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Experimental designs for evaluation of uncertainty — Use of factorial designs for determining uncertainty functions

Plans d'expériences pour l'évaluation de l'incertitude — Utilisation de plans factoriels pour la détermination des fonctions d'incertitude

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Foreword

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This document was prepared by Technical Committee ISO/TC 69, *Applications of statistical methods*, Subcommittee SC 6, *Measurement methods and results*.

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Introduction

This document has been elaborated in response to the need for standardized single laboratory designs to determine measurement uncertainty (JCGM 100[1]) by means of experiments. It applies in situations where the standard deviation of the observations is not constant but depends on the measurand and where the measurement uncertainty is derived by a top-down approach. This need has been expressed in such areas as consumer protection, food safety, environmental analytics and medical diagnostics.

Uncertainty evaluation usually requires the quantification and subsequent combination of uncertainties arising from random variation and uncertainties associated with corrections. Random variation may arise within a particular experiment under the same conditions, or across a range of conditions. The former kind of variation occurs under repeatability conditions, hence usually being characterised as repeatability standard deviation or repeatability coefficient of variation; precision across a range of conditions is generally termed intermediate precision or reproducibility (ISO 5725 (all parts)[3]).

The most common experimental design for estimating the laboratory variance and the repeatability variance is the ANOVA design described in ISO 5725-2. In this design, an equal number of observations are collected under repeatability conditions for each participating laboratory. Alternative designs for interlaboratory studies, in which other factors are varied in addition to the laboratory factor, are described in ISO 5725-3. Evaluation of uncertainties based on such a study design is discussed in ISO 21748[6]. Similarly, where the observations are not grouped in different laboratories but in groups of different measurement conditions (e.g. different weeks or technicians) within the same laboratory, the between-group variance component can be considered to represent the uncertainty contribution arising from random variation in the measurement condition which the grouping factor represents. For example, if test results are obtained under repeatability conditions once a week, analysis of variance can provide an estimate of the effect of variation between weeks.

While nested designs are among the most common designs for estimating random variation, they are not the only useful class of design. Consider, for example, an experiment conducted by using three instruments, three batches of reagents and three batches of a solid phase extraction (SPE) cartridges, where every possible combination is included in the design for a total $3 \times 3 \times 3 = 27$ runs. As every possible combination has the same number of observations, this design is called balanced, and as factors are not nested within each other, the factors instrument, reagent and SPE cartridge are said to be 'crossed'. This type of experiment is considered in ISO/TS 17503[5] for the uncertainty evaluation of the mean in two-factor crossed designs. Just as in the case of the nested design, the aim is to extract the variance components corresponding to the three factors. Suitable models are available and are referred to in the statistical literature as random-effects or (if one factor is a fixed effect) mixed-effects models. This approach can be extended to take more than three factors into account. However, if all factor level combinations are included in the design, the corresponding number of measurements can become very high. For example, for five factors, each with three levels, there are already $3^5 = 243$ factor level combinations. If it is necessary to include five or more factors in the experiment, the number of levels should be as low as possible (two levels), and it is recommended to implement an orthogonal design, whereby only a selection of factor level combinations is included.

It is assumed in this document that the measured values are non-negative numbers and that all variance components consist of two parts: one part which is proportional to the level of the measurand and another which is constant across levels. Estimation of variance components can be achieved by several methods. For balanced designs, computing expected mean squares from classical analysis of variance is straightforward. Restricted (sometimes also called residual) maximum likelihood estimation (REML) is widely recommended for estimation of variance components and is applicable to both balanced and unbalanced designs.

Experimental designs for evaluation of uncertainty — Use of factorial designs for determining uncertainty functions

1 Scope

This document specifies experimental procedures and statistical analysis for the determination of measurement uncertainty in situations where the following conditions are fulfilled:

Condition 1: The level of the measurand is non-negative, e.g. concentration level of a contaminant in a sample.

Condition 2: Measurement error consists of two independent components: for one of these components the relative standard deviation is constant (that is, the absolute deviation is proportional to the level of the measurand), whereas for the other component the absolute standard deviation is constant (that is, independent of the level of the measurand).

Condition 3: Samples for different levels of the measurand can be made available; if the level of the measurand is the concentration of a chemical substance, samples could be obtained e.g. by fortifying (spiking) blank samples.

Conditions 1 and 2 are met for most applications of instrumental chemical analyses. Condition 3 can be met for chemical analyses if blank samples are available.

This document can also be used to determine precision data for a particular laboratory for different technicians, different environmental conditions, the same or similar test items, with the same level of the measurand, over a certain period of time.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 3534-1, *Statistics — Vocabulary and symbols — Part 1: General statistical terms and terms used in probability*

ISO 3534-2, *Statistics — Vocabulary and symbols — Part 2: Applied statistics*

ISO 3534-3, *Statistics — Vocabulary and symbols — Part 3: Design of experiments*

ISO 3534-4, *Statistics — Vocabulary and symbols — Part 4: Survey sampling*

ISO/IEC Guide 98-3, *Uncertainty of measurement — Part 3: Guide to the expression of uncertainty in measurement (GUM:1995)*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 3534-1, ISO 3534-2, ISO 3534-3, ISO 3534-4, ISO/IEC Guide 98-3 and the following apply. ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at https://www.electropedia.org/

3.1
block
group of settings which are conducted in parallel or in a short time interval, and which are used for the same samples

EXAMPLE Two settings:

Technician 1 + culture medium 2 + temperature 1 + incubator 1

AND

Technician 2 + culture medium 1 + temperature 2 + incubator 2

3.2
factor
qualitative or quantitative parameter that is varied with the intent of assessing its effect on the response variable

Note 1 to entry: A factor may provide an assignable cause for the outcome of an experiment.

Note 2 to entry: The use of factor here is more specific than its generic use as a synonym for predictor variable.

Note 3 to entry: A factor may be associated with the creation of blocks.

3.3
factor level
value or assignment of a factor

EXAMPLE Ordinal-scale levels of a catalyst may be presence and absence. Four levels of a heat treatment may be 100 °C, 120 °C, 140 °C and 160 °C. The nominal-scale variable for a laboratory can have levels A, B and C, corresponding to three facilities.

Note 1 to entry: A synonym is the value of a predictor variable.

Note 2 to entry: The term "level" is normally associated with a quantitative characteristic. However, it also serves as the term describing the version or setting of qualitative characteristics.

Note 3 to entry: Responses observed at the various levels of a factor provide information for determining the effect of the factor within the range of levels of the experiment. Extrapolation beyond the range of these levels is usually inappropriate without a firm basis for assuming model relationships. Interpolation within the range may depend on the number of levels and the spacing of these levels. It is usually reasonable to interpolate, although it is possible to have discontinuous or multi-modal relationships that cause abrupt changes within the range of the experiment. The levels may be limited to certain selected fixed values (whether these values are or are not known) or they may represent a purely random selection over the range to be studied.

3.4
in-house repeatability
measurement precision under a set of in-house repeatability conditions of measurement in a particular laboratory

Note 1 to entry: In-house repeatability conditions include the same measurement procedure, same technicians, same measuring system, same operating conditions and same location, and replicate measurements on the same or similar objects over a short period of time in a particular laboratory.

3.5
in-house reproducibility
measurement precision under in-house reproducibility conditions of measurement in a particular laboratory

Note 1 to entry: In-house reproducibility conditions include different technicians, operating conditions, and replicate measurements on the same or similar test items over a certain period of time in a particular laboratory.

3.6
sample material
material from which the samples are made

Note 1 to entry: The choice of sample material can have an effect on the bias of the measurement procedure.

3.7
factor level combination
combination of factor levels

EXAMPLE Technician 1 + culture medium 2 + temperature 1 + etc.

Note 1 to entry: These conditions can be described by the combination of factor levels corresponding to those factors varied within the study.

3.8
test portion
quantity of material, of proper size for measurement of the concentration or other property of interest, removed from the test sample, used for a particular measurement

[SOURCE: ISO 11074:2015[4], 4.3.15, modified — "used for a particular measurement" has been added, and Note 1 to entry and Note 2 to entry have been deleted.]

4 Symbols

A_j	Absolute component of the linear block effect j
$A(j)$	Absolute component of the effect of factor level combination j
a_{ijk}	Absolute component of the repeatability error for measurement result Y_{ijk}
B_j	Relative component of the linear block effect j
$B(j)$	Relative component of the effect of factor level combination j
b_{ijk}	Relative component of the repeatability error for measurement result Y_{ijk}
$df(x)$	Effective degrees of freedom at level x
i	Identifier for a particular level
	Identifier for a particular measurement (see Annex F)
j	Identifier for a particular sample or block or factor level combination
	Identifier for a particular measurement (see Annex F)
$L(\theta)$	Log-likelihood for variance components θ
k	Identifier for a particular measurement result at level $i = 1,\ldots,m$ in block $j = 1,\ldots,n$
	Coverage factor for measurement uncertainty
$\boldsymbol{M}$	Transformation matrix used in REML estimation
m	Number of levels of the measurand
n	Number of samples or blocks or factor level combinations at one level of the measurand
p	Number of measurement results obtained at one level and one sample, block or factor level combination

q	Number of factors
REML	Estimate arising from a restricted maximum likelihood calculation
$s_f(j)$	Factor level of factor $f = 1,\ldots,q$ at factor level combination j
$u\left(\hat{x}_{ij}\right)$	Standard measurement uncertainty of the estimated value of the level x
$u(Y)$	Standard measurement uncertainty of the measured value Y for the true level x
$U(Y)$	Expanded measurement uncertainty of the measured value Y for the true level x
$\boldsymbol{V}(\boldsymbol{\theta})$	Covariance matrix used in REML estimation
$\boldsymbol{X}$	Design matrix for REML estimation
x	True value of the level of the measurand
$\hat{x}$	Estimated value of the level of the measurand
x_{ij}	True value of the level of the sample at level $i = 1,\ldots,m$ in block $j = 1,\ldots,n$.
x_{L}	Lower limit of measurement uncertainty interval
x_{U}	Upper limit of measurement uncertainty interval
Y_{ijk}	Measurement result of the test portion (i,j,k) at level $i = 1,\ldots,m$ in block $j = 1,\ldots,n$ for replicate $k = 1,\ldots,p$
Y	Measured value
$\boldsymbol{Y}$	Vector of measured values for REML estimation
Y_{corr}	Corrected measured value (recovery correction)
α	True value of absolute component of method bias
$\hat{\alpha}$	Estimated value of absolute component of method bias
β	True value of relative component of method bias plus 1 (relative recovery)
	Vector of true value of absolute component of method bias and true value of relative component of method bias plus 1 for REML estimation
$\hat{\beta}$	Estimated value of relative component of method bias plus 1 (relative recovery)
$\boldsymbol{\theta}$	Vector of variance components used in REML estimation
$\mu(x)$	Expected measured value at level x, $\mu(x) = \alpha + \beta x$
σ	True value of a standard deviation
σ^2	True value of a variance
$\hat{\sigma}$	Estimated value of a standard deviation
$\hat{\sigma}^2$	Estimated value of a variance
$\sigma_{\mathrm{ri}}^2(x)$	True value of a variance function under in-house repeatability conditions at level x
$\sigma_{\mathrm{Ri}}^2(x)$	True value of a variance function under in-house reproducibility conditions at level x

$\sigma_{\hat{\mu}}^2(x)$ True value of the standard variance of the linear function of the expected measured value

5 General principles

5.1 General

Top-down procedures for the determination of measurement uncertainty depend on whether a conventional approach (see 5.2) or a factorial approach (see 5.3) is chosen. In any case, all results are valid only for the laboratory within which the study was conducted.

5.2 Principles of conventional approach

The conventional approach assumes that all measurements can be grouped in blocks. For measurements within a block, in-house repeatability conditions are fulfilled. For measurements between blocks, in-house reproducibility conditions are fulfilled. Thus, between blocks, there is variation with respect e.g. to time of measurement, technician, environmental conditions, batches of reagents or measuring instruments.

5.3 Principles of factorial approach

Compared to the conventional approach where measurement conditions vary randomly from one measurement block to the other, in the factorial approach at least some of these measurement conditions are controlled. For instance, half the measurements are conducted with reagents from batch A, and the other half with reagents from batch B. In contrast, the conventional approach where, apart from the grouping factor (e.g. day 1 and day 2), there is no control of measurement conditions. The factorial approach allows the assessment of the measurement uncertainty of the test results obtained under a variety of typical test conditions in a given laboratory, such as different analysts, different instruments, different lots of reagents, different elapsed assay times and different assay temperatures. The factorial approach aims at establishing reliable precision data and measurement data by simultaneous controlled variation of the selected factors. It allows the evaluation of the combined impact of factorial effects.

6 Conventional approach

6.1 General considerations

The conventional approach consists of the following parts:

— selection of levels of the measurand (for example concentration levels) and sample materials;

— design of study and allocation of test portions to different blocks;

— conducting the measurement;

— statistical analyses.

The results (tables and calculations), including discrepant results, if any, shall be given in a study report.

6.2 Selection of samples and levels

The study is typically conducted using m = 4,..., 8 homogeneous sample materials at different levels of the measurand from the same sample type. Samples should differ only with regard to the level of the measurand. The ratio of the maximum level divided by the minimum level should be at least 1,5 but not larger than 50. If the ratio exceeds 4, additional testing of statistical model assumptions (linearity, homoscedasticity) and examination of effective degrees of freedom is required.

6.3 Experimental design

The sample material is available in *m* different levels of the measurand. For each level, *n* samples are randomly allocated to *n* blocks (where $n \geq 8$). Thus, each of the *n* blocks consists of *m* samples, each sample with a different level of the measurand. Each sample consists of *p* test portions, i.e. *p* represents the number of replicates at each level and each block. There is no limit on the number of replicates *p*; even without replication ($p = 1$) precision and uncertainty can be computed, although better reliability is obtained with $p \geq 2$ replicates.

Each block contains $m \times p$ test portions, and altogether there are $m \times n \times p$ test portions. The $m \times p$ test portions of each block shall be analysed under in-house repeatability conditions. Different blocks shall be analysed under different conditions, preferably with different equipment, different personnel and in different weeks. Thus, if the blocking (grouping) factor is *week*, a total of *n* weeks, for instance, are required for measuring $m \times n \times p$ test portions. The blocking factor should be chosen so that temporal autocorrelation can be excluded, i.e. a longer period is generally better than a shorter period.

NOTE 1 Reliability of precision data is highly dependent on the number of blocks (see ISO 5725-1). Relative standard error of uncertainty data can exceed 29 % if there are fewer than $n = 8$ blocks.

6.4 Statistical analysis

6.4.1 Statistical model

Y_{ijk} denotes the measurement result of the test portion (i, j, k) at level $i = 1, \ldots, m$ in block $j = 1, \ldots, n$ for replicate $k = 1, \ldots, p$.

x_{ij} denotes the true value of the level of the corresponding test portion at level $i = 1, \ldots, m$ in block $j = 1, \ldots, n$.

The statistical model is

$$Y_{ijk} = \alpha + \beta x_{ij} + A_j + B_j x_{ij} + a_{ijk} + b_{ijk} x_{ij} \quad (1)$$

where

- α and $\beta - 1$ denote the absolute and the relative component of method bias, respectively;
- A_j and B_j denote the absolute and the relative component of the linear block effect j, respectively;
- a_{ijk} and b_{ijk} denote the absolute and the relative component of the repeatability error for measurement result Y_{ijk}.

NOTE 1 In the model described here, it is assumed that the true value x_{ij} of the measurand is known. In practice, it is an estimated value $\hat{x}_{ij}$ of x_{ij} that is subject to uncertainty. If the uncertainty of this value is small compared to the uncertainty of Y, for computational purposes x_{ij} can be replaced by $\hat{x}_{ij}$. This is the case, for example, when blank material is spiked with a high-purity substance. If spiking is carried out in one step before the material is homogenized and distributed to the individual samples, x_{ij} does not depend on block j. However, if the individual samples are spiked gravimetrically, the concentrations x_{ij} could be different. The same applies if the material cannot be perfectly homogenized and the determination of x_{ij} is carried out by a very accurate reference method.