APPLICATION OF MULTIVARIATE REGRESSION MODELS IN CHROMATOGRAPHY. NEW ADVANCES.

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The aims of the review are the collection, concise description and evaluation of the multivariate mathematical-statistical methodologies used for the elucidation of the similarities and dissimilarities among retention parameters measured under various chromatographic conditions and the determination of the relationship between the physicochemical parameters and chromatographic retention behaviour of solutes.

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Introduction

Chromatographic technologies have been developed and successfully applied for the analysis of a considerable number of organic and inorganic compounds of different molecular mass even present in complicated accompanying matrices at the trace level.

The rapid development of the capacity of personal computers and the corresponding softwares allowed the reliable evaluation of chromatographic retention data measured under different conditions (application of a wide variety of stationary and mobile phases), etc. The extraction of maximal information of large data sets is practically impossible by the application of the traditional linear regression model. Multivariate regression technologies overcome this difficulty making possible the simultaneous evaluation of a considerable number of variables and observations.

Theoretical studies

The number of papers dealing with the development and application of various MLR techniques is rapidly growing. These methods improve the separation capacity and information content of the chromatographic separation process. Thus, multivariate statistical methods and pattern recognition methods were developed for the detection of differential protein expression from pre-processed LC-MS data.[1]

The modification of the three-way PARAFAC model has also been recently reported.[2]

Health care

The relationship between the carotid and femoral plaque burden and the α-linolenic acid (ALA) proportion of serum phospholipids in subject with primary dyslipidemia has been investigated in detail. The investigations were carried out by using gas chromatographic (GC) technique for the assessment of fatty acid composition of serum phosphatidylcholine and various methods for the study of plaque outcomes (frequency, number, maximum height and sum of plaque height). The results were evaluated by multivariate regression analysis Before analysis the data were adjusting for age, gender, lipid genotype, smoking, hypertension, diabetes mellitus, BMI, APOE4 genotype, prior station treatment. Calculations indicated that the concentration of ALA in serum phoshatidylcholine and plaque formation in carotid and femoral arteries is negatively correlated. The consumption of ALA enriched foods is proposed.[3]

The level of p-cresylsulfate and indoxyl sulfate was determined at different stages of chronic kidney disease (CKD) using ultra performance liquid chromatograhy and the relationship between the concentration of toxic compounds and biological parameters was elucidated by multivariate regression analysis. It was established that the amount of p-cresylsulfate and indoxyl sulfate was highly correlated in the samples. It was further found that the concentration of p-cresylsulfate and indoxyl sulfate increased linearly with the decline of renal function.[4]

The compounds 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and its metabolite 4-(methylnitrosamino)-1-3-pyridyl-1-butanol (NNAL) were analysed using liquid chromatography-tandem mass spectrometry. The investigates were motivated by the fact that both NNK and NNAL are considered as biomarkers for cigarette smoking. The objective of the investigation was the elucidation of the impact of NNK and NNAL on the urothelial carcinoma (UC) risk. The relationship between chromatographic and biological parameters was assessed by multivariate logistic

regression. It was concluded from the data that the amount of NNK and NNAL in urine be used for the detection of urothelial risk.[5]

Gas chromatography combined with mass spectrometry (GC-MS) has been used for the elucidation of socioeconomic factors on exposure to persistent organic pollutants such as organochlorine pesticides (OCPs). The relationship between the GC-MS results and the maternal social class was elucidated by multivariate regression analysis. Calculation revealed that the amount of OCPs in placenta markedly depended on the maternal social class.[6]

The prenatal exposure to OCPs has been investigated in detail. Gas chromatographic technique was applied for the analysis of OCPs, and the level of thyroid-stimulating hormone (TSH) was measured in 220 placentas. Multivariate regression analysis was employed for the elucidation of the relationship between pesticide exposure and neonatal TSH levels. The calculations indicated that endrin, encosulfan-sulfate, hexaxchlorobenzene, and p,p'-DDE exerted a marked influence of the TSH level, while the other pesticides showed no activity.[7]

Simple linear and stepwise multiple linear regressions were employed for the determination of the corelations between urinary catechol levels and some physicochemical parameters. The concentrations of noradrenaline, adrenaline and dopamine were assessed by high performance liquid chromatography (HPLC). Regression models were applied for the elucidation of the relationships between catecholamine levels and age, gender, BMI z-score, systolic BP z-score, diastolic BP z-score, and apnea hypopnea index (AHI). Significant relationships were found between noradrenaline and AHI (r=0.32) and age (r=-0.20, $p<0.05$ for both), between adrenaline and AHI (r=0.27) and age (r=-0.25, $p<0.05$ for both). Systolic BP *z*-score and diastolic *z*-score correlated with adrenaline (r=0.22 and r=0.20, respectively, $p<0.05$ for both). Multivariate methods established that AHI was a significant independent predictor of noradrenaline, similarly only AHI and age were were significant predictors of adrenaline.[8]

Multivariate logistic regression analysis was applied for predicting prostate cancer (CaP). The parameters included in the calculations were results of Western blot, liquid chromatography mass spectrometry, expression patterns of PCA3, and TMPRSS2. Calculations indicated that the combination of single biomarkers such as prostate-specific antigen, gene-based, protein-based and metabolite-based markers can be employed for the earlier detection of CaP.[9]

Multivariate logistic regression has also found application in the early detection of hepatocellular carcinoma (HCC) one of the most common malignancies in the word. Samples were analysed by two-dimensional gel electrophoresis and HPLC. Control patients, patients with liver cirrhosis and HCC were included in the experiments. It was established that the application of multivariate logistic regression for the evaluation of various biochemical and biophysical data sets increase considerably the efficacy of the detection of CaP.[10]

The presence of acrylamide metabolised in workers exposed to acrylamide (AA) was measured using liquid chromatography-electron ionization/tandem mass spectrometry (LC-ESI-MS/MS). The metabolites included in the investigations were N-acetyl-S-(2-carbamoylethyl)-cystein (AAMA), N-acetyl-S-(1-carbamoyl-2-hydroxyethyl-cystein (GAMA2) and N-acetyl-S-(carbamoyl-2-hydroxyethyl-cysteine (GAMA3). The enyzmes involved in the detoxification process were cyrochrom P450 2E1 (CYPE1), micosomal epoxide hydrolase (mEH) in exon 3 and exon 4, glutathione transferase θ (GSTT1) and μ (GSTN1). It was concluded from the data that GSTM1 genotypes modify considerably the excretion of urinary AAMA.[11]

The correlation between the concentration of asymmetric dimethyarginine (ADMA) in plasma has been investigated by using HPLC combined with multivariate analysis. The measurements and calculation indicated that the concentration of ADMA was significantly higher in patients with significant coronary artery disease (CAD). Furthermore, calculations revealed that plasma ADMA level is a significant independent risk factor.[12]

Helix pomatia agglutinin binding glycoproteins (HPA) were isolated from specimens of various thyroid tumors and analysed by affinity chromatography, SDS-PAGE and western blotting. The data were analysed by Cox regression analysis. The investigations were motivated by the possible effect of HPA on cellular glycosidation and found considerable differences between the profile of HPA-binding glycoproteins of specimens of various thyroid tumors.[13]

The influence of the concentration of N-acetylaspartate NAA on the amyotropic lateral sclerosis (ALS) has been studied by using liquid chromatography mass spectrometry and multivariate logistic regression analysis. Regression analysis proved the strong relationship between the serum NAA level and the presence of ALS. The results suggest that serum NAAmay be a useful biomarker.[14]

A GC-MS method was employed for the determination of the metabolic profile of Type 2 diabetes mellitus using multivariate resolution method and Monte Carlo PLS—DA. Metabolites suitable as biomarkers were lactate, alanine, cc-hydroxybutyric acid, phosphate seine, pyroglutamic acid, palmitic acid, stearic acid, palmitic acid, 1-monopalmitin and cholesterol.[15]

Pharmaceuticals

Multivariate regression methods have been frequently used for the evaluation of the chromatographic analysis of pharmaceuticals. Thus, the simultaneous detection and quantitation of paracetamol (PAR) pseudoephedrin hydrochloride (PSE), and dextromethorphan hydrobromide (DEX) in tablets was reported. As the spectrograms of the analytes were considerably overlapping the data were evaluated by PCA and principal component regression (PCR). The calculations proved that the multivariate methods make possible the correct separation of analytes. The recoveries were between 0.96.1–100.2% and 97.1–100.4%, the relative error of prediction was 0.5–6.7 and 0.8–7.0% for PLS and PCR, respectively. The results obtained by HPLC and the multivariate methods were not significantly different. It was established that the method

applies a simple mobile phase and shorter analysis time, does no require internal stadard and gradient elution.[16]

A HPLC technology was applied for the simultaneous determination of clavulanic acid (CA) and amoxycillin (AMO). Analytes were detected using Fourier transform technique coupled with ATR/FTIR. The data were analysed by using various calbration model such as PLS, interval PLS (iPLS), synergy PLS (siPLS), and backward PLS (biPLS). Multiplicative scatter correction and mean centering produced th ebest models. Relative standard error of prediction were 3.8 and 5.1 % for CA and AMO %, respectively. It was stated that the method can be applied for the simultaneous analysis of CA and AMO in commercial pharmaceutical products.[17]

HPLC-DAD coupled with partial least squares multivariate calibration was applied for the simultaneous determination of potassium guaiacol sulfonate (PG), guaifenesin (GU), diphenhydramine HCl (DP) and carbetapentane citrate (CP) in syrups. It was stated that the new HPLC-DAD method applies a simple mobile phase and shorter separation time. It was further established that the method does not require internal standard and gradient elution.[18]

Chromatographic profiling and multivariate analysis was applied for the screening and quantifying the contributions from individual components of traditional chinese medicine. It was established that the method is suitable for the assigning bioactivity to individual components in extracts from natural products.[19]

A chromatographic and spectroscopic data fusion analysis was developed for the study of photodegradation processes. Results of HPLC-DAD-MS and UV-Vis were evaluated by hybrid hard- and soft modelling multivariate curve resolution. The photodegradation of ketoprofen was investigated with this method. Four degradation products were identified: (3-(1-hydroperoxyethyl)benzophenone, 3-acetylbenzophenone, 3-(1-hydroxyethyl)benzophenone and 3-ethylbenzophenone). The method was proposed for the study of photodegradation processes.[20]

Food and food products

Quantitative structure-retention relationship methods were employed for the study of the correlations between molecular structure and retention behavior of essential oils. The calculations included genetic algorithm and multiple linear regression (GA-MLR), partial least square (GA-PLS), kernel PLS (GA-KPLS) and Levenberg-Marquardt artificial neural network (L-MAAN). The correlation coefficients between the measured and calculated characteristic were in each case significant: GA-MLR 0.886; GA-PLS 0.912; GA-KPLS 0.937; and L-MANN 0.964.[21]

Similar calculations were carried out on a matrix of retention indices of essential oils. It was established that GA-KPLS can be applied as an alternative modeling tool for Quantitative Structure Retention (QSRR) studies[22]

The GC retention indices of 100 components of essential oils were measured on three GC coumns of different polarity. QSRR models such as ridge regression, PLS, Kernal orthogonal projection to latent structure (KOPLS) were developed for the elucidation of the relationship between calculated molecular parameters and retention parameters. It was found that linear model using only one variable (solvation energy) explains 95 – 94 % of variance. The application of PLS and ridge regression resulted in elevated predictive power.[23]

Various analytical technologies were employed for the following of the ageing of madeira wines. The methods included were UV-vis, GG-MS. and HPLC-DAD The volatile and phenolic composition of the samples were separately determined. Multivariate prediction models were used by applying PLS regression to each chemical data set. The calculations indicated that the complicated GC-MS and HPLC-DAD methods are leading to more precise results, however, UV-vis can also been applied for the prediction of the age of madeira wines.[24]

Stir bar sorptive extraction method (SBSE) coupled to GC/MS was employed for the separation and quantitative determination of the composition of the arome profile of Sherry brandies Analysis of variance indicated that some volatile compounds show considerable differences. Principal component analysis (PCA) established that only one sherry differed markedly from the others. Partial least squares discriminant analysis (PLS-DA) proved the capacity of the method to discriminate among samples. The results of linear discriminate analysis were highly similar.[25]

Quantitative structure-property relationships technologies (QSPR) were developed for the prediction of the lipophilicity of food preservatives employing MLR and genetic algorithm (GA) methodologies. Parameters included in the calculations were theoretical molecular descriptors and experimental chromatographic data.The molecular descriptors were calculated using the DRAGON package. It was established that molecular descriptors such as information indices, topological, 3D-MoRSE and WHIM descriptors are suitable for the prediction of the lipophilicity of food preservatives. It was further established that atomic polarizabilities, atomic Sanderson electronegativities and atomic van der Waals volume of the molecules have the highest predictive power.[26]

HPLC and attenuated total reflectance (ATR) Fourier transform infrared (FT-IR) spectroscopy followed with multivariate analysis were applied for the separation and quantitative determination of quercetin-3,4'-O-diglucoside (3,4'-Qdg) and quercetin-4'-O-glucoside (4'-Qmg) in onion. It was established that the results obtained by HPLC and ATR FT-IR were well correlated ($R<0.95$). Cross-validated (leave-one-out) partial least-squares regression (PLSR). It was further established that this calculation method can be successfully used for the prediction of the concentration of analytes. The data were also evaluated by PCA, discriminant function analysis and soft independent modeling of class analogue method. It was concoded from the data that the ATR FT-IR procedure requires less sample preparation than the traditional HPLC analysis.[27]

The relationship between methanol production of cattle and the fatty acid (FA) production was elucidated by using GC. The data were evaluated by using univariate mixed model regression technique. The calculations suggested that milk FA profiles can be employed for the prediction of methane production in dairy cattle.[28]

GC has also found application in the study of the composition of volatile compounds influencing the sensory and fruit attributes of kiwi fruit. The chromatographic retention data were evaluated by multivariate mathematical-statistical methods (PCA and MLR). It was stated that the method is suitable for the identification of compounds with marke sensory activity.[29]

The biological activity of various green tea cultivars was investigated by combining HPLC measurements with the evaluation of the data with PCA and orthogonal partial least-quares-discriminant analysis (OPLS-DA). It was established that metabolic profiling can be successfully employed for nutraceutical evaluation of tea cultivars.[30]

GC-MS followed with PCA and PLS was employed for the elucidation of the relationships between Godello white wine sensory properties and its aromatic fingerprinting. Calculations indicated that ethyl ethers and acetates accounted 55.1 % of the odour activity values (fruity); spicy (fatty acids, 35.3 %) and floral aroma (terpenes, 3.1 %). It was found that the main aroma components were fruity and floral aromas (floral, apple and citrus).[31]

Environmental studies

The complex composition of environmental samples made necessary the application of various multivariate methods for the evaluation of complicated chromatographic retention profiles. Thus, various analytical methods were employed for the study of biological wastewater treatment plants (WWTP) The considerable number of measured parameters were evaluated by various multivariate mathematical statistical methods such as PCA, and multivariate regression analyses. Size exclusion chromatography was employed for the determination of extra-cellular polymeric substances (EPS), the internal structure was observed by confocal laser scanning microscopy. The main characteristics of the paper mills were the EPS production, the presence of nitrification process and the presence of H_3PO_4.[32]

Computational molecular descriptors were employed for the prediction of the chromatographic lipophilicity of some pesticides and polycyclic aromatic hydrocarbons (PAH). Measurements of lipophilicity were carried out by HPLC using various stationary phases (C18, C8, CN, and Phenyl) and methanol and acetonitrile organic modifiers. The results were evaluated by the traditional multivariate analysis and genetic algorithm. The calculations revealed that quantitative structure property relationship can be employed for the prediction of the lipophilicity of these types of analytes.[33]

Comprehensive two dimensional gas chromatographic method was developed for the determination of the distillation points and relative density of gasoline and similar fuels. These parameters are important for the quality control of gasoline. The new method employs two GC columns with flame ionization detection (FID). The data were evaluated by multivariate analysis. It was established that the root mean square prediction differences (RMSPD) were 0.85%, 0.43%, 1.07%, and 1.71% for 10, 50, and 90% v/v of distillation.[34]

Various multivariate mathematical statistical methods were applied for the prediction of the retention behavior of nitrobenzene derivatives. Quantitative structure-retention relationship calculations (QSSR) inlcuded MLR, PLS, and ANN techniques. Multivariate image analysis (MIA) descriptors were evaluated by correlation ranking-principal component regression (CR-PCR) and correlation ranking principal component artificial neural network (CR-PC-ANN). It was established that the separation power of CR-PC-ANN method was the highest the R^2 values varying between 0.989, 0.999, and 0.999.[35]

Gas chromatography coupled with multivariate evaluation technologies was employed for the estimation of the age of weathered volatile organic compounds. The aging process was followed with GC measurements. The evaluation of the chromatograms was carried out by using different multivariate technologies such as non-linear PLS (PolyPLS), partial least squares discriminant analysis (PLSDA) and locally weighted regression (LWR). The prediction capacity of calculation methods was evaluated according to the root mean square error prediction (RMSEP). The results suggested that LWR has the highest predictive power and can be employed for the estimation the age of more complicated light petroleum mixtures such as gasoline.[36]

A two-dimensional GC method was applied for the study of the profile of weathered gasoline samples. The data were evaluated by various mathematical-statistical techniques such as PLS, PolyPLS, LWR, and partial least squares discriminant analysis. Calculations indicated that the best results can be achieved by the application of LWR method.[37]

The retention behaviour of 50 phenol derivatives was studied in a dual-capillary column system containing SE-54 and OV-17 bonded phase. The correlation between structure and retention of analytes was elucidated by using various quantitative structure, retention calculation techniques such as MLR, PLS, and ANN. It was stated that models with low standard errors and high correlation coefficients can be developed for the prediction of the retention behaviour of this class of phenol derivatives. The squared regression coefficients of prediction for the MLR, PLS and ANN models for DB-5 column were 0.9645, 0.9606, and 0.9808, respectively, while on DB-17 column the respective squared regression coefficients were 0.9757, 0.9757, and 0.9875. It was stated that non-linear model can be successfully employed for the discription between structural descriptors and the chromatographic retention behavior of this class of analytes.[38]

Abbreviations

AAMA	N-acetyl-S-(2-carbamoylethyl)-cystein
ADMA	asymetric dimethylarginine
ALA	α-linoleic acid;
AMO	amoxicillin
ATR	attenuated total reflectance
CAD	coronary artery disease
CA	clavulanic acid
CaP	prostate cancer

CHD	coronary heart disease
CKD	chronic kidney disease
CR-PC-ANN	correlation ranking-principal component artficial neural network
CR-PCR	correlation ranking-principal component regression
DAD	diode array detector
FA	milk fatty acid profile
FID	flame ionization detection
FT-IR	Fourier transform infrared spectroscopy
GA	genetic algorithm
GC	gas chromatography
GC-MS	gas chromatography mass spectrometry
HCC	hepatocellular carcinoma
HPLC	high performance liquid chromatography
biPLS	backward PLS
iPLS	interval PLS
siPLS	synergy PLS
KOPLS	Kernel orthogonal projection to latent structure
KPLS	kernel partial least square
L-MANN	Levenberg-Marquardt artificial neural network
LWR	locally weighted regression
MLR	multiple linear regression
NAA	N-acetylaspartate
NNK	4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone
NNAL	1-(3-pyridyl)-1-butanol (NNAL)
OCPs	organochlorine pesticides
OPLS-DA	orthogonal partial least-squares-discriminant analysis
PCA	principal component analysis
PCR	principal component regression
PLS	partial least squares
PLS-DA	partial least squares
PLSR	partial least-squares regression
PolyPLS	nonlinear PLS
QSPR	quantitative structure-property relationship
QSRR	quantitative structure retention relationship
RMSEP	root mean square error of prediction
RMSPD	root mean square prediction differences
SBSE	stir bar sorptive extraction method
TSH	thyroid-stimulating hormone
TVR	clinically-driven target vessel revascularization

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