

Using pseudo amino acid composition to predict protein subcellular location: Approached with Lyapunov index, Bessel function, and Chebyshev filter

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Summary. With the avalanche of new protein sequences we are facing in the post-genomic era, it is vitally important to develop an automated method for fast and accurately determining the subcellular location of uncharacterized proteins. In this article, based on the concept of pseudo amino acid composition (Chou, K.C. *Proteins: Structure, Function, and Genetics*, 2001, 43: 246–255), three pseudo amino acid components are introduced via Lyapunov index, Bessel function, Chebyshev filter that can be more efficiently used to deal with the chaos and complexity in protein sequences, leading to a higher success rate in predicting protein subcellular location.

Keywords: Covariant-discriminant algorithm – Pseudo amino acid composition – Chaos – Lyapunov index – Bessel function – Chebyshev filter

I Introduction

With the rapid increase in the number of new protein sequences entering into data banks, we are confronted with a critical challenge: How to timely (Chou, 2004) use them to stimulate the development of life science and benefit human beings? The knowledge of subcellular location of a protein is very important because it is closely related to its biological function. The traditional way to determine the localization of a protein in a cell is by biochemical experiments, and is both time-consuming and expensive. During the last decade, many theoretical methods were developed in an attempt to predict the subcellular location of a query protein according to its sequence information. The earlier approaches in this regard were based on the amino acid composition (see,

e.g., Cedano et al., 1997; Chou, 2000b; Chou and Elrod, 1999; Nakashima and Nishikawa, 1994). However, if the prediction was based the amino acid composition, all the sequence order and sequence length effects of a protein would be lost. To improve the situation, Chou introduced the pseudo amino acid composition to partially incorporate the sequence order effect of a protein (Chou, 2001). The introduction of the concept of pseudo amino acid composition has greatly stimulated the development of this area (see, e.g., Chou and Cai, 2002, 2003a, 2003b; Pan et al., 2003; Wang et al., 2004, 2005; Xiao et al., 2005). In this paper, a different approach to define the pseudo amino acid components is used for predicting protein subcellular location.

II Method

In addition to the 20 amino acid components as defined in the classical amino acid composition (Chou and Zhang, 1993, 1994; Nakashima et al., 1986), the Lyapunov index, Bessel function, and Chebyshev filter are used to define the additional three components for the pseudo amino acid composition of a protein, as illustrated below.

1 Lyapunov index

Over the past 20 years, it has been a very important problem to measure chaos and noises in many different fields. Lyapunov index is a useful feature to describe a chaos system. Because protein sequences are extremely complicated and disorder, it would be of help to use Lyapunov index to analyze them. Moreover, the Wolf's re-construction method was

adopted here. First of all, the phase space was reconstructed as follows. Given a series of amino acid sequence: $x_1, x_2, \dots, x_{N-1}$, the reconstructed embed vectors are $X_1, X_2, \dots, X_m$, where

$$X_m = (x_m, x_{m+D}, \dots, x_{m+(M-1)*D})^T \quad (1)$$

where M is the number of the re-constructed dimensions, D the reconstructed-delay which is the number of sampling point between any 2 elements of the embedded vector. The Euclidean distance between two random point X_m and X_n in the re-constructed phase space is:

$$L = \sqrt{(x_m - x_n)^2 + (x_{m+D} - x_{n+D})^2 + (x_{m+2D} - x_{n+2D})^2 + \dots + (x_{m+(M-1)*D} - x_{n+(M-1)*D})^2} \quad (2)$$

Thus, the following equation is used to calculate the Lyapunov index:

$$p_1 = \lambda = \frac{1}{T_Q - T_0} \sum_{k=1}^Q \log_2 \frac{L'(t_k)}{L(t_{k-1})} \quad (3)$$

where Q is the number of the points which can be found, $T_Q - T_0 = Q * I * H$ in which I is the number of iterations, H is the time of iteration. The value of p_1 is the 1st additional component, i.e., the 21st component in the pseudo amino acid composition.

2 Besseli function

First, we use the numeric amino acid sequence of a protein as the input of the Besseli function, the output of the Besseli function is the vector with the same dimension number as the input vector: $y = \beta(1, x)$ where β is the improved Besseli function, and x amino acid sequence of a protein. Thus, it follows

$$p_2 = \text{corr. coef.}(x, y) = \frac{\text{cov}(x, y)}{\text{std}(x) \cdot \text{std}(y)} \quad (4)$$

where std is standard deviation, and cov the covariance; their expressions are as follows:

$$\text{std}(x) = \frac{1}{N} \sum_{i=1}^N |x(i) - M(x)| \quad (5)$$

$$\text{cov}(x) = \frac{1}{N-1} \sum_{i=1}^N (x(i) - M(x))(y(i) - M(y)) \quad (6)$$

The value of p_2 is the 2nd additional component, i.e., the 22nd component in the pseudo amino acid composition.

3 Chebyshev filter

Likewise, if choosing the digital amino acid sequence x of the protein as the input of the Chebyshev filter, we can get an output vector $z = \gamma(1, x)$, where γ is the Chebyshev filter, and x amino acid sequence of a protein. Thus, it follows

$$p_3 = \text{corr. coef.}(x, z) = \frac{\text{cov}(x, z)}{\text{std}(x) \cdot \text{std}(z)} \quad (7)$$

The value of p_3 is the 3rd additional component, i.e., the 23rd component in the pseudo amino acid composition.

4 Numerical coding of protein sequence

To make the current method work, each amino acid in a protein sequence must have a numerical value. Here, let us assign a numerical value for each of the 20 native amino acids; i.e., A=5, C=10, D=15, E=20, F=25, G=30, H=35, I=40, K=45, L=60,

M=65, N=70, P=75, Q=80, R=85, S=90, T=95, V=100, W=105, and Y=110.

As an illustration, let us consider the following two sequences:

$$\text{ADFGHIK} \quad (8)$$

and

$$\text{AFDGIHK} \quad (9)$$

According to the numerical codes, we can transfer above two sequences into discrete stochastic time sequences, which can be converted into a curve as shown in Figs. 1 and 2, respectively.

5 Pseudo amino acid prediction

After we get those three parameters stated above, we can predict protein's subcellular location by the pseudo amino acid prediction approach. According to Chou (2001), a protein can now be represented by a vector in a 23-D (dimensional) space; i.e.,

$$X = \begin{bmatrix} x_1 \\ x_2 \\ \vdots \\ x_{20} \\ x_{21} \\ x_{22} \\ x_{23} \end{bmatrix} \quad (10)$$

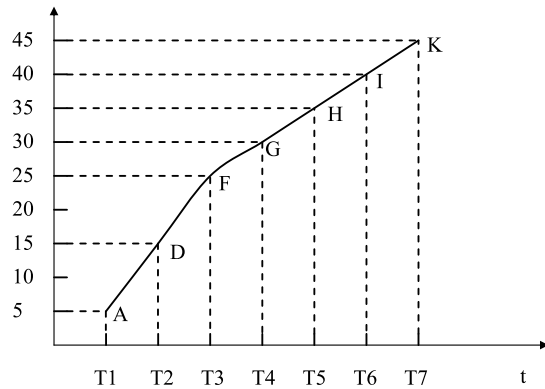


Fig. 1. The curve shape for the sequence of Eq. (8) according to the numerical codes assigned in this paper

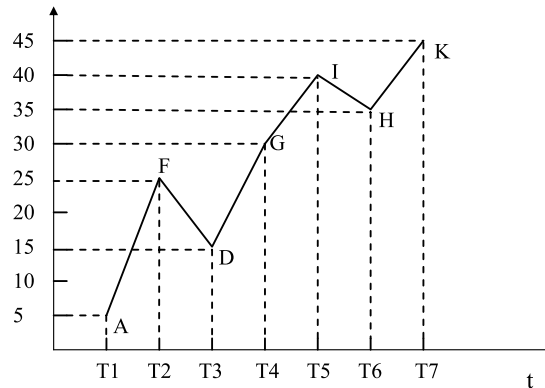


Fig. 2. The curve shape for the sequence of Eq. (9) according to the numerical codes assigned in this paper

where $x_1 \sim x_{20}$ are 20 components defined in the classical amino acid composition space (Chou, 1995; Chou and Zhang, 1994), $x_{21} \sim x_{23}$ are 3 additional components for the pseudo amino acid composition. After imposing the normalization condition, the 23 components are expressed as follows:

$$x_k = \begin{cases} \frac{f_k}{\sum_{i=1}^{20} f_i + \sum_{j=1}^3 w_j p_j}, & (1 \leq k \leq 20) \\ \frac{w_k - 20 \cdot p_k - 20}{\sum_{i=1}^{20} f_i + \sum_{j=1}^3 w_j p_j}, & (21 \leq k \leq 23) \end{cases} \quad (11)$$

where f_k is the normalized occurrence frequency of the k th amino acid in the protein X , p_1, p_2, p_3 are the 3 parameters derived from Eqs. (3), (4), and (7), respectively, and w_1, w_2, w_3 are the corresponding weight factors. For the current study, the weight factors were generated thru an optimal process as given below

$$\begin{bmatrix} w_1 \\ w_2 \\ w_3 \end{bmatrix} = \begin{bmatrix} 0.1 \\ 0.005 \\ 0.1 \end{bmatrix} \quad (12)$$

Now the augmented covariant-discriminant algorithm (Chou, 2000a, 2001) was used to perform the prediction. For the details of the algorithm, the reader is referred to the previous papers (Chou, 1995; Chou et al., 1998; Chou and Zhang, 1994; Zhou, 1998; Zhou and Assa-Munt, 2001).

III Results and discussion

To test the result of the current method, the dataset constructed by Chou and Elrod (1999) was used, which involves 12 subcellular locations (Fig. 3). However, for the reason as explained in Chou (2001), of the 2,319

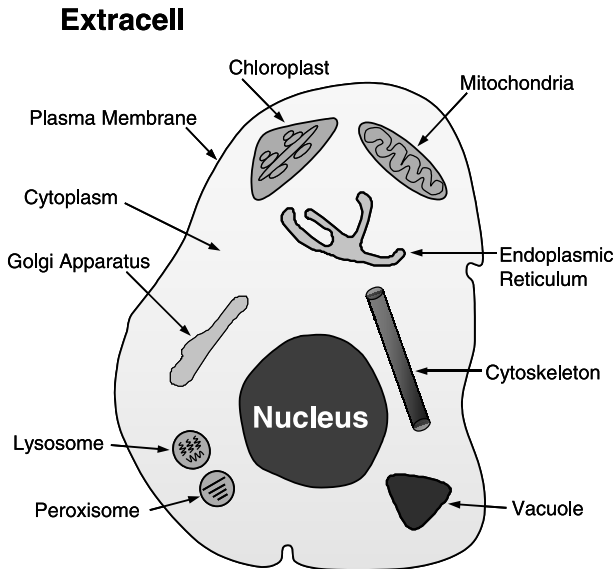


Fig. 3. Schematic illustration to show the twelve subcellular locations of proteins: chloroplast, cytoplasm, cytoskeleton, endoplasmic reticulum, extracell, Golgi apparatus, lysosome, mitochondria, nucleus, peroxisome, plasma membrane, and vacuole. Note that the vacuole and chloroplast proteins exist only in a plant. Reproduced from Fig. 2 of Chou (2001) with permission

Table 1. The overall success rates obtained by different methods^a

	Pan et al. (2003)	This paper
Re-substitution test	81.5%	82.3%
Jackknife test	67.7%	69.6%

^aThe predictions were performed on the dataset taken from Chou and Elrod (1999)

proteins originally listed in Appendix A of Chou and Elrod (1999), only 2,191 protein sequences were retrieved that contains 145 chloroplast proteins, 571 cytoplasm, 34 cytoskeleton, 49 endoplasmic reticulum, 224 extracellular, 25 Golgi apparatus, 37 lysosome, 84 mitochondria, 272 nucleus proteins, 27 peroxisome, 699 plasma membrane, and 24 vacuole.

The test was performed by re-substitution and jackknife. The former is to test the self-consistency (Chou and Zhang, 1995) of the prediction method, while the latter to test its extrapolating effectiveness (Chou and Zhang, 1993). Besides, among the jackknife test, independent dataset test, and sub-sampling test, the jackknife test is deemed the most objective and rigorous examination for cross-validation (Chou and Zhang, 1995; Zhou, 1998; Zhou and Assa-Munt, 2001; Zhou and Doctor, 2003). Therefore, a combination of the results obtained by the re-substitution and jackknifing can well indicate the power of a statistical prediction method. The predicted results thus obtained are given in Table 1, where for facilitating comparison, the corresponding results obtained by Pan et al. (2003) are also shown. As we can see from the table, the current success rates by both the re-substitution and jackknife tests are higher than those of Pan et al. (2003).

IV Conclusions

It is a feasible and effective approach to introduce the pseudo amino acid composition (Chou, 2001) to incorporate, at least partially, the information of the protein sequence order and sequence length for improving the quality of predicting protein subcellular location. It is demonstrated thru the present study that it can better reflect the sequence order effect by using Lyapunov index, Bessel function, and Chebyshev filter to construct the 3 additional components for the pseudo amino acid composition.

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