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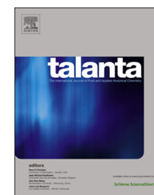

Direct quantitative analysis of aromatic amino acids in human plasma by four-way calibration using intrinsic fluorescence: Exploration of third-order advantages

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ABSTRACT

A novel intrinsic fluorescence method for the direct determination of L-phenylalanine, L-tyrosine, and L-tryptophan in human plasma is presented. By using fluorescence excitation–emission–pH–sample data array in combination with four-way calibration method based on the quadrilinear component model, the proposed approach successfully achieved quantitative analysis of the aromatic amino acids in human plasma, even in the presence of an unknown, uncalibrated serious interferent. It needs little preparation, uses the "mathematical separation" instead of "analytical separation", what makes it fast and environmentally friendly. Satisfactory results have been achieved for calibration set, validation set, and prediction set. The ranges for phenylalanine, tyrosine, and tryptophan are 2.0×10^3–20.0×10^3, 50.0–500.0, and 20.0–200.0 ng mL^{-1} respectively. Average spike recoveries (mean ± standard deviation) are 93.3 ± 7.7%, 104.3 ± 6.6%, and 99.5 ± 9.0% respectively. The real concentrations in human plasma are 10.2 ± 0.3, 6.6 ± 0.1, and 5.3 ± 0.1 μg mL^{-1} respectively, which are consistent with the results obtained by LC–MS/MS method and reference values. In addition, we explored the third-order advantages through the real four-way array; it has shown that higher resolving power is one of the main advantages of higher-order tensor calibration method. These results demonstrated that the proposed method is sensitive, accurate, and efficient for direct quantitative analysis of aromatic amino acids in human plasma.

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1. Introduction

L-phenylalanine, L-tyrosine, and L-tryptophan are α-amino acids and three of the building blocks of polypeptides and proteins. They participate in many functions of the living cell including, signal transduction, and transcription. As important small molecules, they also play important roles in metabolism, such as citric acid cycle. Phenylalanine, tyrosine, and tryptophan are formed from phosphoenolpyruvate and erythrose 4-phosphate, converted to a variety of important compounds in livings. Whether Phenylalanine, tyrosine, and tryptophan concentrations are too high or too low, the normal functions and metabolism of the body can be influenced. Given that the three aromatic amino acids are either neurotransmitters or precursors of neurotransmitters, genetic defects of aromatic amino acid metabolism can cause defective neural development and mental retardation [1]. For example, defective enzyme in phenylalanine metabolism results in excess phenylalanine, leading to the disease phenylketonuria (PKU). Therefore, quantitative analysis of phenylalanine, tyrosine, and tryptophan in biological fluid matrices is of biological significant.

The determination of these three analytes in such complex mixtures is feasible using enzyme sensor array [2] and analytical separations [3–5], such as gas or liquid chromatography–mass spectrometry (GC–MS or LC–MS), capillary electrophoresis–mass spectrometry (CE–MS). Chromatographic methods are highly selective and robust for these biologically relevant chemicals; however, analyte extraction and sample preparation are often required, which are time-consuming and laborious. In addition, the stage of analyte extraction may lose some amount of analyte, which makes bias in prediction of concentration level for analyte.

Considering that phenylalanine, tyrosine, and tryptophan have large bulky aromatic side chains with which the intrinsic fluorescence originates, fluorescence spectroscopy tends to be more attractive for quantitative analysis of them. Fluorescence spectroscopy can be applied to a wide range of problems in the chemical and biological sciences, and fluorescence detection is highly sensitive. However, fluorescence detection cannot provide high selectivity, especially for mixture. For quantitative analysis of phenylalanine, tyrosine, and tryptophan in human plasma, peculiar situations exist: using fluorescence signal at maximum emission wavelength, one can only determine one analyte at a time by

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purifying it from the other two analytes and plasma matrix, since the classical one-way (zero-order tensor) calibration method [6] requires signal must be fully selective for the analyte of interest. With the two-way (first-order tensor) multivariate calibration method [6–13], for example, based on fluorescence emission spectra, the three analytes can be determined simultaneously. However, the spectrum for the analyte of interest must be partially different from the spectra of all other responding species and, calibration standards must be representative of the samples containing any spectral interferent in human plasma [14]. As the rapid development of higher-order fluorescence instrument such as excitation–emission matrix fluorescence spectra (EEMs) [15], this prerequisite can be overcome through three-way (second-order tensor) calibration method [12,16–32]. This is due to the second-order advantage [6,33–35], which means analytes can be analyzed quantitatively even in the presence of uncalibrated interferents. One of most widely accepted models is the parallel factor analysis (PARAFAC) [36,37] (or called trilinear component model), ordinarily decomposed by alternating least-squares algorithm (PARAFAC-ALS) [20,35,38,39].

Because intrinsic protein fluorescence originates with the aromatic amino acids, the intrinsic protein fluorescence in human plasma overlaps seriously with that of phenylalanine, tyrosine, and tryptophan. This makes a challenge on the decomposition in three-way calibration method. Fortunately, the fluorescence intensity of each aromatic amino acid is strongly pH-dependent; this opens the possibility of introducing a pH mode to EEMs to construct four-way fluorescence excitation–emission–pH–sample (EEMs–pH) data array, on which four-way (third-order tensor) calibration method capable of providing higher resolving power [6,18,35,38,40–48] could be used.

As far as we know, simultaneous quantitative analysis of aromatic amino acids in human plasma by excitation–emission–pH intrinsic fluorescence coupled with four-way calibration has not been reported in previous works. This paper presents a novel fluorescence analytical method for simultaneous determination of phenylalanine, tyrosine, and tryptophan in human plasma with little preparation (Fig. 1). The method comprises four-way EEMs–pH measurements, data preprocessing of Rayleigh and Raman scattering using interpolation and four-way calibration. Preprocessing of the four-way array guarantees that the quadrilinear component model holds. Quadrilinear decomposition provides the pure excitation, emission, pH, and relative concentration profiles. Subsequently following the linear regression of decomposed relative concentration profile against real concentration for each analyte of interest which gives accurate prediction for calibration set, validation set, and real contents of analytes in human plasma respectively. Additionally, we explored the third-order advantages through the real four-way array.

2. Theory

2.1. Quadrilinear component model

In three-way (second-order tensor) calibration, one of the most commonly used models is the trilinear component model, which is often called as PARAFAC/CANDECOMP model, proposed by Harshman [36] and Caroll and Chang [37] independently. The concept of the trilinear component model can be naturally extended to the quadrilinear component model. Considering a model of the real-valued four-way array $\underline{\mathbf{X}}_{q}$ with size of $I \times J \times K \times L$, in which each element x_{ijkl} can be expressed as follows:

$$x_{ijkl} = \sum_{n=1}^{N} a_{in} b_{jn} c_{kn} d_{ln} + e_{ijkl}$$
$$\text{for } i = 1, 2, \ldots, I, \quad j = 1, 2, \ldots, J, \quad k = 1, 2, \ldots, K, \quad l = 1, 2, \ldots, L. \quad (1)$$

where a_{in}, b_{jn}, c_{kn}, and d_{ln}, correspond to underlying profile matrices $\mathbf{A}_{I\times N}$, $\mathbf{B}_{J\times N}$, $\mathbf{C}_{K\times N}$, and $\mathbf{D}_{L\times N}$ of $\underline{\mathbf{X}}_{q}$ respectively. The term e_{ijkl} is the element of the four-way residual array $\underline{\mathbf{E}}_{q}$ with size of $I \times J \times K \times L$. Then the modeled part of x_{ijkl} is quadrilinear in the parameter sets a_{in}, b_{jn}, c_{kn}, and d_{ln}, In this work, $\mathbf{A}_{I\times N}$, $\mathbf{B}_{J\times N}$, $\mathbf{C}_{K\times N}$, and $\mathbf{D}_{L\times N}$, represent the excitation, emission, pH, and concentration profiles respectively, what successively make the first, second, third, and fourth mode of the four-way EEMs–pH data array.

Regardless of scaling and permutation, the decomposition of the quadrilinear component model will be a unique one [49,50] given that $k_{\mathbf{A}} + k_{\mathbf{B}} + k_{\mathbf{C}} + k_{\mathbf{D}} \geq 2F + 3$, where $k_{\mathbf{A}}, k_{\mathbf{B}}, k_{\mathbf{C}}$, and $k_{\mathbf{D}}$, are the k-ranks of the profile matrices $\mathbf{A}$, $\mathbf{B}$, $\mathbf{C}$, and $\mathbf{D}$, respectively.

In addition, the quadrilinear component model can be expressed as the following fully stretched matrix forms:

$$\mathbf{X}_{I\times JKL} = \mathbf{A}(\mathbf{D} \odot \mathbf{C} \odot \mathbf{B})^{T} + \mathbf{E}_{I\times JKL} \quad (2)$$

$$\mathbf{X}_{J\times KLI} = \mathbf{B}(\mathbf{A} \odot \mathbf{D} \odot \mathbf{C})^{T} + \mathbf{E}_{J\times KLI} \quad (3)$$

$$\mathbf{X}_{K\times LIJ} = \mathbf{C}(\mathbf{B} \odot \mathbf{A} \odot \mathbf{D})^{T} + \mathbf{E}_{K\times LIJ} \quad (4)$$

$$\mathbf{X}_{L\times IJK} = \mathbf{D}(\mathbf{C} \odot \mathbf{B} \odot \mathbf{A})^{T} + \mathbf{E}_{L\times IJK} \quad (5)$$

where $\odot$ indicates the Khatri-Rao product, Provided that matrices $\mathbf{A} \in \mathbb{R}^{I\times N}$ and $\mathbf{B} \in \mathbb{R}^{J\times N}$, their Khatri-Rao product is a matrix of size $(IJ) \times N$ and defined by

$$\mathbf{A} \odot \mathbf{B} = \begin{bmatrix} a_{11}\mathbf{b}_1 & a_{12}\mathbf{b}_2 & \ldots & a_{1N}\mathbf{b}_N \\ a_{21}\mathbf{b}_1 & a_{22}\mathbf{b}_2 & \ldots & a_{2N}\mathbf{b}_N \\ \vdots & \vdots & \ddots & \vdots \\ a_{I1}\mathbf{b}_1 & a_{I2}\mathbf{b}_2 & \cdots & a_{IN}\mathbf{b}_N \end{bmatrix}$$

2.2. Four-way PARAFAC method

In general, the four-way PARAFAC algorithm is carried out by alternating least-squares principle [38,39,41,43]. According to Eqs. (2)–(5), the updating presentations of four modes can be obtained as follows

$$\mathbf{A} = \mathbf{X}_{I\times JKL}((\mathbf{D} \odot \mathbf{C} \odot \mathbf{B})^{T})^{+} \quad (6)$$

$$\mathbf{B} = \mathbf{X}_{J\times KLI}((\mathbf{A} \odot \mathbf{D} \odot \mathbf{C})^{T})^{+} \quad (7)$$

$$\mathbf{C} = \mathbf{X}_{K\times LIJ}((\mathbf{B} \odot \mathbf{A} \odot \mathbf{D})^{T})^{+} \quad (8)$$

$$\mathbf{D} = \mathbf{X}_{L\times IJK}((\mathbf{C} \odot \mathbf{B} \odot \mathbf{A})^{T})^{+} \quad (9)$$

Through the decomposition of four-way array by the four-way PARAFAC algorithm, the relative profiles of the four different modes can be obtained. The decomposition of the quadrilinear component model joins the calibration set together with the prediction set, and then the concentration information can be obtained in a separate univariate regression step. In this work, we take the real concentration as the independent variable. The univariate regression is expressed as

$$\begin{bmatrix} y_1 \\ y_2 \\ \vdots \\ y_P \end{bmatrix} = \begin{bmatrix} 1 & x_1 \\ 1 & x_2 \\ \vdots & \vdots \\ 1 & x_P \end{bmatrix} \begin{bmatrix} b_0 \\ b_1 \end{bmatrix} + \begin{bmatrix} e_1 \\ e_2 \\ \vdots \\ e_P \end{bmatrix} \quad \text{In matrix notation is } \mathbf{y} = \mathbf{X}\mathbf{b} + \mathbf{e} \quad (10)$$

where P is the number of calibration samples. The model parameter is estimated by $(b_0, b_1)^{\mathrm{T}} = \mathbf{X}^{+}\mathbf{y}$. Then the analyte concentration is predicted by $\overline{x}_{\text{unk}} = (y_{\text{unk}} - \overline{b}_0)/\overline{b}_1$ for an unknown sample, where y_{unk} represents intensity in the decomposed relative concentration profile of the analyte.

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