Figure 5: 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).

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`.

3.8. 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 $H_1^o(i)$, $H_2^o(i)$, $M^o(i)$ $(i = 1, 2, 3, \ldots, 20)$ 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 following qualities by a standard conversion:

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

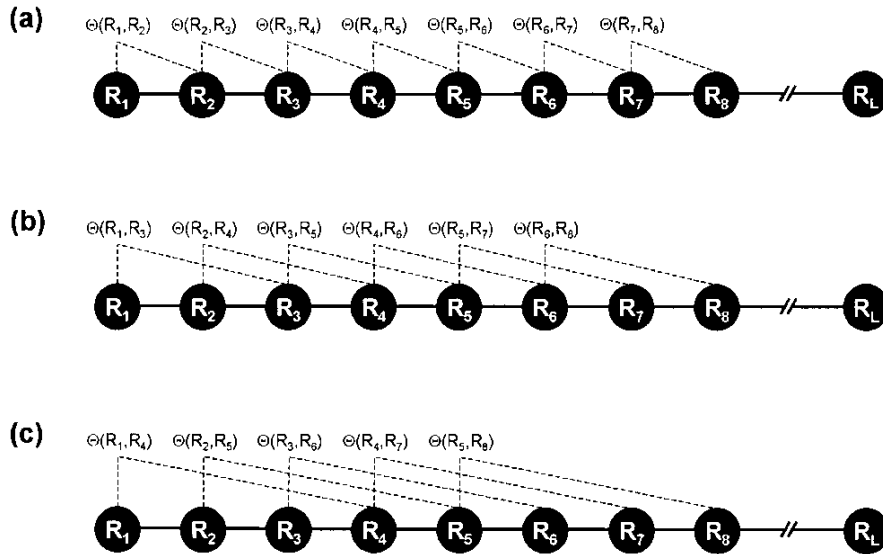$H_2^o(i)$ and $M^o(i)$ are normalized as $H_2(i)$ and $M(i)$ in the same way.

Figure 6: 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

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

22

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:

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

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

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

$$\cdots$$

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

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.

3.9. 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:

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

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

$$\tau_1 = \frac{1}{N-1} \sum_{i=1}^{N-1} H_{i,i+1}^1$$

$$\tau_2 = \frac{1}{N-1} \sum_{i=1}^{N-1} H_{i,i+1}^2$$

$$\tau_3 = \frac{1}{N-2} \sum_{i=1}^{N-2} H_{i,i+2}^1$$

$$\tau_4 = \frac{1}{N-2} \sum_{i=1}^{N-2} H_{i,i+2}^2$$

$$\dots$$

$$\tau_{2\lambda-1} = \frac{1}{N-\lambda} \sum_{i=1}^{N-\lambda} H_{i,i+\lambda}^1$$

$$\tau_{2\lambda} = \frac{1}{N-\lambda} \sum_{i=1}^{N-\lambda} H_{i,i+\lambda}^2$$

Then 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
4.913073e+01	2.456536e+01	1.277399e+01

(a1)

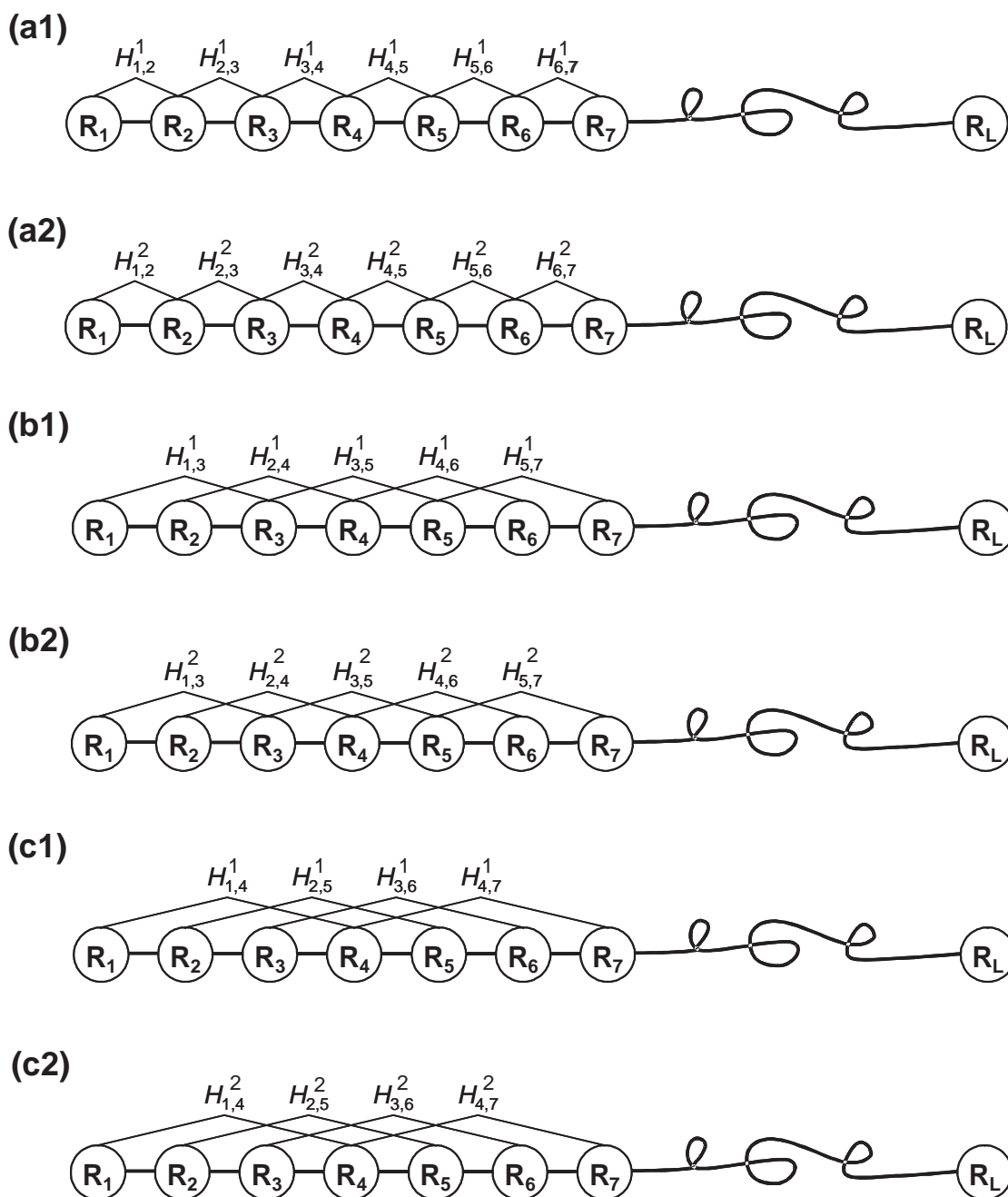**(a2)**

(b1)

(b2)

(c1)

(c2)

Figure 7: 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 $H_{i,j}^1$ and $H_{i,j}^2$ 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).

```
                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()`.

3.10. Profile-based Descriptors

The profile-based descriptors for protein sequences are available in the **protr** package. The feature vectors of profile-based methods were based on the PSSM by running PSI-BLAST, and often show good performance. See Ye *et al.* (2011) and Rangwala and Karypis (2005) for details. The functions `extractPSSM()`, `extractPSSMAcc()` and `extractPSSMFeature()` are used to generate these descriptors. Users need to install the NCBI-BLAST+ software package first to make the functions fully functional.

4. Descriptors for Proteochemometric Modeling

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

- Scales-based descriptors derived by Principal Components Analysis
  - Scales-based descriptors derived by Amino Acid Properties from AAindex (Protein Fingerprint)
  - Scales-based descriptors derived by 20+ classes of 2D and 3D molecular descriptors (Topological, WHIM, VHSE, etc.)
- Scales-based descriptors derived by Factor Analysis
- Scales-based descriptors derived by Multidimensional Scaling
- BLOSUM and PAM matrix-derived descriptors

Note that each of the 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 the 43 to 47 columns (molecular descriptors) in the `AATopo` dataset to use, the parameter `lag` 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
```

Dealing with gaps. In proteochemometrics, (sequence alignment) gaps can be very useful, since a gap in a certain position contains information. The **protr** package has built-in support for such gaps. We deal with the gaps by using a dummy descriptor to code for the 21st type of amino acid. The function `extractScalesGap()` and `extractProtFPGap()` could be used to deal with such gaps. See `?extractScalesGap` and `?extractProtFPGap` for details.

5. 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 highly parallelizable, the **protr** package integrates the function of parallelized 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
```

It should be noted that for a small number of proteins, calculating their pairwise similarity scores derived by sequence alignment in parallel may not significantly reduce the overall computation time, since each of the task only requires a relatively small time to finish, thus, computational overheads may exist and affect the performance. In testing, we used about 1,000 protein sequences on 64 CPU cores, and observed significant performance improvement comparing to the sequential computation.

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

6. Similarity Calculation by GO Semantic Similarity Measures

The **protr** package also integrates the function of similarity score 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
```

7. ProtrWeb

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

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

ProtrWeb (Figure 8) 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.

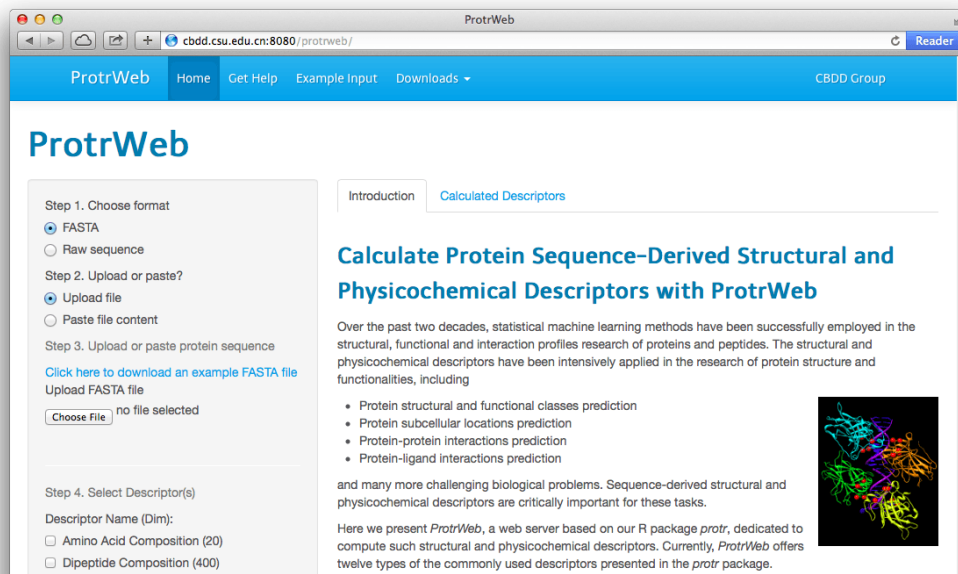A step-by-step instruction on how to use **ProtrWeb** could be found at:

Figure 8: A screenshot of the web server **ProtrWeb**

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

8. Miscellaneous Tools

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

8.1. 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"
```

8.2. 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.

8.3. 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 function to read protein sequences stored in PDB format files. See `?readPDB` for details.

8.4. 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
```

8.5. Protein Sequence Partition

The `protseg()` function partitions the protein sequences to create sliding windows. This is usually required when creating feature vectors for machine learning tasks. 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"
```

8.6. 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.

8.7. 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 scales-based descriptors, see `data(package = 'protr')` for all the datasets included in the **protr** package.

8.8. 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`.

8.9. 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.

9. Summary

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

Table 3: List of commonly used 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 Auto-correlation	240^1	`extractMoreauBroto()`
	Moran Autocorrelation	240^1	`extractMoran()`
	Geary Autocorrelation	240^1	`extractGeary()`
CTD	Composition	21	`extractCTDC()`, `extractCTDCClass()`
	Transition	21	`extractCTDT()`, `extractCTDTClass()`
	Distribution	105	`extractCTDD()`, `extractCTDDClass()`
Conjoint Triad	Conjoint Triad	343	`extractCTriad()`, `extractCTriadClass()`
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 scales-based PCM descriptors in the **protr** package is listed in table 4.

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

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[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 4: List of PCM descriptors in **protr**

Derived by	Descriptor Class	Function Name
Principal Components Analysis	Scales-based descriptors derived by Principal Components Analysis	`extractScales()`, `extractScalesGap()`
	Scales-based descriptors derived by amino acid properties from AAindex (a.k.a. Protein Finger-print)	`extractProtFP()`, `extractProtFPGap()`
	Scales-based descriptors derived by 2D and 3D molecular descriptors (Topological, WHIM, VHSE, etc.)	`extractDescScales()`
Factor Analysis	Scales-based descriptors derived by Factor Analysis	`extractFAScales()`
Multidimensional Scaling	Scales-based descriptors derived by Multidimensional Scaling	`extractMDSScales()`
Substitution Matrix	BLOSUM and PAM matrix-derived descriptors	`extractBLOSUM()`

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

Acknowledgments

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Affiliation:

Nan Xiao
School of Mathematics and Statistics
Central South University
Changsha, Hunan, P. R. China
E-mail: road2stat@gmail.com
URL: http://r2s.name

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

Dong-Sheng 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