

## An Insightful 20-Year Recollection Since the Birth of Pseudo Amino Acid Components

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### Abstract

In this paper, the author has recalled the proposal of pseudo amino acid components, and its significant and substantial impacts to proteome and genome analyses.

**Keywords:** PseAAC; PseKNC; 5-steps rule; Byproducts; Distorted Key Theory.

## Background

Given a protein sequence  $P$  with  $L$  amino acid residues, its most straightforward expression is:

$$P = R_1 R_2 R_3 R_4 R_5 R_6 R_7 \dots R_L \quad (1)$$

where  $R_1$  is its 1<sup>st</sup> amino acid residue,  $R_2$  its 2<sup>nd</sup> residue, and so forth. With the avalanche of protein sequences generated in the postgenomic age, scientists are facing a critical challenge; i.e., how to express a protein sequence of Eq.1 with a vector but still considerably keep its sequential order information or characteristic patterns. This is because all the existing operation engines, such as "Optimization" algorithm [1], "Correlation Angle" algorithm [2-4], "Component Coupled" algorithm [5-10], "Covariance Discriminant" or CD algorithm [7, 11-19], "Principal Component Analysis" algorithm [20], "Top-n-Gram" algorithm [21], "SLLE" algorithm [22], "Neural Network" or NN algorithm [23-25], "Ensemble Classifier" algorithm [26, 27], "Support Vector Machine" or SVM algorithm [28-30], "Random Forest" algorithm [31, 32], "Conditional Random Field" algorithm [14], "Nearest Neighbor" or NN algorithm [33, 34], "K-Nearest Neighbor" or KNN algorithm [35-37], "Optimized Evidence-Theoretic K Nearest Neighbor" or OET-KNN algorithm [38-41], and "Fuzzy K-Nearest Neighbor" algorithm [42-46], can only handle a vector but not a sequence sample. The simplest discrete model used to represent a protein sample is its amino acid (AA) composition or AAC [47]. According to the AAC-discrete model, the protein of Eq.1 can be expressed

by [7].

$$P = [f_1 f_2 f_3 \dots f_{20}]^T \quad (2)$$

where  $f_i$  ( $i = 1, 2, \dots, 20$ ) are the normalized occurrence frequencies of the 20 native amino acids in  $P$ , and  $T$  the transposing operator. Many methods for predicting various protein attributes were based on the AAC-discrete model (see, e.g., [2, 4, 8-11, 15, 17, 20, 23, 48-60]).

Unfortunately, as we can see from Eq.2, a vector defined in a discrete model may completely lose the sample's sequence-order information [61], and hence the prediction quality thus obtained might be limited. This is the main shortcoming of the AAC discrete model.

## Birth of PseAAC

To avoid completely losing the sequence-order information, a completely different discrete model, or the so-called "pseudo amino acid composition" (PseAAC) model [61], was proposed to represent the sample of a protein, as formulated by

$$P = [p_1 \dots p_{20} p_{20+1} \dots p_{20+\lambda}]^T \quad (3)$$

where the first 20 elements are associated with the 20 elements in Eq.2 or the 20 amino acid components of the protein, while the additional " $\lambda$ " factors are used to incorporate some sequence-order information via various modes. Typically, these additional factors are a series of rank-different correlation factors along a protein

chain, but they can also be any combinations of other factors so long as they can reflect some sorts of sequence-order effects in one way or the other. For the convenience of users, a web-server called “PseAAC” [62] was established at <http://www.csbio.sjtu.edu.cn/bioinf/PseAAC/>, by which some commonly used PseAAC forms can be automatically generated. For more about PseAAC, see an insightful Wikipedia article at [https://en.wikipedia.org/wiki/Pseudo\\_amino\\_acid\\_composition](https://en.wikipedia.org/wiki/Pseudo_amino_acid_composition).

## From PseAAC to PseKNC

Shortly afterwards, the idea of PseAAC in dealing with peptide/protein sequences was extended to PseKNC for dealing with DNA/RNA sequences [29, 63-90], which has been found very successful as well. For more about PseKNC, see an insightful Wikipedia article at [https://en.wikipedia.org/wiki/Pseudo\\_K-tuple\\_nucleotide\\_composition](https://en.wikipedia.org/wiki/Pseudo_K-tuple_nucleotide_composition).

## Impacts on Attribute Prediction

Ever since their birth, PseAAC and PseKNC have remarkable impacts in nearly all the areas of computational proteomics and computational proteomics, respectively, such as predicting enzymes and their family/sub-family classification [91-95], protein subcellular location prediction [13, 96-104], apoptosis protein subcellular location prediction [105-109], mycobacterial protein subcellular location prediction [110], predicting protein subnuclear localization [111-113], predicting protein subchloroplast locations [114], predicting protein submitochondria locations [115-117], predicting membrane proteins and their types [40, 43, 118-122], discrimination of outer membrane proteins [123, 124], identifying transmembrane regions in proteins [125], identifying proteases and their types [126, 127], predicting protein solubility [128], identifying GPCRs and their classes [44, 129-133], prediction of nuclear receptors [134], prediction of cyclin proteins [135], identifying bacterial secreted proteins [136], identifying risk type of human papillomaviruses [137], prediction of cell wall lytic enzymes [138], prediction of lipases types [139], predicting conotoxin superfamily and family [140, 141], predicting the cofactors of oxidoreductases [142], predicting DNA-binding proteins [143], predict protein structural classes [19, 144-153], supersecondary structure prediction [154], protein secondary structure content prediction [155], and predicting protein quaternary structural attributes [156-161], fold pattern prediction [162-163], and others (e.g., [164]). Detailed below are just a few.

### Protein structural class prediction

The knowledge of protein 3D (three-dimensional) structures or their complexes with ligands is vitally important for rational drug design. Although X-ray crystallography is a powerful tool in determining these structures, it is time-consuming and expensive, and not all proteins can be successfully crystallized. Membrane proteins are difficult to crystallize and most of them will not dissolve in normal solvents. Therefore, so far very few membrane protein structures have been determined. NMR is indeed a very powerful tool in determining the 3D structures of membrane proteins (see, e.g., [165-182]), but it is also time-consuming and costly. The structural class of a protein can provide useful clues for finding the structure of bovine somatotropin by the heuristic approach [183], and stimulate the modeling of 3D structures for many other proteins [184-202] important for drug development.

### Protein subcellular location prediction

It is the PseAAC, particularly the general PseAAC [203] that have significantly improve the prediction quality for the localization of proteins in a multi-label system [26, 27, 36, 204-228].

### PTM site prediction

Post-translational modification (PTM) refers to the covalent and generally enzymatic modification of proteins following protein biosynthesis. Prediction of PTM (post-translational modification) sites is currently a very hot topic. Again, it is PseAAC or PseKNC that has played the key role in this regard (see, e.g., [14, 75, 85, 229-271]).

## Byproducts

Meanwhile the introduction of PseAAC has also yielded some important byproducts.

### Five-steps rule

Stimulated by the PseAAC and PseKNC, a very important rule, called “5-steps rule”, has been established, as briefed in the Abstract and the 2nd paragraph of a comprehensive review paper [203] and detailed in its Sections 2, 3, 4, 5, and 6. As the guidelines for proteome or genome analysis, the 5-steps rule has been used nearly all the areas of computational proteomics or genomics [28, 29, 64, 70, 74, 77, 86, 215-225, 227, 228, 238, 255-257, 260, 263, 267-269, 271, 292]. For more about the 5-steps rule, see an insightful Wikipedia article at [https://en.wikipedia.org/wiki/5-step\\_rules](https://en.wikipedia.org/wiki/5-step_rules).

### Distorted key theory

Originally proposed in a comprehensive review paper [293], the “distorted key theory” has been further developed [192] and applied [294-297]. For more about the fantastic “distorted key theory, see an insightful Wikipedia article at [https://en.wikipedia.org/wiki/Chou%27s\\_distorted\\_key\\_theory\\_for\\_peptide\\_drugs](https://en.wikipedia.org/wiki/Chou%27s_distorted_key_theory_for_peptide_drugs).

## Conclusion and perspective

PseAAC is indeed a milestone for proteome analysis. Also, it has not escaped our notice that stimulated by the eight master pieces of pioneering papers from the then Chairman of Nobel Prize Committee Sture Forsen [298-305], many follow-up papers have been published [306-349, 257, 271, 278, 350]. They are very useful for in-depth investigation into the topic of the current paper, and we will use them in our future efforts.

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