**Supplementary Data**

1. **Parameters**

**K-tuple**

The K-tuple value refers to the number of amino acid residues in the chain. K=1 means a peptide, K=2 represents a dipeptide, and so on. For each K-tuple of reduced amino acid cluster, the feature vector of the protein sequence contains RAACK dimensions. As the value of K increases, the vector dimension of RAACK will increase dramatically, causing the high-dimension disaster or overfitting, which reduces bias tolerance and cluster tolerance capacity. Therefore, the K value here is useful at a small time, so that we limit the K value to 3 to get a better reduction effect (Supplementary Figure 1A).

**Gap**

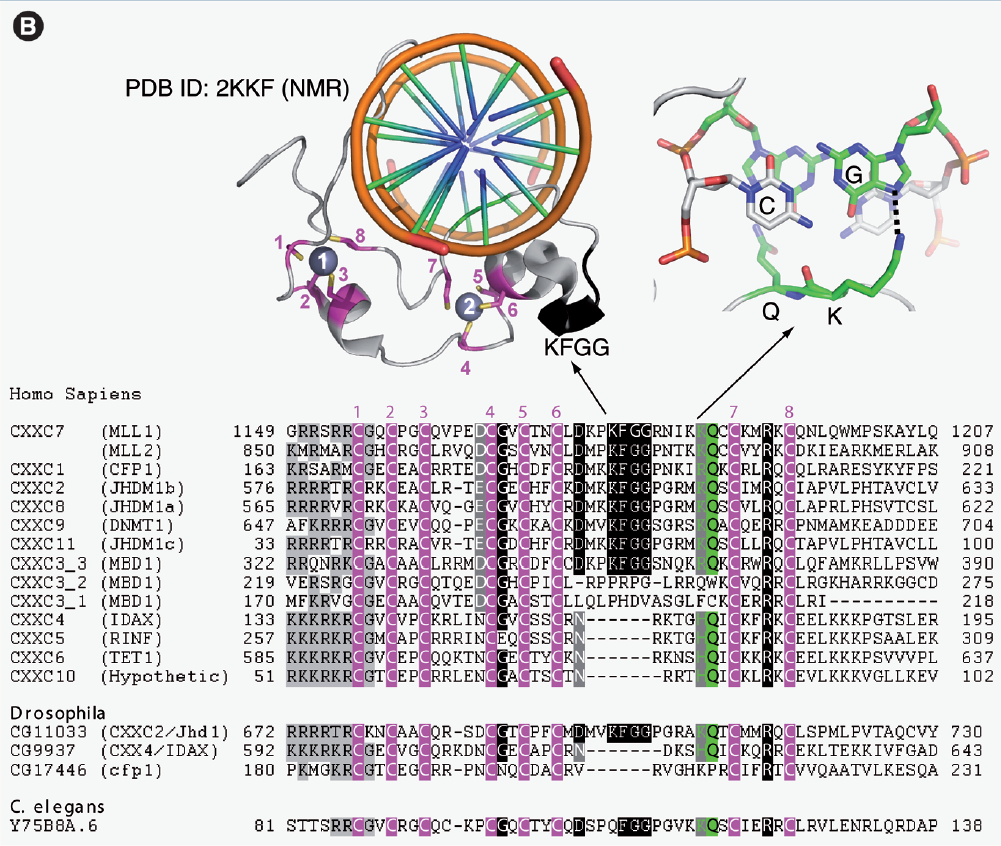
The value of gap is applied to the protein sequence that has been processed by K-tuple and represents the number of amino acid residues in the interval between each K-tuple peptide. That is, the g value reflects the sequence order information of all peptides, with the starting residues separated by g residues. For example, when g=1, the sequence is a peptide (K=1), then its former peptide contains R1R2, R3R4, R5R6, ... etc. (Supplementary Figure 1B).

**λ-correlation**

The λ-correlation of parameters, also called parallel correlation, is an integer and is less than K, where reflects the protein sequence correlation between nearest residue when k-tuple is determined. This is an integer representing the relevant layer, which reveals a protein sequence having a vector containing a RAACK component. For example, when K =3, λ=1, g=2, the combination is R1R3R5, R4R6R8, R7R9R11 and so on (Supplementary Figure 1C).



**Supplementary** **Figure 1.** Parameter of reduced amino acid



**Supplementary Figure 2 from reference** **(1).** CpG-interacting proteins

1. **Reduced amino acids alphabets**

Till 14 August, 2019, 74 types of reduced amino acid alphabets were manually curated in PseRAAC\_Book, which can generate 673 reduced amino acid descriptors for analyzing protein sequence (2-41). In particular, we have added the latest amino acid reduction methods and clusters, such as deep learning, evolutionary algorithms and so on (Supplementary table1).

**Table 1.** Reduced amino acid alphabets.

|  |  |  |  |
| --- | --- | --- | --- |
| Type | Method description | Clusters | Dimension |
| 1 | BLOSUM50 | 2,3,4,5,6,8,10,12,15,18 | RAACK |
| 2 | BLOSUM40 | 2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19 | RAACK |
| 3 | Artificial immune system (AIS) | 6,6,6,7,7,8,8,8,8,9 | RAACK |
| 4 | Maximum information gain | 2,3,4,5,6,7,8,9,10,11,12,13,14 | RAACK |
| 5 | Secondary-structure | 2,3,4,5,6,7,8,9,10,11,12,13,15,16,17,18,19 | RAACK |
| 6 | Structure-Derived matrix（SDM） | 2,3,4,6,7,8,9,10,11,12,13,14,16,17,19 | RAACK |
| 7 | GONNET matrix | 2,3,4,5,6,7,8,9,10,11,12,13,14,15,17 | RAACK |
| 8 | Miyazawa Jernigan (MJ) matrix | 2,3,4,5,6,7,8,9,10,11,12,13,14,15,16 | RAACK |
| 9 | BLOSUM50 matrix | 2,3,4,5,6,7,8,9,10,11,12,13,14,15,16 | RAACK |
| 10 | Genetic algorithm | 5 | RAACK |
| 11 | Boltzmann relation/iteration | 2,3,4,5,6,7,8,9,10,14 | RAACK |
| 12 | Distance matrix | 2,4,7,12 | RAACK |
| 13 | Distance matrix | 2,3,5,8,12 | RAACK |
| 14 | Miyazawa Jernigan (MJ) matrix | 4,8 | RAACK |
| 15 | Protein blocks | 5,8,9,11,13 | RAACK |
| 16 | Hierarchical clustering | 2,3,5,7,8,11,14 | RAACK |
| 17 | Clustering analysis | 4,4,5,5,5,5,5,5,5,5,5,5,5,5,5,6 | RAACK |
| 18 | Physical-chemical property | 3,4,19 | RAACK |
| 19 | Maximized mutual information | 2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19 | RAACK |
| 20 | Variance maximization | 2,3,4,5,6,7,8,9,10,11,12,13,13,14,15,16,17,18,19 | RAACK |
| 21 | Extended compact genetic algorithm (ECGA) | 2,3,4,5 | RAACK |
| 22 | Extended compact genetic algorithm (ECGA) | 2,3,4 | RAACK |
| 23 | Extended compact genetic algorithm (ECGA) | 2,3,4,5,7,9,11 | RAACK |
| 24 | Physicochemical properties | 7,9,11 | RAACK |
| 25 | Extended compact genetic algorithm (ECGA) | 2,3,4,5 | RAACK |
| 26 | Extended compact genetic algorithm (ECGA) | 2,3,4 | RAACK |
| 27 | Extended compact genetic algorithm (ECGA) | 2,3,4,5 | RAACK |
| 28 | Miyazawa and Jernigan (MJ) matrix | 2,3,5,5 | RAACK |
| 29 | JTT rate matrix | 2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19 | RAACK |
| 30 | Grantham Distance Matrix | 2,3,4,5,5,7,8,9,10,11,12,13,14,15,16,17,18,19 | RAACK |
| 31 | Hierarchical clustering | 2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,18,19 | RAACK |
| 32 | Hierarchical clustering | 2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19 | RAACK |
| 33 | Hierarchical clustering | 2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19 | RAACK |
| 34 | Unweighted pair-group method with arithmetic means (UPGMA) | 2,3,4,5,6,7,8,10,11,12,14,15,16,18,19 | RAACK |
| 35 | Dynamic clustering | 2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19 | RAACK |
| 36 | Information theory | 8 | RAACK |
| 37 | Physical-chemical property | 6 | RAACK |
| 38 | BLOSUM62 and Heuristic Monte Carlo (MC) method | 2,3,4,5,6,7,8,9,10,11,12,13,15,15,16,17,18,19 | RAACK |
| 39 | Chemistry properties | 3,4,4,8,10 | RAACK |
| 40 | Protein blocks | 4,8,9,10,10,13 | RAACK |
| 41 | Sequence alignments | 5,5,6,10,10,10,10,10,13,16 | RAACK |
| 42 | Structure alignments | 5,5,6,12,15,17 | RAACK |
| 43 | Contact potential | 5,5,5,5 | RAACK |
| 44 | Miyazawa Jernigan (MJ)matrix & BLOSUM50& BLOSUM62 | 13,14,19 | RAACK |
| 45 | Contact potential | 4,7.7 | RAACK |
| 46 | Miyazawa Jernigan (MJ)matrix and contact potential | 2,5,5 | RAACK |
| 47 | Physico-chdmical properties | 6 | RAACK |
| 48 | K-means | 8 | RAACK |
| 49 | BLOSUM62 and Heuristic Monte Carlo (MC) | 2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19 | RAACK |
| 50 | Dynamic Programming Alignments | 4,10 | RAACK |
| 51 | Unweighted variable group | 2,4,5,6,7,8,10,13,14,15,16,17,18,19 | RAACK |
| 52 | The Point Accepted Mutation (PAM) matrix | 2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19 | RAACK |
| 53 | Whelan and Goldman (WAG) matrix | 2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19 | RAACK |
| 54 | Physico-chdmical properties | 3,3,3,3,3,3,3 | RAACK |
| 55 | Hydrophobic and polar （HP）model | 4 | RAACK |
| 56 | Unweighted pair group method | 2,3,4,5,6,7,8,9,10,11,12,13,14,16,18,19 | RAACK |
| 57 | Unweighted pair group method | 2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19 | RAACK |
| 58 | Unweighted pair group method | 2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19 | RAACK |
| 59 | Unweighted pair group method | 2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19 | RAACK |
| 60 | Particle swarm optimization (PSO) | 5,6,8 | RAACK |
| 61 | Euclidean distance | 3,3,4 | RAACK |
| 62 | Physico-chdmical properties | 4 | RAACK |
| 63 | Miyazawa Jernigan (MJ)matrix | 2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,18,19 | RAACK |
| 64 | Chemistry space | 5 | RAACK |
| 65 | Hierarchical clustering | 2,3,4,5,6,7,8,9,10 | RAACK |
| 66 | Hierarchical clustering | 2,3,5,6,7,10,11,13,15,16,18 | RAACK |
| 67 | Fuzzy clustering technique and matrices | 2,4,5,15,19 | RAACK |
| 68 | Fuzzy clustering technique and matrices | 2,3,5,7,14,19 | RAACK |
| 69 | Fuzzy clustering technique and matrices | 2,4,5,14,19 | RAACK |
| 70 | Fuzzy clustering technique and matrices | 5,7,8,19 | RAACK |
| 71 | Fuzzy clustering technique and matrices | 5,10,13,14,16,19 | RAACK |
| 72 | Fuzzy clustering technique and matrices | 2,3,5,7,14,19 | RAACK |
| 73 | Fuzzy clustering technique and matrices | 6,10,13,14,17,19 | RAACK |
| 74 | Fuzzy clustering technique and matrices | 5,11,15,18,19 | RAACK |

RAACK: K-tuple of reduced amino acid cluster, for example, alphabet type 68, cluster = 7 and K-tuple=2, Dimension=72

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