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INAA method optimization using a 2^k factorial design

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Abstract In this work a 2^3 factorial design was carried out aiming the multivariate optimization of Instrumental Neutron Activation Analysis (INAA) for mass fraction determination of Co, Cr, Fe, Rb, Sc, Se and Zn in biological samples and Co, Cr, Fe, Sc and Zn in geological samples. The factors investigated in this study were sample decay time, sample distance to detector and sample measurement time. The optimal condition for each method was outlined according to the main effect and interactions results. It was observed that sample decay time is the most important factor for the INAA optimization in the different methods.

Keywords Factorial design · Method optimization · INAA · Biological sample · Geological sample

Introduction

The implementation of a quality management system is essential to a measurement laboratory to demonstrate that it has facilities, equipment and suitable analytical measurement methods to the quality assurance of analytical results. By means of the certification and/or accreditation processes, the laboratory can demonstrate that its results are fit for the intended use.

These processes can be formalized by complying with a wide series of standards and protocols, depending on the activities performed by the laboratory. In Brazil, for measurements in chemistry, the ISO/IEC 17025 Standard is the most important regulation standard. In this context, the validation of measurement methods is a prerequisite for the implementation and suitability of the quality system in a laboratory [1].

Before starting the experiments required by the method validation scope (limit of detection, limit of quantification, selectivity, specificity, linearity, limit of repeatability, intermediate precision, limit of reproducibility and trueness), it is usually appropriate to conduct an in-depth study on the characteristics of the technique, analytical interferences, reagents, among others, aiming to identify possible factors that may jeopardize the quality of results. In other words, a measurement method optimization should be carried out.

Several factors can affect the result accuracy in INAA as thermal neutron flux, irradiation time, interfering reactions arising from the irradiation process, difference in the sample to standard geometry, gamma ray measurement conditions, measurand losses in the analytical process, among others. However, the largest challenge is not the identification of these factors, but the quantification of the influence assigned to each factor in the method optimization procedure. In this context, the application of a 2^k factorial design is the solution of the problem.

In this study, a 2^3 factorial design was applied to identify the importance of sample decay time, sample distance to detector and sample measurement time factors to the accurate end result, aiming an optimization to subsequent validation of two INAA methods. There are no reports in the literature regarding the application of factorial design for performing of INAA method optimization. In this context, an original study is presented in this manuscript.

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Theory

A classical method optimization consists of varying each investigated variable while holding all others as constant terms. This method is widely used but usually requires a large number of experiments to be performed and the optimization procedure does not consider the results of the main effect and interaction contrasts among variables [2].

Often, these studies are virtually impossible to be carried out or simply do not generate significant results for the method optimization. As alternative, some authors have reported the use of the factorial design[1] as an important tool for the optimization of methods and processes in several areas of research and manufacture, particularly for monoelemental methods [2–8]. For a better understanding of the 2^3 factorial design carried in this study, it is necessary to define some terms, such as factor, level, main effect, interaction and standard error. These concepts are presented below [9].

Factor

Each variable investigated for the method optimization. In this study, three factors were considered: sample decay time (A), sample distance to detector (B) and sample measurement time (C).

Level

Experimental condition assigned to each factor investigated. In a 2^3 factorial design, two different levels are assigned for each factor. These levels are denominated level (-1) (assigned to less favorable condition) and level $(+1)$ (assigned to more favorable condition). The assignment of $(+1)$ or (-1) levels is given arbitrarily and does not interfere with the experiments or the interpretation of results.

Main effect

Result obtained with the variation of different levels assigned to a factor. Mathematically, it is calculated according to (1).

$$\mathrm{ME} = 2\frac{\sum(y^{+1}) - \sum(y^{-1})}{n} \qquad (1)$$

where ME is the main effect value of a factor; $\sum(y^{+1})$ and $\sum(y^{-1})$ are summation of the results obtained for all experiments in level $(+1)$ and (-1) respectively (including replicates); n is the number of experiments (including replicates).

Interaction

Half of the difference between the main effect of a factor in the level of another factor. Briefly, it can be defined as the change in the level of a factor affecting the result for another factor [10];

Standard error

Measurement error in the result of an effect and/or interaction. It is calculated according to (2).

$$E = \frac{s}{\sqrt{2^{(k-1)}}} \qquad (2)$$

where E is the measurement error in the result of an effect; s is the standard deviation of the results obtained for all experiments (including replicates); k is the number of factors investigated.

Depending on the experimental conditions and number of factors to be investigated, different models of factorial design can be used. Among then we have the x^k (x levels for k factors), whereas $x \geq 2$ and $k \geq 2$ and the x^{k-p} when the number of factors investigated is greater than 4. According to the model chosen and the number of replicates of the experiments, we can perform different methods for obtain the results. The full factorial design is the most widely used for studies with three or fewer factors and levels. For studies with larger number of factors, the models of randomized blocks or fractional factorial design are the most appropriate ones [11].

The major advantage of the factorial design is the conduction of a multivariate optimization which needs a smaller number of experiments when compared to classical optimization methods (univariate procedure). By means of main effect and interaction contrasts it is possible to explain how the different factors are correlated and just how important these correlations are for the method optimization. Thus, it is possible to evaluate and understand the contribution of each factor to the end result [11, 12].

Nevertheless, the main assumptions required by factorial design are an complete randomization of experiments, independent results for each measurement and a normal distribution for the obtained results [11, 12].

Experimental

Instrumental neutron activation analysis

Subsamples of Mussel Tissue Reference Material (RM) [13] and Estuarine Sediment Certified Reference Material (CRM) [14] of 150 ± 10 mg were weighed in polyethylene packaging previously cleaned, using a Shimadzu

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[1] Factorial design it is also named in the literature as experimental design, factorial experiment and/or design of experiment (DOE). All these terms are common for the factorial design literature.

AEM-5200 analytical balance. The standard working solution was prepared by dilution of Spex CRM element solutions in volumetric flask. Multielemental synthetic standards were prepared by pipetting of the standard element solution onto Whatman paper filters using Eppendorf micropipette. After drying, the paper filters were folded, placed and sealed in polyethylene packaging with the same sample geometry (10 mm × 8 mm × 1 mm).

INAA comparative method was performed for the mass fraction determination of Co, Cr, Fe, Rb, Sc, Se and Zn in biological samples and Co, Cr, Fe, Sc and Zn in geological samples. Samples and multielemental standards were simultaneously irradiated for 8 h under 0.5 to 1.0×10^{13} cm^{-2} s^{-1} thermal neutron flux at IEA-R1 Nuclear Research Reactor. ^{60}Co, ^{51}Cr, ^{59}Fe, ^{86}Rb, ^{46}Sc, ^{75}Se and ^{65}Zn radionuclides were quantified by gamma-ray spectrometry, using a GC2018 Canberra HPGe detector (with resolution of 1.0 keV for the 122 keV peak of ^{57}Co and 1.78 keV for the 1332 keV peak of ^{60}Co) coupled to a DSA 1000 multichannel analyzer.

Genie 2000—Gamma Acquisition & Analysis 3.1 software was used to obtain gamma ray spectra. Mass fraction calculations were carried out using a Microsoft Excel spreadsheet (in-house spreadsheet) for suitable radionuclide photopeak energies. Three replicate analyses for biological samples and two replicate analyses for geological samples were randomly performed.

Factorial design

In this study, a 2^3 factorial design was applied for optimization of two multielemental methods of INAA at the Neutron Activation Analysis Laboratory (LAN, IPEN—CNEN/SP). Three factors of the detection step were investigated: sample decay time (A), sample distance to detector (B) and sample measurement time (C). Table 1 presents the values assigned to the different levels for each factor.

Different levels were designed according to the standard configuration of the methods. Originally, biological samples are measured 14–15 days after irradiation for a period of 10 h in shelf 1 (33 mm) and geological samples are measured 14–15 days after irradiation for 3 h in shelf 0 (3 mm). The main objective of this work was to perform a decrease in sample measurement time without impairing the accuracy of the results, aiming an increase in the analytical output of the laboratory.

Results obtained for each measurand in different levels were evaluated for accuracy (precision and trueness) by means of z-score and relative standard deviation (RSD) calculations. Main effect and interaction contrasts analyses were outlined considering the relative error of the results and the calculations were performed in R 2.5.1 software [12, 15]. Graphics presented at this study were performed in Microsoft Excel spreadsheet.

For assessing the statistical significance of the results, a t test was carried at the 95 % confidence level. H_0 hypothesis (null hypothesis) was accepted when there was no statistically significant difference between the means, i.e., when the means are statistically equivalent. On the other hand, H_1 hypothesis (alternative hypothesis) was accepted for means not statistically equivalent. In short, for $p \geq 0.05$ H_0 was accepted. Otherwise, H_0 was rejected and H_1 accepted [16].

Results and discussion

Levels and factors

In order to check whether the values assigned to the different levels were properly delineated, the samples were analyzed in the (−1) and (+1) level conditions (according to Table 1). Figure 1 shows z-scores according to Thompson's criteria [17, 18] and RSD results for the mean results obtained in different levels for the biological matrix sample while Fig. 2 shows the results for the geological matrix sample.

According to z-score analysis, results obtained to level (+1) presented best results for trueness when compared to level (−1), with exception of Se, where the level (−1) was the most favorable condition. Results for biological samples varied from 0.17 to 3.98 (level (−1)) and 0.04 to 0.99 (level (+1)) and for geological samples from 0.10 to 2.14 (level (−1)) and 0.01 to 0.92 (level (+1)).

An estimate of the precision was obtained according to the RSD results. For biological matrix sample it was

Table 1 Values assigned to different levels of each factor

Factor	Biological matrix samples		Geological matrix samples	
	Level −1	Level +1	Level −1	Level +1
Sample decay time (A)	10 days	22 days	10 days	22 days
Sample distance to detector (B)	Shelf 3 (98 mm)	Shelf 0 (3 mm)	Shelf 3 (98 mm)	Shelf 0 (3 mm)
Sample measurement time (C)	6 h	10 h	2 h	6 h

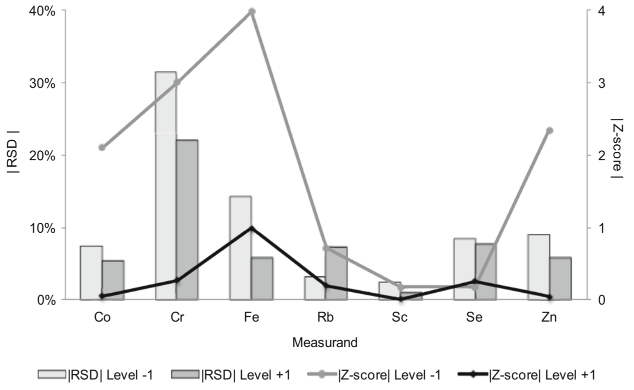

Fig. 1 *Z* score and RSD results for the different levels assigned to the factors (biological matrix sample) from 2^3 factorial design

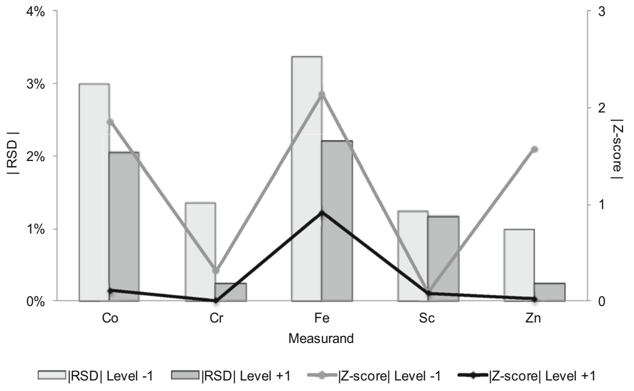

Fig. 2 *Z* score and RSD results for the different levels assigned to the factors (geological matrix sample) from 2^3 factorial design

verified that more precise results were obtained for Co, Fe, Sc, Se and Zn in the level (+1), with values between 1.0 % for Sc and 21 % for Cr. Rb presented the least RSD for the conditions of level (−1) (3.1 %). On the other hand, results for the geological matrix sample were more precise for all measurands in the level (+1) (2.0, 0.24, 2.2, 1.2 and 0.25 % for Co, Cr, Fe, Sc and Zn, respectively).

Best results for trueness and precision were obtained for geological matrix sample when compared to the biological matrix sample results in similar analytical conditions. This fact can be attributed to differences in the matrix characteristics as well as element composition, mass fraction content, granulometry and particle size distribution.

Factorial design

Biological matrix samples

The matrix of the 2^3 factorial design was compounded of 168 results, as three replicate analyses were performed for the 7 measurands, resulting in a experimental matrix with 160 degrees of freedom. For each result it was calculated the relative error to the reference value aiming to a data standardization. With the relative error for all measurands were outlined the main effect and interaction to the method. Mean results and standard deviation obtained for the factorial design experiments are presented in Table 2. Table 3 present main effect and interaction results.

Experiments e_8 and e_4 presented the best results for all measurands and experiments e_1 and e_5 presented the worst results (trueness and precision). Analyzing the configuration of the experiments e_8 and e_4, it is possible to verify that C was changed from the level (+1) to level (–1), namely, there were not evidences that the change from 6 to 10 h gave rise to a positive or negative influence on the end result. Nevertheless, there was no significant change of the results because A and B were maintained in level (+1).

Factor A was the main factor for the multielemental optimization in biological matrix sample ($p < 0.001$). Factor B and interactions A:B, A:C, B:C and A:B:C were

Table 2 Mass fraction results obtained by INAA at a 2^3 factorial design in biological matrix sample (mean value ± SD, $n = 3$)

Experiment	Factor and level			Mass fraction (mg kg^{-1})						
	A	B	C	Co	Cr	Fe	Rb	Sc	Se	Zn
e1	−1	−1	−1	1.229 ± 0.091	0.83 ± 0.26	774 ± 110	4.52 ± 0.14	0.2070 ± 0.0049	4.52 ± 0.38	144 ± 13
e2	+1	−1	−1	0.854 ± 0.071	0.87 ± 0.24	633 ± 54	4.04 ± 1.11	0.2072 ± 0.0041	4.29 ± 0.42	121.9 ± 8.0
e3	−1	+1	−1	1.014 ± 0.084	1.15 ± 0.43	670 ± 84	4.53 ± 0.15	0.2063 ± 0.0057	4.76 ± 0.59	122.2 ± 9.3
e4	−1	−1	+1	1.200 ± 0.087	1.17 ± 0.23	682 ± 102	4.56 ± 0.14	0.2050 ± 0.0042	4.56 ± 0.38	142 ± 11
e5	+1	+1	−1	0.839 ± 0.071	1.21 ± 0.27	632 ± 33	4.73 ± 0.32	0.1998 ± 0.0033	4.73 ± 0.27	118.2 ± 6.7
e6	+1	−1	+1	0.853 ± 0.067	0.91 ± 0.46	627 ± 44	4.61 ± 0.79	0.2049 ± 0.0019	4.45 ± 0.30	123.3 ± 6.5
e7	−1	+1	+1	1.001 ± 0.080	1.29 ± 0.33	667 ± 93	4.59 ± 0.14	0.2075 ± 0.0044	4.59 ± 0.47	118.8 ± 8.9
e8	+1	+1	+1	0.836 ± 0.045	1.19 ± 0.26	631 ± 36	4.81 ± 0.35	0.2001 ± 0.0020	4.57 ± 0.35	118.1 ± 6.9
Reference values[a]				0.829 ± 0.077	1.24 ± 0.28	593 ± 53	4.93 ± 0.92	0.199 ± 0.023	4.42 ± 0.45	118.5 ± 9.5

[a] Certified value and expanded uncertainty, $k = 2$ [13]

Table 3 Main effects (A; B; C) and interactions (A:B; A:C; B:C; A:B:C) for the INAA method of biological matrix samples

Effect	Estimate ± Standard Error	*t*-value	*p* value	Significant
Global mean	3.1 E−02 ± 1.3 E−02	2.4	1.6 E−02	–
Main				
A	−8.9 E−02 ± 2.6 E−02	−3.5	7.0 E−04	Yes
B	−6.9 E−05 ± 2.6 E−02	−2.7 E−03	0.99	No
C	8.7 E−03 ± 2.6 E−02	0.34	0.74	No
Interactions				
A:B	4.7 E−02 ± 2.6 E−02	1.8	6.7 E−02	No
A:C	1.4 E−03 ± 2.6 E−02	5.4 E−02	0.96	No
B:C	−8.5 E−03 ± 2.6 E−02	−0.33	0.74	No
A:B:C	−7.1 E−03 ± 2.6 E−02	−0.28	0.78	No

$n = 160$; $t_{(\alpha=0.05)} \sim 1.98$ [19]

not statistically significant for the optimization of multielemental method.

The second step of this work was the evaluation of each effect for one-to-one-measurand, aiming to investigate which factors are statistically significant for a monoelemental optimization. In this investigative step, it was obtained two distinct behaviors for the group of measurands.

It was observed that for Rb, Sc and Se, obtained results of main effect and interactions did not present statistically significant differences for any factors. One possible reasons for this observation is the possibility that the values assigned to different levels were not sufficiently different to cause the expected significant differences.

On the other hand, Co, Cr, Fe and Zn presented distinct results. According to the results of main effect and interactions it was possible to observe an important influence assigned to the factor A for Fe ($p = 0.043$), Co ($p < 0.001$) and Zn ($p = 0.001$), factor B for Cr ($p = 0.034$), Co ($p = 0.002$) and Zn ($p = 0.003$) and A:B interaction for Co ($p = 0.006$) and Zn ($p = 0.030$).

If a univariate optimization procedure was used, conditions of the experiment e_8 (level (+1) to A, level (+1) to B and level (+1) to C) would be chosen as the optimized condition. However, with the multivariate procedure it was possible to show that A and B are the most important factors to the detection step in INAA and that the interaction between these variables is of great importance for best results (trueness and precision), particularly to Zn and Co.

AC, BC and ABC interactions did not present as important interactions for the monoelemental method optimization for the levels attributed to the different factors in this study. Thus, the optimal condition for measurement of Co, Cr, Fe, Rb, Sc, Se and Zn in biological matrix sample was: 22 days to sample decay time (A; +1), shelf 0 to sample distance to detector (B; +1) and 6 h to counting time of sample (C; −1).

Geological matrix samples

The matrix of geological 2^3 factorial design was compounded of 80 results (two replicate analyses for five measurands), resulting in a experimental matrix with 72 degrees of freedom. The same data treatment performed to the biological matrix sample was applied. Table 4 present the mean results for each experiment of factorial design and Table 5 presents the main effect and interaction results for geological samples.

Over again, if a univariate optimization procedure was used, conditions of the experiment e_8 (level (+1) to A, level (+1) to B and level (+1) to C) would be chosen as the optimized condition. With exception of Sc, the best results were obtained in this condition. Analyzing the significance of the effects it was verified that factor A was the most important factor for the method optimization in geological matrix samples ($p = 0.001$). On the other hand, B and C factors, A:B, A:C, B:C and A:B:C interactions are not statistically significant for this group of measurands.

By means of the evaluating one-to-one measurand, it was observed a significant influence assigned to the factor A for Co ($p < 0.001$) and Zn ($p < 0.001$), factor B for Co ($p < 0.001$), Cr ($p = 0.012$) and Zn ($p = 0.006$) and A:B interaction for Co ($p = 0.003$), Cr ($p = 0.018$) and Zn ($p < 0.001$). Results for Fe and Sc did not present statistically significant differences for any factor and/or interaction.

According to the results, A and B factors and A:B interaction presented the most significant contribution for the optimization of INAA methods for most measurands (Co, Cr and Zn). On the other hand, factor C does not present significant influence on the final results.

Table 4 Mass fraction results obtained by INAA at a 2^3 factorial design in geological matrix sample (mean value ± SD, $n = 2$)

Experiment	Factor and level			Mass fraction (mg kg^{-1})				
	A	B	C	Co	Cr	Fe	Sc	Zn
e1	−1	−1	−1	4.03 ± 0.12	42.10 ± 0.57	19332 ± 648	4.940 ± 0.061	42.79 ± 0.42
e2	+1	−1	−1	4.75 ± 0.17	40.88 ± 0.18	20428 ± 387	4.929 ± 0.066	49.77 ± 0.42
e3	−1	+1	−1	4.69 ± 0.21	39.22 ± 0.13	21289 ± 401	4.929 ± 0.057	45.21 ± 0.13
e4	−1	−1	+1	4.08 ± 0.20	41.72 ± 0.29	20840 ± 177	4.931 ± 0.061	42.38 ± 0.98
e5	+1	+1	−1	4.85 ± 0.13	40.81 ± 0.10	19982 ± 170	4.942 ± 0.056	49.00 ± 0.11
e6	+1	−1	+1	4.73 ± 0.13	41.03 ± 2.05	20347 ± 508	4.925 ± 0.064	49.84 ± 0.15
e7	−1	+1	+1	4.73 ± 0.15	39.85 ± 0.14	20219 ± 950	4.926 ± 0.066	44.92 ± 0.16
e8	+1	+1	+1	4.93 ± 0.10	40.92 ± 0.10	20417 ± 446	4.948 ± 0.057	48.99 ± 0.12
Certified reference values[a]				5[b]	40.9 ± 1.9	20080 ± 380	5[b]	48.9 ± 1.6

[a] Certified value and expanded uncertainty, $k = 2$

[b] Informative values (non-certified) [14]

Table 5 Main effects (A; B; C) and interactions (A:B; A:C; B:C; A:B:C) for the INAA method of geological matrix samples

Effect	Estimate ± Standard Error	*t*-value	*p* value	Significant
Global mean	2.6 E−02 ± 6.0 E−03	−4.3	5.2 E−05	–
Main				
A	4.0 E−02 ± 1.2 E−02	3.32	1.4 E−03	Yes
B	1.6 E−02 ± 1.2 E−02	1.32	0.19	No
C	3.2 E−03 ± 1.2 E−02	0.26	0.79	No
Interactions				
A:B	−1.5 E−02 ± 1.2 E−02	−1.26	0.21	No
A:C	4.7 E−04 ± 1.2 E−02	0.04	0.97	No
B:C	−2.8 E−03 ± 1.2 E−02	−0.23	0.82	No
A:B:C	7.2 E−03 ± 1.2 E−02	0.60	0.55	No

$n = 72$; $t_{(\alpha=0.05)} \sim 1.99$ [19]

In this work, the optimal condition for the measurement of Co, Cr, Fe, Sc, and Zn in geological matrix samples was: 22 days to sample decay time (A; +1), shelf 0 to sample distance to detector (B; +1) and 2 h to counting time of sample (C; −1).

Conclusion

In this study a new strategy was proposed for the optimization of multielemental methods using a full factorial design. Coherent results were found for optimization of two different matrix samples (biological and geological). According to the results, factor A (sample decay time) was the main factor for the optimization of the INAA methods. Factor B (sample distance to detector) and A:B interaction presented important contribution for the monoelemental optimization of Co, Cr, Fe and Zn in biological matrix samples and Co, Cr and Zn in geological matrix samples. Hence it is concluded that the 2^3 factorial design may present suitable results when employed for the optimization of multielemental methods. The authors suggest the performance of INAA method optimization (monoelemental and multielemental) by means of factorial design in others laboratories, considering different factors and for different methods and measurands, aiming to evaluate the reproducibility and applicability of this technique for studies in INAA.

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