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Four- and five-way excitation-emission luminescence-based data acquisition and modeling for analytical applications. A review

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Abstract

The latest advances in both theory and experimental procedures on third-order/four-way and fourth-order/five-way calibration methods are discussed. This report is focused on excitation–emission (fluorescence and phosphorescence) matrices generation, employing different variables as the third data mode (time retention in chromatography, pH gradient, fluorescence/phosphorescence lifetime, kinetics, or other chemical treatments). Fully capitalizing on the second-order advantage, it has been possible to develop appealing analytical applications in despite of the complexity of the data. Extraction of the significant chemical information about the system under study as well as the individual abundance of the contributing constituents after proper higher-order data decomposition has allowed to analytical researchers performing quantitative analysis of complex samples. The experimental works reported up to the present are introduced and discussed in order to illustrate concepts. Throughout this work, the analytical benefits achieved by modeling third- and fourth-order data are exposed, attempting to contribute to the ongoing debate in the chemometric community regarding the existence and the true nature of the third-order advantage.

Keywords: Four- and five-way data; Third- and fourth-order data; Excitation-emission luminescence matrices; Modeling; Multi-way calibration

1. Introduction

The field of multivariate calibration has been expanding in the last years with uncountable analytical applications of a large number of compounds of interest, in complex samples, in several research areas. In this context, several reviews, books and articles about recent advances in multivariate calibration can be found in the literature, becoming an indicator of the growing interest in chemometrics. These reports mainly deal with second-order calibration, although third-order calibration sections are included [1–8] and, specifically for chromatographic data, several recent reviews and a book chapter cover second- and third-order calibration [9–13].

A pioneering excellent work of Booksh and Kowalski, in 1994 [14], entitled The Theory of Analytical Chemistry, has defined and established a concept in the context of second-order calibration, the 'second-order advantage', still in use nowadays, which has opened the multivariate calibration scenario. The outstanding advantage of second-order calibration relies in the fact that, under certain circumstances, the concentrations of individual components of interest can be accurately achieved through separating the signals of target analytes from those of uncalibrated background or interferences [1,8]. Interestingly, the authors dedicated a few premonitory words at the end of the paper about third-order calibration as follows: "*[…] One advantage of third-order calibration is known: with trilinear data from one sample, the intrinsic profiles in each order can be determined uniquely for each species in the sample. […] However, the complete third-order advantage, or the Nth-order advantage for that matter, is unknown. […] The limits and advantages of third-order and higher-order analysis are unknown […]*". At present, twenty-five years later, these words are still topical and different authors are discussing the limitations and advantages of third- or higher-order calibration. At this respect, Olivieri established that there

71 is no general consensus on the existence of additional advantages when working with four-
72 way data [15]. On the contrary, Wu et al. [16] defended that four-way data should have more
73 obvious advantages, that is, the so-called 'third-order advantage'. It not only retains the
74 second-order advantage but also has additional benefits that have been demonstrated: 1) the
75 possibility of decomposing a unique data array of a given sample independent of other
76 samples [14,17,18], 2) the enhancement in sensitivity and selectivity as well as the
77 improvement of other analytical figures of merits [8,15], and 3) the feasibility of solving
78 collinearity effects when an extra instrumental mode is included. This is the direct
79 consequence of Kruskal´s condition; generalized Kruskal´s fundamental results on the
80 uniqueness of trilinear decomposition of three-way arrays, to the case of multilinear
81 decomposition of four- and higher-way arrays [19]. In consequence, the introduction of
82 fourth mode can relieve the serious problem of collinearity [20]. However, these authors also
83 recognized that more intense research should be dedicated to the basic theory of multiway
84 calibrations to explore the essence of third-order or higher-order methodologies [21].
85 The main body of the current developed methodologies is related with first- and
86 second-order based analytical applications. However, the report of third- and fourth-order
87 methods is still scarce in spite of the potential of third- and higher-order multivariate
88 calibration. Multivariate calibration models are being applied to third- and higher-order data
89 in several fields. The calibration based on this kind of data can be named as third-order or
90 four-way calibration; the former one is related to the number of modes of a single sample,
91 whereas the latter focuses on the number of modes of a set of samples. When third-order data
92 are joined for several samples into a fourth direction, a four-way array is obtained.
93 Most of the third- and fourth-order applications have been developed using excitation-
94 emission luminescence as analytical detection technique. This is due to the fact that a

spectrofluorimeter is a second-order instrument that can straightforwardly generate a complete luminescence data matrix (a second-order data) per sample, i.e. the excitation-emission luminescence matrix (EEM).

The present article serves as a review with intent to summarize the advances in the generation of third- and fourth-order experimental excitation-emission luminescence data, as well as to provide a succinct survey of the multi-way algorithms used for data modeling in different analytical applications.

2. Data properties, algorithms and figures of merit

Multilinearity is a property of paramount importance when modeling multi-way data, which must be strongly considered before selecting the chemometric modeling. For third-order data, where signal additivity is maintained, a trilinear third-order array for a given sample should be the sum of the individual contribution of the constituents. Equation (1) represents the response x_{jkl} at sensors j, k and l of a third-order data:

$$\boldsymbol{x}_{jkl} = \sum_{n=1}^{N} b_{jn} c_{kn} d_{ln} + e_{jkl} \qquad (1)$$

where b_{jn}, c_{kn} and d_{ln} are the elements along the first, second and third instrumental data mode for the component n, respectively, and N is the number of responsive constituents. e_{jkl} represents the residues of the modeling. Hence, an array fulfills the 'low-rank trilinearity' property (commonly called as trilinear) when the signal is described following Eq. (1) in which the three data modes are mutually independent. It should be remarked that this equation is also valid to explain trilinearity of a three-way array utilized in second-order calibration methods.

When an additional mode is included, i.e. the concentration mode, the four-way data array, obtained by joining several three-dimensional data arrays for a sample set, fulfills quadrilinearity property only if each element of the array is defined as:

$$\boldsymbol{x}_{ijkl} = \sum_{n=1}^{N} a_{in} b_{jn} c_{kn} d_{ln} + e_{ijkl} \quad (2)$$

being all symbols the same as in Eq. (1), with a_{in} describing the changes in constituent concentrations along the concentration mode.

In the case of four-way calibration, a classification for four-way data was presented by Olivieri and Escandar [7] to facilitate the evaluation of the gathered data. An adaptation of the original scheme is depicted in Fig. 1.

The quadrilinearity property can be lost in case of presence of one or more quadrilinearity-breaking modes, i.e. constituent profiles changing among samples along the mode, for example, lack of reproduction of the chromatographic retention time. In case the four-way data presents one, two or three quadrilinearity-breaking modes, the non-quadrilinear four-way data are classified as type 1, 2 or 3, respectively (see Fig. 1).

In the case of five-way data modeling, extensions of known four-way models were adapted maintaining the multilinear decomposition philosophy. In comparison with four-way data, five-way data comprises an additional dimension which represents an extra experimental variable of the data. The quinquelinear model follows the expression:

$$\boldsymbol{x}_{ijklm} = \sum_{n=1}^{N} a_{in} b_{jn} c_{kn} d_{ln} f_{mn} + e_{ijklm} \quad (3)$$

being $b_{jn,}$ c_{kn} d_{ln} and f_{mn} the individual elements of each instrumental variable and a_{in} the elements of the concentration mode. In this case, quinquelinearity can be broken in presence of loss of reproducibility in at least one of the five data modes.

Table 1 summarizes the most common algorithms used to model four- and five-way data. For detailed information of the algorithms, see the cited literature. It should be mentioned that each algorithm requires a specific data array structure in base on the multilinearity property of the data, which is depicted in Table 1.

To initiate the decomposition, the algorithms used for multi-way data modeling require knowing in advance the number of active species that are involved in the system under study. In the case of fluorescence, the number of components (N) that explains the system should be in accordance with the real number of the spectroscopically active species that constitute the samples. However, in complex systems or samples of unknown composition, the number of components may not be intuitive and, then, must be estimated. The estimation of N can be accomplished by following different procedures depending on the model implemented for the data analysis. For instance, core consistence diagnostic analysis (CORCONDIA) [22] is the most used approach to estimate the value of N when parallel factor analysis (PARAFAC) is chosen as trilinear model. Despite this analysis aids to establish the magnitude of N, this value should lead to the best fit of the model and to the minimal residual fit [7]. It should be highlighted that most of the trilinear decomposition (TLD)-based algorithms require an accurate estimation of N to avoid overfitting although AQLD series algorithms demonstrated to be insensitive to the excess number of components.

For quantitative evaluation of the chemometric modeling performance, analytical figures of merit are computed. Several expressions have been presented by Olivieri et al. [8]

for obtaining sensitivity (SEN) figures for the different multi-way models. Equation (4) presents the SEN computation for four-way PARAFAC modeling:

$$\mathrm{SEN}_{\mathrm{PARAFAC,4-way}} = s_n \left\{ \left[\left(\mathbf{B}_{\mathrm{cal}}^{\mathrm{T}} \mathbf{P}_{\mathrm{B,unx}} \mathbf{B}_{\mathrm{cal}} \right) * \left(\mathbf{C}_{\mathrm{cal}}^{\mathrm{T}} \mathbf{P}_{\mathrm{C,unx}} \mathbf{C}_{\mathrm{cal}} \right) * \left(\mathbf{D}_{\mathrm{cal}}^{\mathrm{T}} \mathbf{P}_{\mathrm{D,unx}} \mathbf{D}_{\mathrm{cal}} \right) \right]^{-1} \right\}^{-1/2} \quad (4)$$

where s_n is the slope of the PARAFAC pseudo-univariate plot, $\mathbf{B}_{cal}$, $\mathbf{C}_{cal}$ and $\mathbf{D}_{cal}$ collect the loading matrices for the calibrated analytes, '*' is the element-wise and $\mathbf{P}_{B,unx}$, $\mathbf{P}_{C,unx}$ and $\mathbf{P}_{D,unx}$ are projection matrices given by $\mathbf{I}$-$\mathbf{B}_{unx}\mathbf{B}_{unx}^{+}$, $\mathbf{I}$-$\mathbf{C}_{unx}\mathbf{C}_{unx}^{+}$ and $\mathbf{I}$-$\mathbf{D}_{unx}\mathbf{D}_{unx}^{+}$, respectively, being $\mathbf{I}$ the identity matrices, $\mathbf{B}_{unx}$, $\mathbf{C}_{unx}$ and $\mathbf{D}_{unx}$ collect the loading matrices for the unexpected samples constituents, and the superscript '+' indicates the generalized inverse operation. Moreover, Olivieri has presented extensions of Eq. (4) to utilize when computing SEN in unfolded and N-way partial least-squares with residual trilinearization (U-PLS/RTL and N-PLS/RTL, respectively) [8]. For five-way data modeling evaluation, extensions derived from the aforementioned expressions for $\mathrm{SEN}_{4\text{-way}}$ estimation are utilized.

A different expression to estimate SEN is utilized when multivariate curve resolution-alternating least–squares (MCR-ALS), is used:

$$\mathrm{SEN}_{\mathrm{MCR}} = s_n [J(\mathbf{C}^{\mathrm{T}}\mathbf{C})^{-1}]^{-1/2} \quad (5)$$

where s_n is the slope of the MCR-ALS pseudo-univariate plot, J is the number of data points in each submatrix in the augmented mode, and $\mathbf{C}$ is a matrix containing the profiles for all sample components in the non-augmented direction [8].

Once the SEN is computed, both the limit of detection (LOD) and the limit of quantitation (LOQ) can be obtained through Eq. 6 and Eq. 7, respectively:

$$\mathrm{LOD} = 2 \times t_{0.05,\infty} \frac{s_{dtest}}{\mathrm{SEN}} = 3.3 \frac{s_{dtest}}{\mathrm{SEN}} \quad (6)$$

$$\mathrm{LOQ} = 10 \frac{s_{dtest}}{\mathrm{SEN}} \quad (7)$$

where $t_{0.05,\infty}$ is the one-tail t value assuming a large number of calibration samples and α value of 0.05, and s_{dtest} represents the standard deviation of the estimated net signal when its true value is zero.

3. Fluorescence EEMs

3.1. EEMs-kinetics

One of the most used approaches to induce four-way data is by including the kinetic behavior as additional information, laying on the fact that the compounds can degrade, oxide/reduce or new spectroscopically active products can arise. Hence, the modes of the four-way data shall be the excitation wavelengths, the emission wavelengths, the kinetic profiles and the sample concentrations. In all the presented cases, the chemical reaction involved in the analysis follows first-order kinetics. Details of the described analytical approaches are summarized in Table 2.

The first analytical application reported was a method to quantitate mixtures of catecholamines, adrenaline and noradrenaline, in which the lutine reaction was accomplished in a flow system, to obtain the corresponding fluorescing lutines (3,5,6-trihydroxyindole derivatives). PARAFAC and N-PLS were chosen to solve the system achieving similar results. [22].

PARAFAC is the most widespread multilinear model and has been widely utilized for several analytical applications. For instance, it was utilized for the analysis of polycyclic aromatic hydrocarbons (PAHs) by photocatalytic degradation [23]. It was demonstrated that

198 this methodology offered a good resolution for three PAHs (benz[a]anthracene (B[a]A),
199 benzo[k]fluoranthene (B[k]F and dibenz[a,h]anthracene (B[2,a,h]A)), whose signals were
200 strongly overlapped. Another example of the good performance of PARAFAC was presented
201 by Nahorniak et al. [24], who proposed a photochemical degradation based methodology for
202 the analysis of fenvalerate, a non-fluorescent compound. The degradation products were
203 monitored by EEMs registering and the further chemometric data analysis achieved
204 satisfactory analytical results.

205 Another common reaction employed in kinetics studies is based on the oxidation with
206 potassium permanganate. In this regard, Olivieri et al. [25] determined methotrexate (MTX)
207 and leucovorin (LV) in human urine with PARAFAC and trilinear least-squares (TLLS). The
208 successful resolution of the individual analytes was accomplished in spite of the presence of
209 uncalibrated interferences arising from the urine background components. This fact was
210 possible by means of the third-order advantage achieved by using four-way EEM-kinetics
211 arrays. On the other hand, owing to exploit the advantages of the known bilinear
212 decomposition methods, Arancibia et al. [26] introduced two new trilinear decomposition
213 algorithms for four-way data based on TLLS and U-PLS coupled to RTL. These algorithms
214 were utilized for the evaluation of MTX and LV in presence of interferents by oxidation with
215 potassium permanganate. It was demonstrated that TLLS/RTL and U-PLS/RTL were able to
216 exploit the second-order advantage and enabled to satisfactorily quantitate the analytes in
217 presence of uncalibrated interferents.

218 Muñoz de la Peña et al. [27] reported an approach to determine folic acid and MTX in
219 urine samples by oxidation with potassium permanganate with PARAFAC and N-PLS data
220 analysis. For the kinetics monitoring, several EEMs were collected between 0 and 5 minutes
221 after reaction initiated. Then different multi-way calibration methods were assessed. Results

222 demonstrated that the best performance was obtained when third-order calibration was
223 employed. In addition, as an extension of this work, this chemical reaction was reported for
224 the analysis of folic acid and methotrexate in human serum [28]. Here, the authors compared
225 N-PLS, PARAFAC and U-PLS/RTL performances. Although PARAFAC and N-PLS
226 offered satisfactory results in urine samples, poor analytical figures of merit were obtained
227 for human serum samples (relative error of prediction (REP)> 30 %). In this regards, U-
228 PLS/RTL improved the latter results, reaching REP values lower than 12 %. This
229 improvement was explained by the fact that U-PLS/RTL can handle the analyte-background
230 interaction, which is a troublesome condition for the other algorithms.

231 Pursuing an improvement in the analytical performance, Damiani et al. developed a
232 new third-order multivariate calibration algorithm based on the combination of N-PLS with
233 RTL [29]. This algorithm was employed to determine procaine and its metabolite p-
234 aminobenzoic acid in equine serum by means of the hydrolysis reaction of procaine at pH =
235 13 and T^a = 40 ºC. Results demonstrated the ability of the algorithm to successfully predict
236 the analyte concentrations in presence of uncalibrated interferences. Thereafter, N-PLS/RTL
237 was used for the determination of folic acid and its metabolites (5-methyltetrahydrofolic acid
238 and tetrahydrofolic acid) in serum samples which were subjected to photochemical
239 degradation by means of on-line UV irradiation [30]. The EEMs registering was performed
240 as a function of the irradiation time by using a fast scanning spectrofluorimeter. In this case,
241 since quadrilinearity property was not fulfilled, PARAFAC and TLLS did not provide
242 satisfactory results. In contrast, N-PLS/RTL and U-PLS/RTL offered the uttermost in
243 efficiency by predicting the analytes in presence of non-modeled interferences.

244 In a study performed by García-Reiriz et al. [31], the Hantzsch reaction between
245 malonaldehyde and methylamine, which provides a highly fluorescent compound, was

246 utilized. Due to the non-linear nature of the kinetics, the data were subjected to unfolded
247 principal component analysis, residual trilinearization with further radial basis functions
248 analysis (U-PCA/RTL/RBF), allowing the successfully determination of malonaldehyde in
249 olive oil samples. Following the same data analysis procedure, Ni et al. [32] developed a
250 method based on the alkaline hydrolysis of nitrofurans (nitrofurazone and nitrofurantoin) for
251 their determination in fish samples. EEM-kinetics data were subjected to multi-way
252 decomposition through PARAFAC and U-PCA/RTL aiming to obtain the instrumental
253 profiles and the individual contribution of the analytes. Furthermore, the scores obtained
254 from the chemometric modeling were subjected to RBF-artificial neural network (ANN) to
255 build the calibration model due to the non-linear relationship between the nominal
256 concentration and the fluorescence contribution of the analytes. It was demonstrated that U-
257 PCA/RTL coupled to RBF-ANN accomplished better results whose were comparable to the
258 chromatographic reference method.

259 Over the last years, several researches have been focused on the determination of
260 carabaryl, a carbamate insecticide that mainly degrades to 1-naphtol by hydrolysis in alkaline
261 medium. One of the reported works was centered on the carbaryl determination in effluent
262 water by following the hydrolysis reaction trough EEMs acquisition and utilizing PARAFAC
263 as chemometric modeling [33]. On the other hand, Maggio et al. extended the approach to
264 simultaneously determine carbaryl and its degradation product in natural water by employing
265 U-PLS/RTL for the data analysis [34]. Last, carbaryl, 1-naphtol and propoxur were
266 simultaneously determined in river water and the data were analyzed through U-PLS/RTL
267 and N-PLS/RTL [35]. It should be highlighted that carbaryl and 1-naphtol present large linear
268 dependence under the hydrolysis reaction, due to the fact that 1-naphtol is a hydrolysis
269 product of carbaryl. Nevertheless, by implementing U-PLS/RTL and N-PLS/RTL models

instead of PARAFAC, quantitative results were significantly improved, since the former algorithms can tackle the linear dependence situation.

The determination of tyrosine and levodopa in human plasma by oxidation catalyzed by polyphenol oxidase has been reported as model system to assess the performance of different quadrilinear decomposition models. Alternating quadrilinear decomposition (AQLD) [36], slicing AQLD (SAQLD) [37] and a four-way algorithm combination method (FACM) [38], all developed by the same research group, were reported as novel four-way calibration models and the ability of decomposing the same EEM- kinetics four-way data was assessed. The latter was proposed as an alternative of quadrilinear modeling that merges the individual particularities of PARAFAC and AQLD. In all cases, the proposed algorithms allowed the proper determination of the two analytes exploiting the second-order advantage and satisfactory analytical figures were reached. All the results aid to conclude that the inclusion of a fourth mode enhances the analytical performance over three-way calibration methods. In the case of SAQLD and FACM, comparison analysis with known quadrilinear decomposition algorithms, i.e. PARAFAC and AQLD, among others, proved that these algorithms converge faster, tolerate overestimations of the number of components and can cope with severe collinearity effects. However, results support the fact that FACM is the most suitable alternative to process four-way data with high level of noise and strong collinearity. In addition, FACM allowed accomplishing better quantitative figures than those obtained with the individual involved algorithm, i.e. PARAFAC and AQLD.

Fragoso et al. [39] have employed PARAFAC to determine thiamine (vitamin B1) in multivitamin complexes by following the thiamine conversion to thiochrome, by oxidation catalyzed by Hg^{2+} in alkaline medium. Although PARAFAC can exploit the second-order advantage, it cannot deal with matrix effects, inner filter effects or compounds that interfere

294 with the reaction mechanism or the kinetic properties. Hence, standard addition was
295 accomplished for the quantitative analysis of the analyte in multivitamin complexes.

296 In addition, Kang et al. developed a method for the quantitative kinetic analysis of the
297 degradation reaction of nicotinamide adenine dinucleotide (NADH) and the formation
298 reaction of flavin adenine dinucleotide (FAD) in human plasma [40]. These authors showed
299 good results when three-way calibration was applied. However, they suggested the four-way
300 calibration as a potential alternative, which was used to indicate if the half-life of an analyte
301 is independent of its initial concentration, being able to provide a correct decomposition and
302 regression in complex systems. The algorithms employed for the quantitation in this case
303 were PARAFAC, regularized self-weighted alternating quadrilinear decomposition
304 (RSWAQLD) and constrained alternating trilinear decomposition (CATLD).

305 Carabajal et al. employed four-way calibration for the simultaneous determination of
306 five PAHs in environmental aqueous samples by Fenton degradation [41]. In this work, it
307 was demonstrated the superiority of four-way PARAFAC modeling over three-way
308 calibration methods by mean of figures of merit and predictive ability (REP % was between
309 8 - 11 % for the four-way calibration and 11 - 17 % for the three-way calibration).
310 Interestingly, these results might support the existence of a third-order advantage. Later, the
311 Fenton reaction was utilized to quantitate bisphenol A and nonylphenol in food-contact
312 plastic by monitoring the fluorescence signal evolution. PARAFAC demonstrated being able
313 to decompose the system in absence of interferents, whereas U-PLS/RTL and MCR-ALS
314 showed to be capable to successfully solve the system in presence of uncalibrated
315 components. In all cases, satisfactory analytical figures of merit were obtained [42].

316 In 2017, a four-way method to determine azinphos-methyl (AZM) in fruits [43] by
317 means of a photochemical reaction was published. In this work, third-order data were built

318 with EEMs registered at different UV-irradiation times. The evolution of the fluorescence
319 intensity against irradiation time is depicted in the Fig. 2. The application of PARAFAC and
320 U-PLS/RTL to the gathered data enabled to favorably quantitate the analyte in presence of
321 the non-modeled interferences arising from the fruit matrix.

322 By monitoring the hydrolysis reaction, Wu's research group has recently developed a
323 method to determine irinotecan (CPT-11) in human plasma, by means of four-way data
324 analysis through alternating weighted residual constraint quadrilinear decomposition
325 (AWRCQLD) and alternating penalty quadrilinear decomposition (APQLD) [44]. The
326 results were compared with those obtained by three-way calibration and it was demonstrated
327 that even though both three- and four-way calibration methods are able to accomplish real-
328 time quantitative analysis of CPT-11 in human plasma, three-way calibration methods seem
329 to be suitable for several types of dynamic reactions, while four-way calibration methods can
330 only be applied for the analysis of first-order kinetics.

331

332 *3.2. EEMs-LC (liquid chromatography)*

333 In the multivariate calibration field, liquid chromatography (LC) coupled to
334 fluorescence spectral detection has gained increasing interest due to the potential to combine
335 high-resolution with high-sensitivity, allowing solving extremely complex systems. Over the
336 last years, several LC strategies were proposed involving the registering of EEMs to enhance
337 this potentiality. However, this analytical procedure is not a trivial matter from the
338 chemometrics standpoint. Notwithstanding modern instrumentation aids obtaining multi-
339 way data from EEM-LC experiments, the challenge of performing discrete acquisition of
340 complete fluorescence matrices in a continuous chromatographic procedure has encourage

the development of different instrumental setups, and even the development of a new fluorescence spectrophotometer.

It was in 1981 when Apellof and Davidson published the original idea of monitoring a chromatographic run through EEMs registering [45]. The report describes a method for the qualitative evaluation of effluent samples containing a mixture of fluorophores, aimed to obtain estimates on the number of components and the fluorescence spectra of each component. The data processing was performed on a unique EEM-LC three-dimensional data matrix, which was obtained by injecting the effluent sample in a HPLC system and recording the fluorescence signal with a video fluorometer. For data analysis, nonlinear iterative least squares (NILES) procedure was utilized. This work was presented as a proof of concept, to demonstrate the advantage of incrementing the number of instrumental modes, to enhance the selectivity in the resolution of the mixture components.

On the other hand, the first known research about acquisition and chemometric analysis of EEM-LC four-way data for an analytical application was reported by R. Bro, 1998 [46], who described an approach for the identification of molecular entities of thick juice. The procedure consisted in the collection of 28 discrete fractions eluting from the chromatograph, whose were then individually analyzed in a spectrofluorimeter by acquiring a complete EEM for each fraction. In that way, a three-way object was built comprising excitation spectra, emission spectra and the elution time (or fractions) for each sample. Moreover, different juice samples were identically analyzed, and a four-way array was subjected to chemometric decomposition. The author clarifies that even though the three-dimensional object corresponding to the individual samples fulfills the trilinearity property, differences in the elution time among samples cause a lack of quadrilinearity in the four-way array, which impairs the application of multilinear models, such as PARAFAC. Hence, to cope with this

situation, PARAFAC2 was proposed as the alternative to modeling this kind of data, maintaining the uniqueness of the multi-way model, obtaining the individual attributes of each components and allowing their identification.

In 2013, a new alternative to acquire EEM-LC third-order data was proposed by the Muñoz de la Peña's group for the analysis of olive oils [47]. In this work, only a chromatograph equipped with an auto-sampler and a fast-scanning fluorescence detector was used. For the acquisition of the third-order data, emission spectra were scanned at every elution time of the run; therefore, elution time-emission spectra matrices (TEMs) were gathered for each run. The third instrumental mode was obtained by recording several TEMs at different excitation wavelengths. The analysis of green pigments in olive oils was performed in 7 samples by injecting 8 aliquots of a given sample and registering the emission spectra at different excitation wavelengths. This strategy was later utilized for the determination of pesticides in fruits [48], but only 6 aliquots by sample were injected. In both works, PARAFAC and U-PLS/RTL were used for the chemometric analysis of the four-way array and prediction ability of each algorithm was assessed. Besides, N-PLS/RTL and MCR-ALS were used. The authors demonstrated that the best results were achieved when using U-PLS/RTL, due to the flexible inner structure of the algorithm, which is less sensitive to the lack of multilinearity.

The described approach was after implemented for the determination of pharmaceuticals in water in a comparative study of different EEM-LC data generation approaches. In this work, it was demonstrated that lack of quadrilinearity, as a result of differences in elution time among runs, was accompanied by a loss of trilinearity [10]. This phenomenon derives from the fact that trilinearity/quadrilinearity are only fulfilled in case the elution times are perfectly reproducible among runs. Hence, following the classification

tree for four-way data introduced by Olivieri and Escandar elsewhere [7] (see Fig. 1), non-quadrilinear data type 4 is generated since elution time and excitation wavelength modes are mutually dependent. It must be mentioned that quadrilinear decomposition models are not able to cope with this kind of data, except in case of very low degree of lack of trilinearity/quadrilinearity.

In order to improve the aforementioned results, a new data processing approach was proposed [49]. The so-called *A*PARAFAC algorithm was developed to solve four-way data using an augmented three-way structure, allowing decomposing non-quadrilinear type 1 data. It was demonstrated that this algorithm retrieves improved results in comparison to PARAFAC and similar to those obtained from U-PLS/RTL and MCR-ALS. These observations lie in the assumptions that *A*PARAFAC overcomes the lack of multilinearity drawback by virtue of the augmented structure of the data, presenting the additional advantage of obtaining physically interpretable results.

Following the path pioneered by R. Bro [46], Alcaraz et al. presented an approach [10,50,51] describing the determination of 3 fluoroquinolones in drinking water, by using EEM-LC data and chemometric analysis. Here, an automated custom-made device allowed the collection of the chromatographic fractions in 96-well plates. Subsequently, the plate with the fractions was placed into a fluorescence spectrophotometer equipped with a plate reader, allowing performing the EEMs acquisition of every individual well-plate. Once the EEMs were registered, a three-way object was built comprising the EEMs collected for every fraction. An important point to be highlighted is the fact that every EEM was individually registered in static conditions; therefore, elution time, excitation wavelength and emission wavelength modes are mutually independent, which guarantees the trilinearity of the data array. However, lack of reproducibility in elution time mode among samples leads to a break

413 in the quadrilineality of the four-way object. To model this data, several data structures were
414 built, and different algorithms were utilized to demonstrate the ability to extract meaningful
415 information of the system. For this purpose, MCR-ALS, *A*PARAFAC and PARAFAC were
416 applied to augmented two-way, augmented three-way and four-way arrays, respectively. For
417 the augmented two-way matrices, each EEM corresponding to every fraction was unfolded
418 generating row vectors that were then utilized to assembling the matrices of individual
419 samples, generating a two-dimensional data array, (elution time × excitation-emission rows).
420 Eventually, the individual samples were combined to a column-wise data object along the
421 quadrilinearity breaking-mode (Fig. 3), obtaining the augmented two-way data matrix. To
422 build the augmented three-way data array, the three-dimensional data objects of individual
423 samples (elution time × excitation wavelength × emission wavelength) were appended along
424 the elution time mode (Fig. 4) fulfilling the requirements of the trilinear modeling. The results
425 demonstrated that MCR-ALS and *A*PARAFAC are the utmost in performance dealing with
426 non-quadrilinear data and obtaining reliable and meaningful quantitative figures. The results
427 obtained in the analysis of the four-way data by MCR-ALS and APARAFAC were compared
428 to those obtained in second-order calibration method (LC × emission × samples), which
429 enables corroborate that incorporating the excitation mode, better figures of merit are
430 obtained in terms of SEN and limit of detection and quantitation. For instance, SEN figures
431 for second- and third-order calibration were 5.2 and 7.2, respectively, when MCR-ALS was
432 utilized while for PARAFAC, an increment of about 3-times the SEN value obtained for
433 second-order calibration was observed for third-order calibration [50].
434 Another strategy was recently proposed and encouraged diverse applications including
435 variations in the instrumental setup. The basis of the approach relies in the hyphenation of a
436 chromatograph and a fast-scanning spectrofluorimenter through a flow cell, allowing the

registering of EEM while the chromatographic flow is running. The first description of this procedure was reported in a review in 2017 [10]. In this work, the authors introduced the instrumental configuration that would permit the registering of successive discrete EEMs, covering the total chromatographic run. The main inconvenient found by the authors is the incompatibility between the elution rate of the analytes and the fluorescence scanning rate of the EEMs, leading to strong elution time mode-dependence with both spectral modes, which, in chemometric terms, represents a significant loss of trilinearity in the three-dimensional array for individual samples. This kind of data is classified as non-quadrilinear data of type 4, phenomenon that was firstly demonstrated and described in this report.

The first strategy that was reported to cope with the time-dependence inconvenience was published in 2017 by Escandar's group for the simultaneous quantitation of heavy-PAHs (h-PAHs) in natural water samples [52]. This work describes an interesting instrumental modification that would diminish the time-dependence effect, by a reduction in the linear flow rate of the mobile phase, which becomes as the product of the incorporation of a large inner-diameter tube between the column and the flow-cell. Thus, according to the authors, the time-dependence effect is negligent, and the third-order data of individual samples are considered as trilinear. Moreover, no lack of reproducibility in the elution time among samples was observed, then, quadrilinearity concept was fulfilled. Hence, four-way PARAFAC model was successfully implemented and satisfactory analytical figures were achieved.

Another alternative to face the time-dependence phenomenon was described for the quantitation of h-PAHs in tea leaves [53]. The authors detailed a way to deal with non-quadrilinearity data type 4 obtained from EEM-LC experiments, performed by using a conventional hyphenated instrumental setup. This work reported for the first time the

461 resolution of data with mutually dependent instrumental modes by means of the application
462 of MCR-ALS. To achieve this goal, unfolded matrices were used to build a super-augmented
463 two-way array. Unlike the strategy proposed by Alcaraz et al. [50,51], the super augmented
464 two-way data matrices were built by assembling unfolded elution time-excitation
465 wavelength × emission wavelength matrices. In that way, bilinear elution time-excitation
466 wavelength × emission wavelength matrices were obtained for individual samples that were
467 then appended along the unfolded mode generating the super-augmented two-way data
468 matrix (Fig. 5). The analytical results obtained with this strategy were similar than those
469 previously obtained [52], but experimental improvements were accomplished, e.g. shorter
470 time of analysis, less reagent consumption and less solvent waste.

471 The hyphenated instrumental configuration with a large i.d. tube earlier described [52]
472 was further applied for the determination of organic pollutants in environmental water [54].
473 Since the evaluated contaminants do not exhibit native fluorescence, a post-column
474 photoreactor was included and photoinduced EEMs were obtained. Lack of reproducibility
475 in elution time among samples was observed, and then quadrilinearity condition was not
476 fulfilled. Hence, data could not be subjected to quadrilinear decomposition and MCR-ALS
477 was applied instead. For this purpose, an augmented data matrix was assembled following
478 the strategy proposed by Alcaraz et al. [50,51]. The results demonstrated that the combination
479 of the instrumental configuration and MCR-ALS data resolution are a powerful tool to solve
480 complex systems, considering both the complexity of the sample composition and the
481 generated data.

482 At last, a new EEM detector was presented as a very promising solution to the problem
483 of non-multilinear data acquisition in time-dependent experiments [55]. Here, the basic idea
484 proposed by Myrick et al. in 1996 [56] to perform direct measurements of fluorescence

485 matrices by bidimensional excitation and emission spatial dispersion was implemented. The
486 developed device is presented as a simple, very fast, in-flow fluorescence matrix
487 spectrometer, which allows the registering of complete fluorescence images in the order of
488 milliseconds by means of a CCD camera. Figure 6 illustrates the images collected during the
489 chromatographic analysis of three dyes in water samples. The feasibility of the setup in
490 obtaining trilinear EEM-LC third-order data was successfully assessed by the evaluation of
491 a model system containing several well-known analytes through PARAFAC. A
492 chromatographic validation model was built and the data were satisfactory decomposed with
493 *A*PARAFAC by using an augmented three-way object. An additional advantage of the
494 presented approach is the capability of obtaining a large number of matrices for a short
495 chromatographic run (1450 matrices – 4.5 min run), which could not be possible
496 accomplishing until then.
497
498 *3.3. EEMs-pH*
499 In the literature, a scarce number of reports concerning four-way fluorescence
500 excitation-emission matrices coupled to pH variation has been published. Most of them are
501 focused on the development of new quadrilinear algorithms for the analysis of four-way data
502 arrays, based on the fact that, in absence of inner filter, the consequent four-way data object
503 built with several EEMs fulfills the quadrilinearity property. Under the assumption of the
504 fulfilment of the quadrilinearity principle in EEM-pH four-way data, Wu and his
505 collaborators have made important contributions to chemometrics by developing different
506 four-way decomposition algorithms (see Table 1), whose performances were properly
507 demonstrated. APQLD [20] was developed and applied for the analysis of procaine
508 hydrochloride (PRH) and its hydrolysate product, *p*-aminobenzoic acid (PAA), in plasma

509 samples. On the other hand, aiming at demonstrating a way to deal with systems that present
510 high level of collinearity, the same research group introduced the extension of self-weighted
511 alternating normalized residue fitting (SWANRF) model, for the determination of serotonin
512 in human plasma by the analysis of four-way pH-EEM data [57]. The efficiency of
513 decomposing EEM-pH four-way data through the novel AQLD algorithm was further
514 assessed by means of the simultaneous analysis of four fluoroquinolones in river water
515 samples [58]. In all cases, four-way PARAFAC decomposition was utilized as the reference
516 quadrilinear model and results were then compared.

517 In addition, a very recent work manifests that FACM algorithm can be implemented as
518 a suitable alternative to model four-way data in some particular complex cases. To
519 demonstrate the performance of the proposed combined method, a multivariate calibration
520 method based on EEM-pH data analysis was developed for the simultaneous quantitation of
521 cancer biomarkers (xanthopterin and isoxanthopterin), in plasma and urine. All the results
522 were compared with those obtained from existing four-way algorithms and demonstrated that
523 the FACM is suitable for modeling four-way data in case of high noise level and strong
524 collinearity, exploiting the individual qualities of the involved algorithms, i.e. fast
525 convergence, insensitiveness to initial estimates and excess number of components,
526 overpassing the performance of each individual algorithm [38]. Moreover, in order to explore
527 the presence of possible additional advantages achieved by third-order calibration models,
528 two recent works were published in which four-way PARAFAC models were utilized in the
529 determination of three fluorescent amino acids (L-phenylalanina, L-tyrosine and L-
530 tryptophan) in human plasma [59] and in the quantitation of three phenolic acids (gallic acid,
531 caffeine and *p*-hydroxybenzoic acid) in cosmetic samples [60]. In the latter, a comparison
532 with second-order calibration model was carried out.

A last work introduces a modification of the well-known AQLD allowing imposing constraints on the decomposition. The CAQLD algorithm was utilized in the analysis of intracellular metabolic coenzymes, FAD and flavin mononucleotide (FMN). These analytes present fluorescence spectra of strong similarity. Moreover, the samples of the cell contain several fluorescent constituents which overlap with the analyte signals. The authors demonstrated that several three-way calibration alternatives, i.e. (excitation × emission × samples), (pH × excitation × samples) and (pH × emission × samples), were not capable to solve the system due to the strong overlapping between spectra, and then, the quantitative analysis was not successful in all cases (average recoveries between 104-114 % with errors oscillating between 32-243%). Hence, four-way calibration of EEM-pH data empowered the modeling to get meaningful information about the system and to retrieve the individual contribution of the analytes. In that way, satisfactory analytical figures were reported and the analytes were successfully quantitated (average recoveries of 99.9 ± 8.4 % and 101.0 ± 10.6 % for FAD and FMN, respectively). These achievements were possible by exploiting the second-order advantage, besides the additional benefits gathered from the incorporation of the fourth instrumental mode [61].

In the all aforementioned works, the basic experimental calibration procedure, which is schematically depicted in Fig. 7, involved the preparation of several samples at different analyte concentration levels. To obtain the three instrumental modes, different pH values were adjusted to aliquots of the prepared samples and EEMs were acquired to each aliquot. In that way, the EEM-pH third-order data object was built for each sample, and the four-way data array was thereby assembled and subjected to the chemometric analysis. The results have demonstrated that second-order advantage is successfully accomplished and also have shed light on the presence of additional advantages. The authors emphasized the fact that

557 increasing the number of instrumental modes mitigates the effect of high collinearity present
558 in some systems, which represents a troublesome condition for three-way modeling.
559 Moreover, an improvement of the analytical figures was observed when the dimension of the
560 data is increased [60], a fact that has been already demonstrated by Olivieri et al. [8]. These
561 observations led the authors to the conclusion that third-order advantage may exist but need
562 to be supported with further experimental and theoretical evidences. In this regard, it is worth
563 mentioning that the majority of the evidences about the existence of the third-order advantage
564 were demonstrated through the application of quadrilinear models on data that fulfill the
565 quadrilinerity property and the results were directly compared against those obtained by
566 trilinear models on trilinear data. Hence, extensions of these studies are also needed in order
567 to strengthen the existence of the third-order advantage even in data that do not fulfill the
568 concept of multilinearity.

569 Unlike the experimental strategy described above, an in-flow methodology was
570 implemented to generate a double pH-gradient for the acquisition of four-way fluorescence
571 data. This methodology was employed for the quantitative analysis of 3 fluoroquinolones in
572 urine [62]. In this case, a fast-scanning spectrofluorimeter was connected to the end of the
573 flow injection system, through a flow-cell, and successive EEMs were registered while the
574 pH was changing. Owing to produce the double pH gradient into the flow stream, a sample
575 at alkaline pH was injected into the carrier that consisted in the same sample solution but
576 adjusted at low pH. The authors clarify that, in in-flow pH-gradient systems, loss of
577 quadrilinearity in the data can occur due to the lack of reproducibility in the generation of the
578 pH gradient and by virtue of the pH-spectral modes dependency. Moreover, the closure
579 relationship between pH-equilibrating species should be considered in pH-dependence
580 experiments, due to the fact that the involved species are mutually correlated. However, the

581 authors did not find these inconveniences and the resolution were successfully accomplished
582 by using four-way PARAFAC. The authors ascribed this achievement to the fact that changes
583 in the total contribution of the analytes in the flow stream, and undesired effects of the
584 instrumental mode-dependence, are avoided by implementing the proposed experimental
585 procedure.
586
587 *3.4. EEMs - Time resolved fluorescence*
588 Interesting, the original reported paper using time resolved fluorescence four-way data
589 date back to as early as 1990 [63]. In that report, a three-way excitation × emission × lifetime
590 array was generated. To generate the array, several EEMs were acquired at different
591 modulation frequencies. Using this approach, a binary mixture of benzo[b]fluoranthene
592 (B[b]F) and B[k]F was successfully resolved through generalized rank annihilation method
593 (GRAM) [63].
594 Twenty two years later, a work using fluorescence time resolved excitation-emission
595 cube arrays (TREECs) was reported for the quantitation of 15 PAHs in soil samples [64].
596 The target analytes were extracted from soil samples and analyzed through laser excited time-
597 resolved Shpol'skii spectroscopy (LETRSS). Here, the third instrumental mode was achieved
598 by selecting six different time delays in the order of the nanoseconds. Owing to the presence
599 of matrix effect, a standard addition method was implemented for calibration and four
600 TREECs were recorded for each sample. It was noticed that, for non-spiked samples, the
601 relative signal contribution of each PAH changes with the time window, affecting positively
602 the selectivity of the method. With the acquired TREECs data, a four-way array was
603 constructed, and two different models were applied: PARAFAC and U-PLS/RTL, which
604 enabled achieving highly satisfactory results.

605 *3.5. EEMs - other chemical treatment*

606 In addition to the above described techniques, there are other reported alternatives that
607 allow incrementing the number of instrumental modes of the data, by using a distinct
608 chemical treatment.

609 The pioneering strategy implemented was the reported by Ross et al. who used different
610 levels of potassium iodide as fluorescence quencher to solve a system composed by a mixture
611 of dyes [65]. After, same group developed a method based on the variation of Mg^{2+} to resolve
612 the fluorescence spectra of pigment-complexes in pea thylakoids by utilizing PARAFAC
613 [66]. Here, the resolution relied on the fact that Mg^{2+} differently affects the different pigment-
614 complexes. In a similar way, Ross and Leurgans evaluated the fluorescence behavior of 2-p-
615 toluidinonphthalene-6-sulphonate (TNS) in presence of different concentrations of Tb^{3+} in a
616 suspension of chloroplast membranes [67]. In 2001, other study reported a work that employs
617 several concentrations of nitromethane as quencher for the resolution of different synthetic
618 mixtures of PHAs [68]. Here, several EEMs were registered varying the quencher
619 concentrations and the third-order data were further decomposed by TLD method. All these
620 works were developed with qualitative aims, in which a unique three-dimensional array was
621 decomposed with trilinear method decomposition.

622 It is known that in the analysis of samples of complex composition, the matrix effect
623 negatively affects the development of quantitative methods. To overcome this phenomenon,
624 a clever strategy was proposed by utilizing different volumes of sample acting as quencher
625 as the third instrumental mode in the acquisition of the third-order data. In this regard, a
626 method for the quantitation of tetracycline in tea solutions was reported in 2009 [69]. The
627 change in the fluorescence intensity of fluorescence caused by the quencher quantity was
628 employed to obtain the four-way array. The data analysis was accomplished with PARAFAC

629 and N-PLS, obtaining better results with the latter model. The same strategy was followed
630 for the determination of several carbamate pesticides (carbaryl, carbendazim and 1-naphthol)
631 implementing the standard addition method for the quantitation in lettuce [70]. Here, three
632 dilution levels of the matrix extract were utilized to create the third instrumental mode of the
633 data. Further, a four-way array was built and decomposed by PARAFAC. Similarly, in 2011,
634 another publication reports a third-order calibration method for the determination of
635 oxaprozin in human plasma in presence of inherent plasma interferents [71]. For this purpose,
636 EEMs of every sample were acquired at different volume of plasma in order to create the
637 third mode of the data. PARAFAC and AWRCQLD were used to decompose the four-way
638 data for the quantitative analysis. The obtained results were compared to those obtained by
639 second-order calibration, in which no standard addition was performed. This comparison
640 demonstrated an improvement in the quantitative results when the extra mode (volume of
641 sample) was included, principally in the predictive analysis (average recoveries between 155-
642 367% and 95-97% for second- and third-order calibration, respectively). These figures
643 validate the hypothesis that problems of collinearity are solved by the introduction of the
644 extra mode, leading to an improvement in the resolution and the quantitative performance of
645 the method. Moreover, this evidence shed light on the existence of the third-order advantage.
646 Exploiting the particularity of fluorescence components in being sensitive to the nature
647 of the solvent medium, Zhang et al. introduced the strategy of varying the solvent medium
648 as third instrumental mode in a four-way calibration method. The purpose of the method was
649 the quantitation of active ingredients of Schisandra chinensis (schizandrol A and schizandrol
650 B) in Dulbecco´s modified eagle medium (DMEM) samples [72]. SWANRF and PARAFAC
651 were chosen as chemometric tools, which allowed tackling problems of high overlapping

652 degree between components and significant chemical information about the system was
653 successfully gathered.

654 Differences in solvent solutions have been also employed as fourth mode. Hence, two
655 solvent media, with presence and absence of β-cyclodextrin in 10 % methanol-water solution,
656 were used for the determination of aflatoxins B1 and B2 in peanut samples. EEMs were
657 collected in both solvents obtaining the four-way data. After converting the data to
658 augmented three-way data, several three-way methods, BLLS-RBL and PARAFAC, were
659 applied [73].

660 Interesting, to best of our knowledge, only one work based on the generation of four-
661 way data for classification analysis has been published [74]. This study informs a
662 methodology for the classification of grapes (*Tempranillo*) according the maturation stage
663 and the hydric status. For EEM data acquisition, front-face fluorescence modality was used.
664 The extra mode was built by changing the nature of the solvent of extraction (extracts in
665 water were re-extracted with diethyl ether). Hence, the excitation × emission × extraction
666 solvent × samples four-way array was obtained. PARAFAC-linear discriminant analysis
667 (LDA) and LDA-U-PLS were further employed to discriminate the samples. The addition of
668 a second solvent allowed discrimination of samples with different hydric status whose EEMs
669 were quite similar, increasing both selectivity and sensitivity. The results obtained for the
670 differentiation between maturation stages were the same, independently of the data order
671 used.

672

673 *3.6. EEMs-five-way*

674 Although *N*th-order multivariate calibration is possible to accomplish with modern
675 instrumentation, only three analytical applications of fluorescence fourth-order/five-way data

676 have been reported. The first reported method allowed the determination of carbaryl in water
677 samples in presence of other two pesticides, fuberidazole and thialbendazole, acting as
678 interferents [75]. The fourth-order data corresponding to individual samples were obtained
679 by registering several EEMs during the kinetic hydrolysis reaction of carbaryl to 1-naphtol
680 at different pH values. The gathered data were processed with U-PLS with residual
681 quadrilinearization (U-PLS/RQL) algorithm, which is the quadrilinear extension of U-
682 PLS/RTL. The obtained results demonstrated the superiority in performance of this algorithm
683 over PARAFAC in terms of predictive ability. In comparison to PARAFAC (RMSE of 9.3
684 μg L^{-1} and REP of 6.2 %), lower RMSE and REP values were obtained with U-PLS/RQL
685 model (7.0 μg L^{-1} and 4.7 %). These results are consequences of the inherent latent-structured
686 flexibility of U-PLS/RQL, which allows processing data that are not strictly quadrilinear.
687 A second report introduced a new fourth-order calibration algorithm, alternating fitting
688 weighted residue quinquelinear decomposition (AFWRQQLD). The algorithm was
689 employed for the analysis of the imidacloprid in environmental waters. Since the analyte has
690 no intrinsic fluorescence in aqueous medium, samples were irradiated with UV light in
691 alkaline medium in order to obtain a fluorescent product. The fourth-order data of each
692 sample was obtained by recording EEM at different UV irradiation times for different
693 volumes of sample, and the five-way data were built by joining the fourth-order objects
694 obtained for different samples. The five-way object was further decomposed by
695 AFWRQQLD, allowing to overcome the matrix effect by introducing the volume of
696 environmental water as an extra instrumental mode [76]. This observation was demonstrated
697 with the RMSE and REP % values, which were extraordinarily lower (7.4 ng mL^{-1} and
698 8.4 %) than those obtained in four-way calibration methods, utilizing AFRQLD, AWRCQLD

699 and PARAFAC algorithms to model four-way EEM-kinetics data (47.2-51.9 ng mL^{-1} and
700 17.3 -19.6 %) [76].

701 At last, the most recent article reports the determination of diclofenac sodium in river
702 water samples. It should be remarked that diclofenac sodium shows unstable fluorescence in
703 aqueous medium and, then, its fluorimetric determination is challenging. This work proposed
704 a five-way calibration method to deal with this phenomena, which is based in the registering
705 of several EEM at different irradiation time by varying the pH [77]. The obtained data array
706 (excitation × emission × irradiation × pH × concentration) was decomposed by
707 AFWRQQLD, PARAFAC and alternating quinquelinear decomposition (AQQLD)
708 algorithms [78]. This procedure allowed to successfully determinate the analyte in real
709 complex samples, even in the presence of indomethacin as interferent.
710

711 **4. Phosphorescence EEMs**

712 *4.1. EEMs - kinetics (room temperature phosphorescence)*

713 The unique report on room-temperature phosphorescence (RTP) based approach is the
714 one combining RTP data with kinetics [79]. The RTP four-way data were obtained by
715 following the kinetic evolution of phosphorescence EEMs (EEPMs). PARAFAC, AQLD and
716 AWRCQLD were used for the data decomposition. The three methodologies gave
717 satisfactory results, but AQLD seemed to provide better results in terms of recovery study,
718 SEN and selectivity figures, as well as demonstrated to be insensitive to the excess of factors
719 used in calculation, indicating that it was a promising alternative to existing chemometric
720 tools. The method was applied for the determination of carbaryl in tap water samples by
721 following the hydrolysis kinetics of the analyte in presence of uncalibrated phosphorescence
722 backgrounds, unexpected components and spectral background drift.

723

724 *4.2. EEMs - time resolved phosphorescence*

725 A literature search reveals that the unique work reported employing EEMs time
726 resolved phosphorescence was carried out by setting different excitation wavelengths in
727 order to obtain wavelength–time matrices (WTMs) [80]. This array is a series of emission
728 spectra at a single excitation wavelength registered at different time delays after a laser
729 excitation pulse. In this way, the third-order data, excitation-modulated WTM (EMWTM),
730 is finally obtained, which can be appreciated in Fig. 8. These particular data, based on laser-
731 excited time-resolved Shpol'skii phosphorescence spectroscopy, were used for the
732 quantitation of 2,3,7,8-tetrachloro-dibenzo-para-dioxin in extremely contaminated waters.
733 Interestingly, both high sensitivity and significant increasing on selectivity were
734 accomplished by means of a proper four-way PARAFAC modeling. Concentrations of the
735 analyte in the order of parts-per-trillion were reached even in samples with a large number
736 of spiked compounds acting as interferents.

737

738 **5. Conclusions**

739 The growing interest in multi-way analysis is reflected in the large number of reports
740 that are found in the literature. Numerous analytical applications based on multivariate
741 calibration have been developed capitalizing on the advantages offered by the higher-order
742 modeling. Nonetheless, third- and fourth-order analytical applications are still scarce despite
743 all the benefits that have been demonstrated for third- and fourth-order calibration analysis.

744 In the field of the third-order/four-way and fourth-order/five-way calibrations,
745 luminescence-based analytical protocols are the most utilized for the determination of a large
746 number of compounds in samples of diverse composition. Luminescence techniques

747 (fluorescence and phosphorescence) offer exceptional analytical properties, such as high-
748 sensitivity and selectivity, that enabled solving complex samples. It has been demonstrated
749 that the analysis of total excitation-emission luminescence signals coupled to an additional
750 instrumental variation, e.g., chromatography, kinetics, pH variation, empowers the
751 performance of the analytical procedures. Consequently, the synergistic effect of combining
752 excitation-emission luminescence data with higher-order calibration has been widely
753 exploited. In this regards, environmental, biological and food samples, among other, have
754 been successfully analyzed through higher-order multivariate calibration.

755 The main conclusions about benefits, limitations and potentials of the developed
756 methodologies using four- and five-way luminescence have been summarized in this review,
757 and the existence of additional advantages over the known second-order advantage was
758 exposed. The main benefits that have been supported with experimental evidences by a
759 number of authors are 1) the possibility of decomposing a data array for each sample and
760 independent of other samples, 2) the enhancement of the sensitivity and selectivity and more
761 resolving power than three-way methods, by incorporation of additional information of the
762 sample through a third instrumental mode and 3) the possibility to tackle collinearity
763 problems. However, more works on the development on the fundamental theories are needed
764 to fully understand the properties of third– and fourth-order calibration. In addition, new
765 applications methods are needed to elucidate the advantages associated to higher–order
766 calibration strategies, even in data that do not fulfill the concept of multilinearity. In these
767 regards, it should be highlighted that beside all the analytical benefits that were widely
768 demonstrated in terms of analytical figures and chemometric matter, a comprehensive
769 evaluation involving instrumental requirements and experimental work is recommended to

770 provide stronger evidences about the potentialities of the higher-order based calibration
771 methods.
772
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References

[1] G.M. Escandar, N.K.M. Faber, H.C. Goicoechea, A. Muñoz de la Peña, A.C. Olivieri, R.J. Poppi, Second- and third-order multivariate calibration: data, algorithms and applications, Trends Anal. Chem. 26 (2007) 752–765.

[2] A.C. Olivieri, G.M. Escandar, A. Muñoz de la Peña, Second-order and higher-order multivariate calibration methods applied to non-multilinear data using different algorithms, Trends Anal. Chem. 30 (2011) 607–617.

[3] A.C. Olivieri, Recent advances in analytical calibration with multi-way data, Anal. Methods. 4 (2012) 1876–1886.

[4] G.M. Escandar, H.C. Goicoechea, A. Muñoz de la Peña, A.C. Olivieri, Second- and higher-order data generation and calibration: A tutorial, Anal. Chim. Acta. 806 (2014) 8–26.

[5] G.M. Escandar, A.C. Olivieri, A road map for multi-way calibration models, Analyst. 142 (2017) 2862–2873.

[6] A. Muñoz de la Peña, A.C. Olivieri, G.M. Escandar, H.C. Goicoechea, Fundamentals and analytical applications of multiway calibration, Elsevier, Amsterdam, 2015.

[7] A.C. Olivieri, G.M. Escandar, Practical Three-Way Calibration, Elsevier, Waltham, 2014.

[8] A.C. Olivieri, Analytical figures of merit: From univariate to multiway calibration, Chem. Rev. 114 (2014) 5358–5378.

[9] J.A. Arancibia, P.C. Damiani, G.M. Escandar, G.A. Ibañez, A.C. Olivieri, A review on second- and third-order multivariate calibration applied to chromatographic data, J. Chromatogr. B Anal. Technol. Biomed. Life Sci. 910 (2012) 22–30.

[10] M. Montemurro, G.G. Siano, M.R. Alcaráz, H.C. Goicoechea, Third order chromatographic-excitation–emission fluorescence data: Advances, challenges and prospects in analytical applications, Trends Anal. Chem. 93 (2017) 119–133.

[11] K.M. Pierce, B. Kehimkar, L.C. Marney, J.C. Hoggard, R.E. Synovec, Review of chemometric analysis techniques for comprehensive two dimensional separations data, J. Chromatogr. A. 1255 (2012) 3–11.

[12] G.M. Escandar, A.C. Olivieri, Multi-way chromatographic calibration — A review, J. Chromatogr. A. 1587 (2019) 2–13.

[13] A.C. Olivieri, P.L. Pisano, A. Muñoz de la Peña, H.C. Goicoechea, Data Analysis, in: S. Fanali, P.R. Haddad, C.F. Poole, M.L. Riekkola (Eds.), Liq. Chromatogr. Vol. 1. Fundam. Instrumentation., 2nd ed., Elsevier, Netherlands, 2017: pp. 515–528.

[14] K.S. Booksh, B.R. Kowalski, Theory of Analytical Chemistry, Anal. Chem. 66 (1994) 782A–791A.

[15] A.C. Olivieri, Analytical advantages of multivariate data processing. One, two, three, infinity?, Anal. Chem. 80 (2008) 5713–5720.

[16] H.L. Wu, J.F. Nie, Y.J. Yu, R.Q. Yu, Multi-way chemometric methodologies and applications : A central summary of our research work, Anal. Chim. Acta. 650 (2009) 131–142.

[17] A.E. Sinha, J.L. Hope, B.J. Prazen, C.G. Fraga, E.J. Nilsson, R.E. Synovec, Multivariate selectivity as a metric for evaluating comprehensive two-dimensional gas chromatography – time-of-flight mass spectrometry subjected to chemometric peak deconvolution, J. Chromatogr. A. 1056 (2004) 145–154.

[18] A.E. Sinha, B.J. Prazen, R.E. Synovec, Trends in chemometric analysis of comprehensive two-dimensional separations, Anal Bioanal Chem. 378 (2004) 1948–1951.

[19] N.D. Sidiropoulos, R. Bro, On the uniqueness of multilinear decomposition of N -way arrays, J. Chemom. 14 (2000) 229–239.

[20] A.L. Xia, H.L. Wu, S.F. Li, S.H. Zhu, L.Q. Hu, R.Q. Yu, Alternating penalty quadrilinear decomposition algorithm for an analysis of four-way data arrays, J. Chemom. 21 (2007) 133–144.

[21] H.L. Wu, Y. Li, R.Q. Yu, Recent developments of chemical multiway calibration methodologies with second-order or higher-order advantages, J. Chemom. 28 (2013) 476–489.

[22] R.P.H. Nikolajsen, K.S. Booksh, Å.M. Hansen, R. Bro, Quantifying catecholamines using multi-way kinetic modelling, Anal. Chim. Acta. 475 (2003) 137–150.

[23] Y.C. Kim, J.A. Jordan, M.L. Nahorniak, K.S. Booksh, Photocatalytic degradation-excitation - emission matrix fluorescence for increasing the selectivity of polycyclic aromatic hydrocarbon analyses, Anal. Chem. 77 (2005) 7679–7686.

[24] M.L. Nahorniak, G.A. Cooper, Y.C. Kim, K.S. Booksh, Three- and four-way parallel factor (PARAFAC) analysis of photochemically induced excitation-emission kinetic fluorescence spectra, Analyst. 130 (2005) 85–93.

[25] A.C. Olivieri, J.A. Arancibia, A. Muñoz de la Peña, I. Durán-Merás, A. Espinosa Mansilla, Second-order advantage achieved with four-way fluorescence excitation-emission-kinetic data processed by parallel factor analysis and trilinear least-squares. Determination of methotrexate and leucovorin in human urine, Anal. Chem. 76 (2004) 5657–5666.

[26] J.A. Arancibia, A.C. Olivieri, D.B. Gil, A.E. Mansilla, I. Durán-Merás, A. Muñoz de la Peña, Trilinear least-squares and unfolded-PLS coupled to residual trilinearization: New chemometric tools for the analysis of four-way instrumental data, Chemom. Intell. Lab. Syst. 80 (2006) 77–86.

[27] A. D, Muñoz de la Peña, I. Durán Merás, A. Jiménez Girón, Four-way calibration applied to the simultaneous determination of folic acid and methotrexate in urine samples, Anal. Bioanal. Chem. 385 (2006) 1289–1297.

[28] A. Muñoz de la Peña, I.D. Merás, A. Jiménez Girón, H.C. Goicoechea, Evaluation of unfolded-partial least-squares coupled to residual trilinearization for four-way calibration of folic acid and methotrexate in human serum samples, Talanta. 72 (2007) 1261–1268.

[29] P.C. Damiani, I. Durán-Merás, A. García-Reiriz, A. Jiménez-Girón, A. Muñoz de la Peña, A.C. Olivieri, Multiway partial least-squares coupled to residual trilinearization: A genuine multidimensional tool for the study of third-order data. Simultaneous analysis of procaine and its metabolite p-aminobenzoic acid in equine serum, Anal. Chem. 79 (2007) 6949–6958.

[30] A. Jiménez Girón, I. Durán-Merás, A. Espinosa-Mansilla, A. Muñoz de la Peña, F. Cañada Cañada, A.C. Olivieri, On line photochemically induced excitation-emission-kinetic four-way data. Analytical application for the determination of folic acid and its two main metabolites in serum by U-PLS and N-PLS/residual trilinearization (RTL) calibration, Anal. Chim. Acta. 622 (2008) 94–103.

[31] A. García-Reiriz, P.C. Damiani, A.C. Olivieri, F. Cañada-Cañada, A. Muñoz de la Peña, Nonlinear four-way kinetic-excitation-emission fluorescence data processed by a variant of parallel factor analysis and by a neural network model achieving the second-order advantage: malonaldehyde determination in olive oil samples, Anal. Chem. 80 (2008) 7248–7256.

[32] Y. Ni, Y. Gu, S. Kokot, Multiway calibrations based on spectrofluorimetric data derived from kinetic analysis of the hydrolysis reaction of nitrofurans - A comparison of prediction performance, Chemom. Intell. Lab. Syst. 112 (2012) 55–64.

[33] S.H. Zhu, H.L. Wu, A.L. Xia, J.F. Nie, Y.C. Bian, C.B. Cai, R.Q. Yu, Excitation-emission-kinetic fluorescence coupled with third-order calibration for quantifying carbaryl and investigating the hydrolysis in effluent water, Talanta. 77 (2009) 1640–1646.

[34] R.M. Maggio, P.C. Damiani, A.C. Olivieri, Four-way kinetic-excitation-emission fluorescence data processed by multi-way algorithms. Determination of carbaryl and 1-naphthol in water samples in the presence of fluorescent interferents, Anal. Chim. Acta. 677 (2010) 97–107.

[35] P. Santa-Cruz, A. García-Reiriz, Application of third-order multivariate calibration algorithms to the determination of carbaryl, naphthol and propoxur by kinetic

spectroscopic measurements, Talanta. 128 (2014) 450–459.

[36] L.X. Xie, H.L. Wu, Y. Fang, C. Kang, S.X. Xiang, L. Zhu, X.L. Yin, H.W. Gu, Z. Liu, R.Q. Yu, Simultaneous determination of tyrosine and levodopa in human plasma using enzyme-induced excitation-emission-kinetic third-order calibration method, Chemom. Intell. Lab. Syst. 148 (2015) 9–19.

[37] L.X. Xie, H.L. Wu, X.H. Zhang, T. Wang, L. Zhu, S.X. Xiang, Z. Liu, R.Q. Yu, "Slicing" data array in quadrilinear component model: An alternative quadrilinear decomposition algorithm for third-order calibration method, Chemom. Intell. Lab. Syst. 167 (2017) 12–22.

[38] T. Wang, H. Wu, L. Xie, W. Long, L. Cheng, R. Yu, A novel quadrilinear decomposition method for four-way data arrays analysis based on algorithms combination strategy : Comparison and application, Chemom. Intell. Lab. Syst. 185 (2019) 92–104.

[39] W.D. Fragoso, A.C. Olivieri, Chemometric modeling of kinetic-fluorescent third-order data for thiamine determination in multivitamin complexes, Microchem. J. 128 (2016) 42–46.

[40] C. Kang, H.L. Wu, C. Zhou, S.X. Xiang, X.H. Zhang, Y.J. Yu, R.Q. Yu, Quantitative fluorescence kinetic analysis of NADH and FAD in human plasma using three- and four-way calibration methods capable of providing the second-order advantage, Anal. Chim. Acta. 910 (2016) 36–44.

[41] M.D. Carabajal, J.A. Arancibia, G.M. Escandar, Excitation-emission fluorescence-kinetic data obtained by Fenton degradation. Determination of heavy-polycyclic aromatic hydrocarbons by four-way parallel factor analysis, Talanta. 165 (2017) 52–63.

[42] M.D. Carabajal, J.A. Arancibia, G.M. Escandar, Excitation-emission fluorescence-kinetic third-order/four-way data: Determination of bisphenol A and nonylphenol in food-contact plastics, Talanta. 197 (2019) 348–355.

[43] M. Montemurro, G.G. Siano, M.J. Culzoni, H.C. Goicoechea, Automatic generation of photochemically induced excitation-emission-kinetic four-way data for the highly selective determination of azinphos-methyl in fruit juices, Sensors Actuators B Chem. 239 (2017) 397–404.

[44] X.L. Yin, H.W. Gu, X.L. Liu, S.H. Zhang, H.L. Wu, Comparison of three-way and four-way calibration for the real-time quantitative analysis of drug hydrolysis in complex dynamic samples by excitation-emission matrix fluorescence, Spectrochim. Acta - Part A Mol. Biomol. Spectrosc. 192 (2018) 437–445.

[45] C.J. Appellof, E.R. Davidson, Strategies for analyzing data from video fluorometrics monitoring of liquid chromatographic effluents, Anal. Chem. 53 (1981) 2053–2056.

[46] R. Bro, Multi-way analysis in the food industry. Models, algorithms and applications., University of Amsterdam, Nethterlands, 1998.

[47] V.A. Lozano, A. Muñoz de la Peña, I. Durán-Merás, A. Espinosa, G.M. Escandar, Four-way multivariate calibration using ultra-fast high-performance liquid chromatography with fluorescence excitation – emission detection. Application to the direct analysis of chlorophylls a and b and pheophytins a and b in olive oils, Chemom. Intell. Lab. Syst. 125 (2013) 121–131.

[48] M. Montemurro, L. Pinto, G. Véras, A. De Araújo, Highly sensitive quantitation of pesticides in fruit juice samples by modeling four-way data gathered with high-performance liquid chromatography with fluorescence excitation-emission detection, Talanta. 154 (2016) 208–218.

[49] S.A. Bortolato, V.A. Lozano, A. Muñoz de la Peña, A.C. Olivieri, Novel augmented parallel factor model for four-way calibration of high-performance liquid chromatography – fluorescence excitation – emission data, Chemom. Intell. Lab. Syst. 141 (2015) 1–11.

[50] M.R. Alcaraz, G.G. Siano, M.J. Culzoni, A. Muñoz de la Peña, H.C. Goicoechea, Modeling four and three-way fast high-performance liquid chromatography with fluorescence detection data for quantitation of fluoroquinolones in water samples,

Anal. Chim. Acta. 809 (2014) 37–46.

[51] M.R. Alcaráz, S.A. Bortolato, H.C. Goicoechea, A.C. Olivieri, A new modeling strategy for third-order fast high-performance liquid chromatographic data with fluorescence detection. Quantitation of fluoroquinolones in water samples, Anal. Bioanal. Chem. 407 (2015) 1999–2011.

[52] M.D. Carabajal, J.A. Arancibia, G.M. Escandar, On-line generation of third-order liquid chromatography – excitation-emission fluorescence matrix data . Quantitation of heavy-polycyclic aromatic hydrocarbons, J. Chromatogr. A. 1527 (2017) 61–69.

[53] M.D. Carabajal, J.A. Arancibia, G.M. Escandar, Multivariate curve resolution strategy for non-quadrilinear type 4 third- order / four way liquid chromatography – excitation-emission fluorescence matrix data, Talanta. 189 (2018) 509–516.

[54] R.B. Pellegrino Vidal, A.C. Olivieri, G.A. Ibañez, G.M. Escandar, Online third-order liquid chromatographic data with native and photoinduced fluorescence detection for the quantitation of organic pollutants in environmental water, ACS Omega. 3 (2018) 15771–15779.

[55] M.R. Alcaraz, E. Morzán, C. Sorbello, H.C. Goicoechea, R. Etchenique, Multiway analysis through direct excitation-emission matrix imaging, Anal. Chim. Acta. 1032 (2018) 32–39.

[56] A.R. Muroski, K.S. Booksh, M.L. Myrick, Single-measurement excitation/emission matrix spectrofluorometer for determination of hydrocarbons in ocean Water. 1. Instrumentation and background correction, Anal. Chem. 68 (1996) 3534–3538.

[57] Y.J. Liu, H.L. Wu, C. Kang, H.W. Gu, J.F. Nie, S.S. Li, Z.Y. Su, R.Q. Yu, Four-way self-weighted alternating normalized residue fitting algorithm with application for the analysis of serotonin in human plasma, Anal. Sci. 28 (2012) 1097–1104.

[58] C. Kang, H.L. Wu, Y.J. Yu, Y.J. Liu, S.R. Zhang, X.H. Zhang, R.Q. Yu, An alternative quadrilinear decomposition algorithm for four-way calibration with application to analysis of four-way fluorescence excitation – emission – pH data array, 758 (2013)

45–57.

[59] C. Kang, H.L. Wu, L.X. Xie, S.X. Xiang, R.Q. Yu, Direct quantitative analysis of aromatic amino acids in human plasma by four-way calibration using intrinsic fluorescence: Exploration of third-order advantages, Talanta. 122 (2014) 293–301.

[60] X. Zhang, X. Qing, H. Wu, Discussion on the superiority of third-order advantage : Analytical application for four-way data in complex system, Microchem. J. 145 (2019) 1078–1085.

[61] C. Kang, H. Wu, M. Xu, X. Yan, Y. Liu, R. Yu, Simultaneously quantifying intracellular FAD and FMN using a novel strategy of intrinsic fluorescence four-way calibration, Talanta. 197 (2019) 105–112.

[62] A.P. Pagani, G.A. Ibañez, Four-way calibration applied to the processing of pH-modulated fluorescence excitation-emission matrices . Analysis of fluoroquinolones in the presence of significant spectral overlapping, Microchem. J. 132 (2017) 211–218.

[63] D.W. Burdick, D.S.; Tu, X.M.; McGown, L.B.; Millican, Resolution of multicomponent fluorescent mixtures by analysis of the excitation-emission-frequency array, J. Chemom. 4 (1990) 15–28.

[64] H.C. Goicoechea, S. Yu, A.F.T. Moore, A.D. Campiglia, Four-way modeling of 4.2 K time-resolved excitation emission fluorescence data for the quantitation of polycyclic aromatic hydrocarbons in soil samples, Talanta. 101 (2012) 330–336.

[65] R.T. Leurgans, S.; Ross, Multilinear models: Applications in spectroscopy, Stat. Sci. 7 (1992) 289–319.

[66] R.T. Ross, C. Lee, C.M. Davis, B.M. Ezzeddine, E.A. Fayyad, S.E. Leurgans, Resolution of the fluorescence spectra of plant pigment-complexes using trilinear models, Biochim. Biophys. Acta. 1056 (1991) 317–320.

[67] R.T. Ross, S. Leurgans, Component resolution using multilinear models, in: K. Sauer (Ed.), Methods Enzymol., Academic Press, 1995: pp. 679–700.

[68] P.D. Wentzell, S.S. Nair, R.D. Guy, Three-way analysis of fluorescence spectra of polycyclic aromatic hydrocarbons with quenching by nitromethane, Anal. Chem. 73 (2001) 1408–1415.

[69] N. Rodríguez, M.C. Ortiz, L.A. Sarabia, Fluorescence quantification of tetracycline in the presence of quenching matrix effect by means of a four-way model, Talanta. 77 (2009) 1129–1136.

[70] L. Rubio, L.A. Sarabia, M.C. Ortiz, Standard addition method based on four-way PARAFAC decomposition to solve the matrix interferences in the determination of carbamate pesticides in lettuce using excitation-emission fluorescence data, Talanta. 138 (2015) 86–99.

[71] H.Y. Fu, H.L. Wu, Y.J. Yu, L.L. Yu, S.R. Zhang, J.F. Nie, S.F. Li, R.Q. Yu, A new third-order calibration method with application for analysis of four-way data arrays, J. Chemom. 25 (2011) 408–429.

[72] X.H. Zhang, H.L. Wu, X.L. Yin, Y. Li, X.D. Qing, H.W. Gu, C. Kang, R.Q. Yu, Exploiting third-order advantage using four-way calibration method for direct quantitative analysis of active ingredients of Schisandra chinensis in DMEM by processing four-way excitation-emission-solvent fluorescence data, Chemom. Intell. Lab. Syst. 155 (2016) 46–53.

[73] S.M. Sajjadi, H. Abdollahi, R. Rahmanian, L. Bagheri, Quantifying aflatoxins in peanuts using fl uorescence spectroscopy coupled with multi-way methods : Resurrecting second-order advantage in excitation – emission matrices with rank overlap problem, Spectrochim. Acta Part A Mol. Biomol. Spectrosc. 156 (2016) 63–69.

[74] M. Cabrera-Bañegil, E. Valdés-Sánchez, A. Muñoz de la Peña, I. Durán-Merás, Combination of fluorescence excitation emission matrices in polar and non-polar solvents to obtain three- and four-way arrays for classification of Tempranillo grapes according to maduration stage and hydric status, Talanta. 199 (2019) 652–661.

[75] R.M. Maggio, A. Muñoz de la Peña, A.C. Olivieri, Unfolded partial least-squares with

residual quadrilinearization: A new multivariate algorithm for processing five-way data achieving the second-order advantage. Application to fourth-order excitation-emission-kinetic-pH fluorescence analytical data, Chemom. Intell. Lab. Syst. 109 (2011) 178–185.

[76] J. Nie, B. Li, Y. Zhang, J. Fan, Z. Yi, Z. Cai, High-order calibration for the spectrofluorimetric determination of pesticides based on photochemical derivatization. A solution of the problems of inner- filter effects and matrix interferences in complex environmental water., Chemom. Intell. Lab. Syst. 156 (2016) 36–53.

[77] J. Li, J. Xu, W. Jin, Z. Yi, C. Cai, X. Huang, J. Nie, Y. Zhang, Fluorescent kinetics combined with fourth-order calibration for the determination of diclofenac sodium in environmental water, Anal. Bioanal. Chem. (2019).

[78] X.D. Qing, H.L. Wu, X.H. Zhang, Y. Li, H.W. Gu, R.Q. Yu, A novel fourth-order calibration method based on alternating quinquelinear decomposition algorithm for processing high performance liquid chromatography – diode array detection – kinetic-pH data of naptalam hydrolysis, Anal. Chim. Acta. 861 (2015) 12–24.

[79] X.D. Qing, H.L. Wu, X.F. Yan, Y. Li, L.Q. Ouyang, C.C. Nie, R.Q. Yu, Development of a novel alternating quadrilinear decomposition algorithm for the kinetic analysis of four-way room-temperature phosphorescence data, Chemom. Intell. Lab. Syst. 132 (2014) 8–17.

[80] H.C. Goicoechea, S. Yu, A.C. Olivieri, A.D. Campiglia, Four-way data coupled to parallel factor model applied to environmental analysis: Determination of 2,3,7,8-tetrachloro-dibenzo-para-dioxin in highly contaminated waters by solid-liquid extraction laser-excited time-resolved Shpol'skii spectroscopy, Anal. Chem. 77 (2005) 2608–2616.

[81] R. Bro, PARAFAC. Tutorial and applications, Chemom. Intell. Lab. Syst. 38 (1997) 149–171.

[82] S.J. Mazivila, S.A. Bortolato, A.C. Olivieri, Chemometrics and Intelligent Laboratory

Systems MVC3 _ GUI : A MATLAB graphical user interface for third-order multivariate calibration . An upgrade including new multi-way models, Chemom. Intell. Lab. Syst. 173 (2018) 21–29.

[83] X. Qing, H. Wu, X. Yan, Y. Li, L. Ouyang, C. Nie, R. Yu, Development of a novel alternating quadrilinear decomposition algorithm for the kinetic analysis of four-way room-temperature phosphorescence data, Chemom. Intell. Lab. Syst. 132 (2014) 8–17.

[84] J. Jaumot, R. Gargallo, A. de Juan, A graphical user-friendly interface for MCR-ALS: a new tool for multivariate curve resolution in MATLAB, Cheometrics Intell. Lab. Syst. 76 (2005) 101–110.

[85] H.A.L. Kiers, J.M.F. Berge, R. Bro, PARAFAC2 - Part I. Direct fitting algorithm for the PARAFAC2 model, J. Chemom. 294 (1999) 275–294.

Table 1: Principal algorithms and properties for modeling four-way data.

Algorithms	Required data array[a]	Multilinear property[b]	Software[c]	Reference
Parallel factor analysis (PARAFAC)	Four-way ($I\times J\times K\times L$)	Quadrilinear	The N-way Toolbox MVC3_GUI PLS_Toolbox	[81,82]
	Five-way ($I\times J\times K\times L\times M$)	Quinquelinear	PLS_Toolbox	[81]
Alternating quadrilinear decomposition (AQLD) and Alternating penalty quadrilinear decomposition (APQLD)	Four-way ($I\times J\times K\times L$)	Quadrilinear	MVC3_GUI	[20,83]
Alternating weighted residual constraint quadrilinear decomposition (AWRCQLD)	Four-way ($I\times J\times K\times L$)	Quadrilinear	MVC3_GUI	[71]
Four-way self-weighted alternating normalized residue fitting algorithm (SWANRF)	Four-way ($I\times J\times K\times L$)	Quadrilinear		[57]
Regularized self-weighted alternating quadrilinear decomposition (RSWAQLD)	Four-way ($I\times J\times K\times L$)	Quadrilinear		[58]
Slicing alternating quadrilinear decomposition (SAQLD)	Four-way ($I\times J\times K\times L$)	Quadrilinear		[37]
Four-way algorithm combination method (FACM)	Four-way ($I\times J\times K\times L$)	Quadrilinear		[38]
Constrained alternating quadrilinear decomposition (CAQLD)	Four-way ($I\times J\times K\times L$)	Quadrilinear		[61]
Multivariate curve resolution coupled to alternating least squares (MCR-ALS)	Two-way ($IL\times JK$)	Quadrilinear and non-quadrilinear Type 1	MCR-ALS 2.0 toolbox	[84]
	Two-way ($IJL\times K$)	Quadrilinear and non-quadrilinear Type 4	MVC3_GUI	[53]
PARAFAC2	Four-way ($I\times J\times K\times L$)	Quadrilinear and non-quadrilinear Type 1	MVC3_GUI	[85]
Augmented parallel factor analysis (*A*PARAFAC)	Three-way ($IL\times J\times K$)	Quadrilinear and non-quadrilinear Type 1	MVC3_GUI	[49]

Table 1: Principal algorithms and properties for modeling four-way data.

Algorithms	Required data array[a]	Multilinear property[b]	Software[c]	Reference
Unfolded partial least-squares/residual trilinearization (U-PLS/RTL)	- Calibration step: two-way ($I \times JKL$) - Second- and higher-order advantage step (RTL): three-way ($L \times J \times K$)	Quadrilinear and non-quadrilinear Types 2 and 3	MVC3_GUI	[26]
N-way partial least-squares/residual trilinearization (N-PLS/RTL)	- Calibration step: two-way ($I \times JKL$) - Second- and higher-order advantage step (RTL): three-way ($L \times J \times K$)	Quadrilinear and non-quadrilinear Types 2 and 3	MVC3_GUI	[29]
Alternating fitting weighted residue quinquelinear decomposition (AFWRQQLD)	Five-way ($I \times J \times K \times L \times M$)	Quinquelinear		[76]
Alternating quinquelinear decomposition algorithm (AQQLD)	Five-way ($I \times J \times K \times L \times M$)	Quinquelinear		[78]
Unfolded partial-least squares/residual quadrilinearization (U-PLS/RQL)	Five-way ($I \times J \times K \times L \times M$)	Quinquelinear		[75]

[a] J, K and L are the first, second and third instrumental data modes. In this case, J, and K correspond to the fluorescence signal modes (excitation and emission wavelength, respectively), L is the experimental variable mode (elution time, time resolved, reaction time, pH or other chemical treatment), and I refers to the concentration mode (number of samples).

[b] According to Fig. 1.

[c] The N-way Toolbox for MATLAB: http://www.models.life.ku.dk/algorithms; MVC3_GUI: www.iquir-conicet.gov.ar/descargas/mvc3.zip; PLS_Toolbox: http://www.eigenvector.com; MCR-ALS 2.0 toolbox: https://mcrals.wordpress.com/.

Table 2: Methods employing EEM-kinetics third-order data.

Analytes	Matrix	Algorithms	Reaction details	Reference
Adrenaline and noradrenaline from catecholamine standards	-	PARAFAC N-PLS	Lutine reaction. $K_3Fe(CN)_6$ as oxidizing agent. $ZnSO_4$ as catalyst. Alkaline solution (pH 10). $C_6H_8O_6$ as antioxidant	[22]
Methotrexate and leucovorin	Urine	PARAFAC TLLS	Oxidation with potassium permanganate	[25]
benz[a]anthracene, benzo[k]fluoranthene and dibenz [a,h]anthracene	-	PARAFAC	Photocatalytic degradation with a reactor	[23]
Fenvalerate	-	PARAFAC	Photochemically induced degradation.	[24]
Folic acid and methotrexate	Urine	PARAFAC N-PLS	Oxidation with potassium permanganate. pH 3.4, chloroacetic/chloroacetate buffer and 20 ºC	[27]
Leucovorin and metotrexate	-	PARAFAC TLLS/RTL U-PLS/RTL	Oxidation with potassium permanganate. Presence of uncalibrated components	[26]
Folic acid and methotrexate	Human serum	N-PLS PARAFAC U-PLS/RTL	Oxidation with potassium permanganate	[28]
Procaine and its metabolite p-aminobenzoic acid	Equine serum	N-PLS/RTL	Hydrolysis reaction of procaine. pH 13 and T^a = 40 ºC	[29]
Folic acid, 5-methyltetrahydrofolic acid and tetrahydrofolic acid.	Human serum	U-PLS/RTL N-PLS/RTL	On line photochemical reaction with a UV lamp in a flow system	[30]
Malonaldehyde	Olive oil	U-PCA/RTL/RBF	Reaction between malonaldehyde and methylamine to obtain 1,4-disubstituted-1,4-dihydropyridine-3,5-dicarlbaldehyde. Solutions in sodium acetate/acetic acid buffer (pH 3.8) and isopropanol	[31]
Carbaryl	Effluent water	PARAFAC	Hydrolysis reaction in alkaline buffer (pH 9.3). Presence of unknown interferences	[33]
Carbaryl and 1-naphtol	Water	U-PLS/RTL	Alkaline hydrolysis of carbaryl with a buffer phosphate (pH 10.2). Presence of potential interferents (fuberidazole and thiabendazole)	[34]

Table 2: Methods employing EEM-kinetics third-order data.

Analytes	Matrix	Algorithms	Reaction details	Reference
Nitrofurans	Fish	PARAFAC UPCA/RTL/RBF-ANN	Alkaline hydrolysis	[32]
Carbaryl, 1-naphtol and propoxur	River water	U-PLS/RTL N-PLS/RTL	Alkaline hydrolysis with a buffer phosphate (pH 10.2). Carbendazim and thiabendazole as interferents	[35]
Tyrosine and levodopa	Human plasma	AQLD	Enzyme-induced kinetics with polyphenol oxidase	[36]
Nicotinamide adenine dinucleotide and flavin adenine dinucleotide	Human plasma	CATLD RSWAQLD PARAFAC	Degradation reaction of NADH and formation of FAD. Uncalibrated components present	[40]
Thiamine	Multivitamin complexes	PARAFAC	Oxidation of thiamine-Hg (II) complex to thiochrome. Standard addition calibration. Reaction to 25 ºC. Unknown interferents	[39]
Tyrosine and Levodopa	Human plasma	SAQLD	Enzyme-induced kinetics with polyphenol oxidase	[37]
Benzo[*a*]pyrene, dibenz[*a,h*]anthracene, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene and Benzo[*a*]anthracene	Natural water	PARAFAC	Fenton degradation. Acetate/acetic acid buffer (pH 5), Fe (II) ion concentration of 2 mg/L, H_2O_2 concentration of 5 g/L, T^a = 20 ºC, M-β–CD concentration of 0.01 mol/L	[41]
Azinphos-methyl	Apple, pear, peach	PARAFAC U-PLS/RTL	Irradiation with UV-light	[43]
Irinotecan	Human plasma	AWRCQLD APQLD	Hydrolysis of CPT-11	[44]
Tyrosine and levodopa	Human plasma	FACM	Enzyme-induced kinetics with polyphenol oxidase	[38]
Bisphenol A and nonylphenol	Food-contact plastics	PARAFAC U-PLS/RTL MCR-ALS	Fenton degradation. Reaction with hydrogen peroxide catalyzed by iron, generating strong non-specific oxidant hydroxyl radicals	[42]

Table 3: Methods employing EEM-LC third-order data.

Analytes	Matrix	Algorithms	Experimental System	Reference
Perylene, fluoranthene, tethracene and 9,10-dimethylanthracene	Effluent	Nonlinear iterative least squares	HPLC connected to a video fluorometer	[45]
Molecular entities	Thick juice	PARAFAC PARAFAC2	Collection of chromatographic fractions	[46]
Chlorophlylls *a* and *b* and pheophytins *a* and *b*	Olive oils	PARAFAC U-PLS/RTL N-PLS/RTL	Multiple injections at different excitation wavelength, collecting time-emission spectra matrix	[47]
Carbendazim, fuberidazole, thiabendazole, carbofuran, carbaryl and naphtol	Fruit juice	PARAFAC U-PLS/RTL MCR-ALS	Multiple injections at different excitation wavelength, collecting time-emission spectra matrix	[48]
Chlorophlylls *a* and *b* and pheophytins *a* and *b*	Olive oils	APARAFAC MCR-ALS	Multiple injections at different excitation wavelength, collecting time-emission spectra matrix	[49]
Ofloxacin and ciprofloxacin	Drinking water	PARAFAC U-PLS/RTL MCR-ALS	Collection of chromatographic fractions and further fluorescence detection to each fraction	[50]
Ofloxacin, ciprofloxacin and danofloxacin	Drinking water	APARAFAC MCR-ALS	Collection of chromatographic fractions and further fluorescence detection to each fraction	[51]
Fluoroquinolones	Drinking water	PARAFAC APARAFAC MCR-ALS	Collection of chromatographic fractions and further fluorescence detection to each fraction Multiple injections at different excitation wavelength, collecting time-emission spectra matrix On-line EEM registering using an hyphenated LC-fast-scanning fluorimeter system	[10]
Fluoranthene, pyrene, benz[*a*]anthracene, chrysene, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene, benzo[*a*]pyrene and dibenz[*a,h*]anthracene	Underground and stream water	PARAFAC	On-line EEM registering using an hyphenated LC-fast-scanning fluorimeter system	[52]

Table 3: Methods employing EEM-LC third-order data.

Analytes	Matrix	Algorithms	Experimental System	Reference
Rimsulfuron, fuberidazole, carbaryl, naproxen, albendazole, tamoxifen	Well and river water	MCR-ALS	On-line EEM registering using an hyphenated LC-fast-scanning fluorimeter system with on-line photoreactor	[54]
Benz[*a*]anthracene, chrysene, benzo[*b*]fluoranthene and benzo[*a*]pyrene	Tea leaves	MCR-ALS	On-line EEM registering using an hyphenated LC-fast-scanning fluorimeter system	[53]
7-Hidoxyquinoline, Eosin Y and Resorufin	Water	PARAFAC APARAFAC	On-line EEM registering using an hyphenated LC-CCD based spectrometer system	[55]

Table 4. Methods employing EEM-pH third-order data

Analytes	Matrix	Algorithms	Experimental System	Reference
Procaine hydrochloride and *p*-aminobenzoic acid	Human plasma	PARAFAC APQLD	Discrete pH levels: 6.0 8.0. 11.5 12.2 12.8	[20]
Serotonin	Human plasma	PARAFAC SWANRF	Discrete pH levels: 9.10, 9.22, 9.40, 9.50	[57]
Flumequine, enoxacin, ciprofloxacin and marbofloxacin	River water	PARAFAC RSWAQLD	Discrete pH levels: 2.2, 3.0, 4.0	[58]
L-phenylanaline, L-tyrosine, L-tryptophan	Human plasma	PARAFAC	Discrete pH levels: 3.6, 4.0, 4.4, 4.8, 5.2	[59]
Ofloxacin, norfloxaxin and ciprofoxacin	Urine	PARAFAC	In-flow pH gradient: Carrier solution pH 3 Injection solution pH 7	[62]
Xanthopterin and isoxanthopterin	Human urine and serum	FACM AQLD PARAFAC	Discrete pH levels: 6.5, 7.0, 7.5, 8.0	[38]
Gallic acid, caffeine acid and *p*-hydroxybenzoic acid	Drinking water	PARAFAC	Discrete pH levels: 7.0, 7.3, 7.5, 7.8	[60]
Flavin adenine dinucleotide and flavin mononucleotide	Cancer cells	CAQLD	Discrete pH levels: 2.2, 2.6, 3.0, 3.4, 3.8, 4.2	[61]

Figure captions

Fig. 1. Classification scheme for four-way data for a set of samples according to whether the individual three dimensional arrays data are trilinear or not and according to the number of quadrilinearity-breaking modes. Adapted from [7].

Fig. 2. Evolution of the fluorescence intensity of AZM (λ_{exc} = 240 nm; λ_{em} = 390 nm) and EEMs, as a function of irradiation time. Reprinted with permission from [43]. Copyright 2017 Elsevier.

Fig. 3. Schematic representation of MCR-ALS model to third-order EEM-LC data processing. Reprinted with permission from [10]. Copyright 2017 Elsevier.

Fig. 4. Schematic representation of *A*PARAFAC model to third-order EEM-LC data processing. Reprinted with permission from [10]. Copyright 2017 Elsevier.

Fig 5. Schematic illustration of the application of MCR-ALS to type 4 non-quadrilinear data proposed by Carabajal et al [53].

Fig. 6. Chromatographic profiles of Eosine Y (red), Resorufin (blue) and Fluorescein (green) obtained from four-way PARAFAC decomposition and original fluorescence images at different times acquired with the CCD-based fluorescence detector. Dotted gray line represents the chromatographic profile of the ternary mixture as would be measured at single excitation and emission wavelengths. A total number of 1450 matrices were registered in a run of 4.5 min.

Fig 7. Experimental procedure to acquire EEM-pH data in static conditions.

Fig 8. Schematic representation of the third-order array EMWTM obtained for each analyzed sample.

Figures

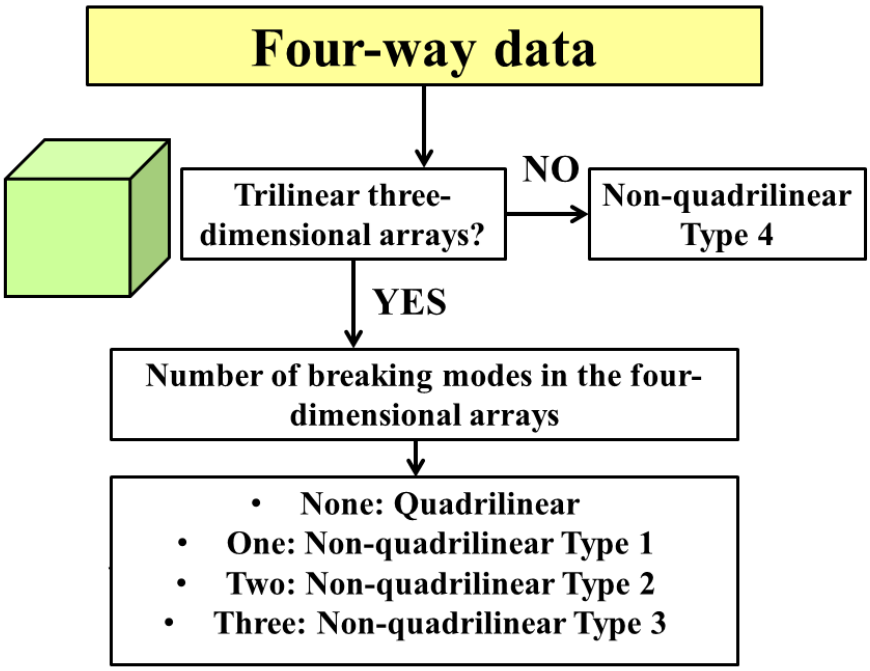

Figure 1

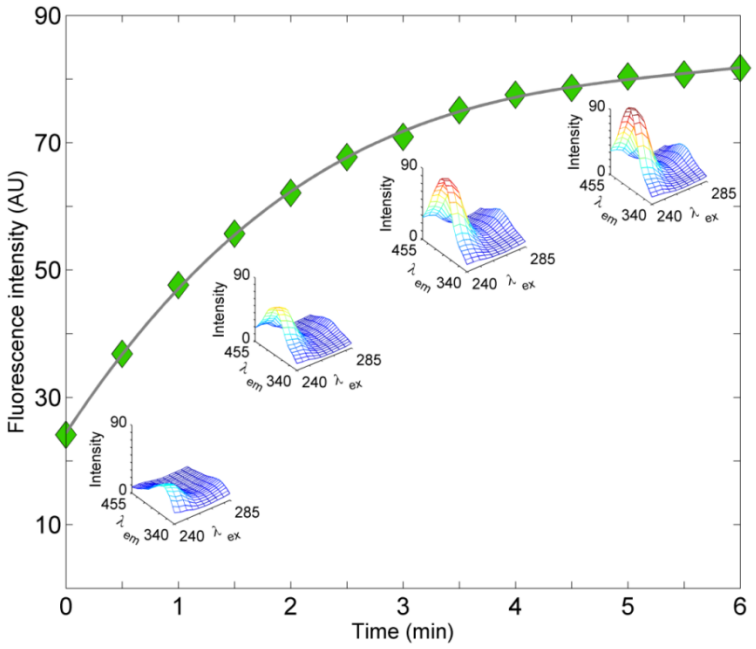

Figure 2

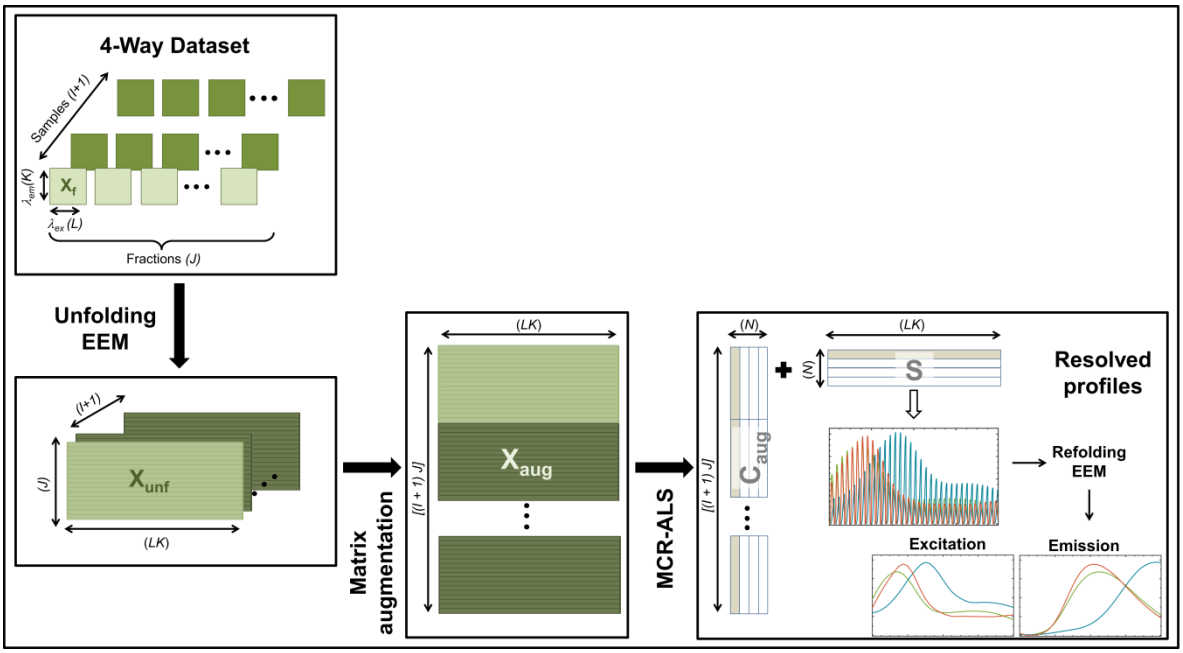

Figure 3

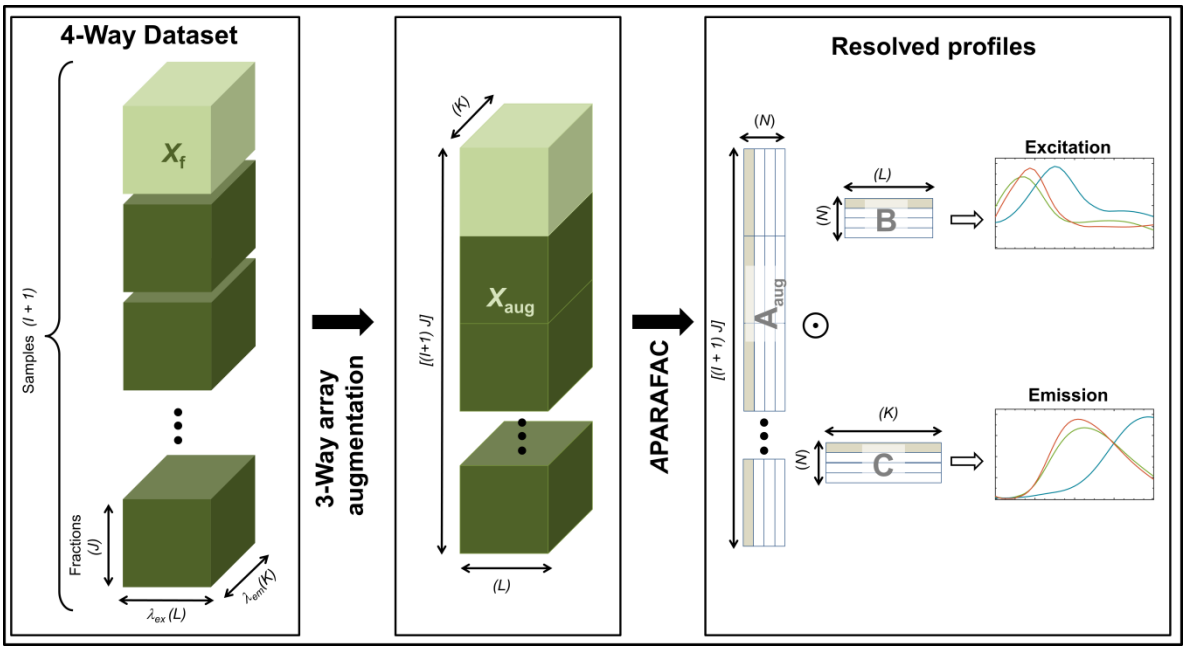

Figure 4

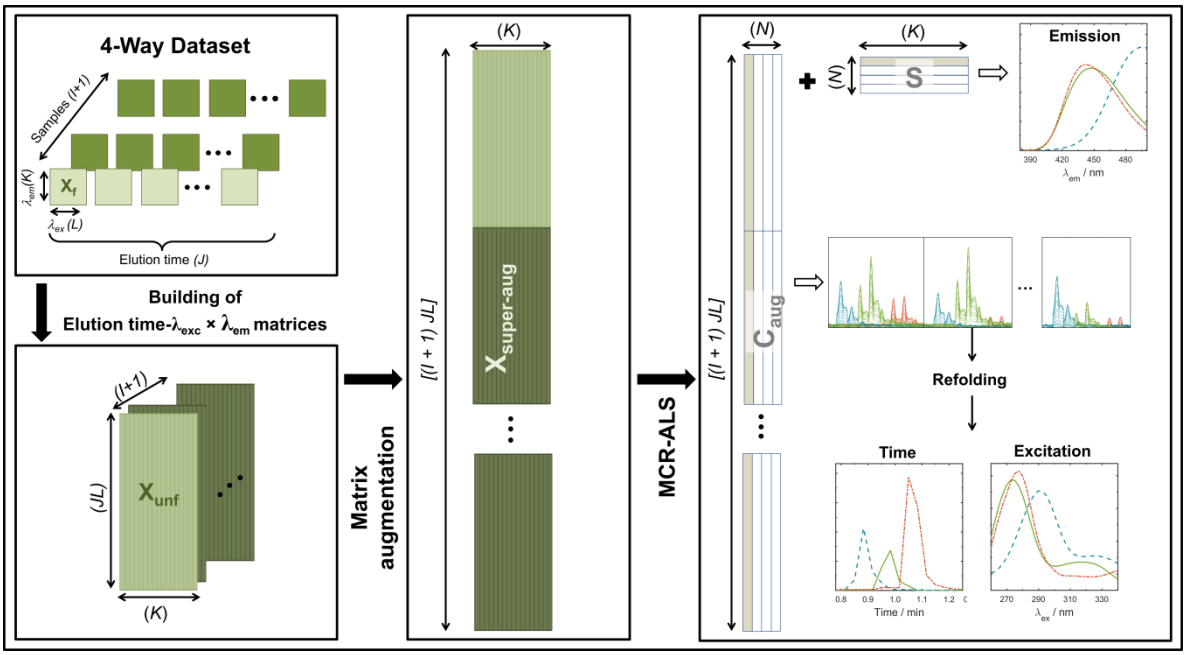

Figure 5

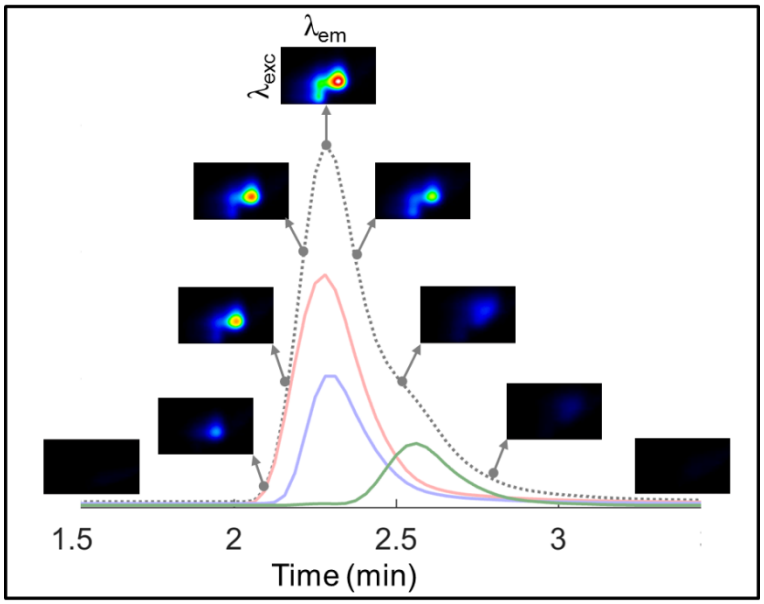

Figure 6

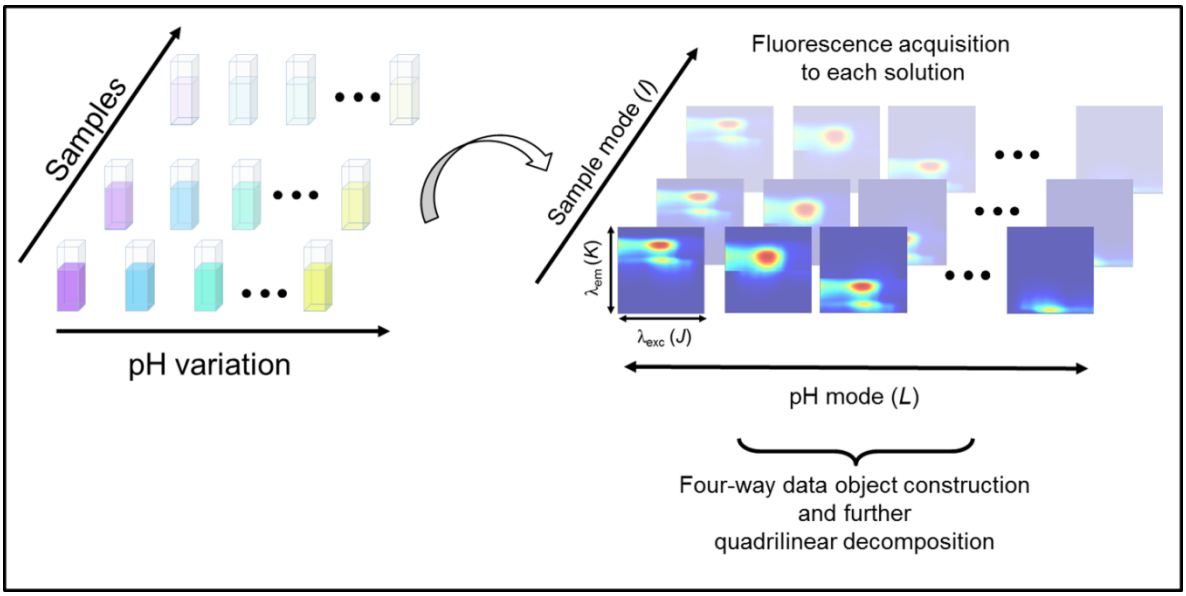

Figure 7

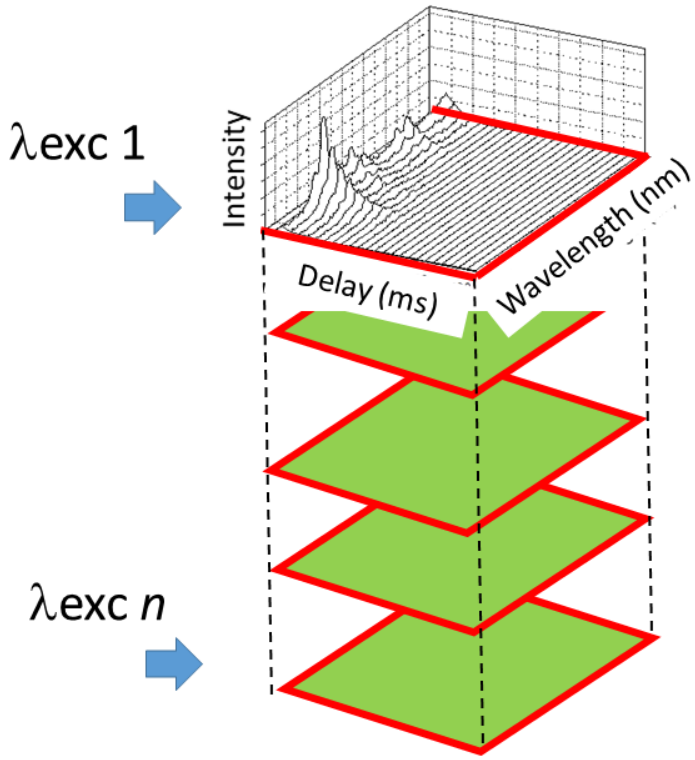

Figure 8