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SELECTIVITY IN ANALYTICAL CHEMISTRY

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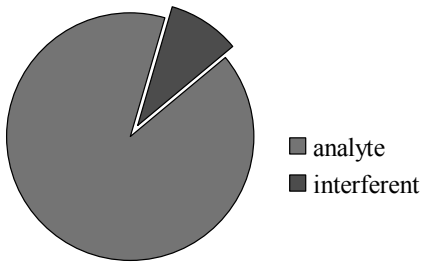
Quantitative chemical analysis in mixtures requires methods of appreciable selectivity. There is also an ever increasing pressure towards analytical chemists to prove the level of performance of analytical methods by appropriate figures of merit. Selectivity is a property of analytical methods and tools which appears to defy efforts for defining and measuring it. We analyze here a broad spectrum of books, papers, and official documents about selectivity. The approaches and definitions that we have found are quite divergent and sometimes obscure. The greatest dilemma appears to be if selectivity can be meaningfully graded or numerically characterized, *i.e.*, if a figure of merit can be attributed to it. The question is raised if a general definition of analytical selectivity is possible at all.



INTRODUCTION

Probably any analytical chemist would agree that selectivity is a very important or even a central idea of analytical chemistry. Yet there appears to be much confusion in the literature about the meaning of analytical selectivity.

Most analytical chemistry textbooks avoid any detailed discussion of selectivity. Typically they only cite a IUPAC definition.

National and international agencies and organizations devoted to the quality of analytical measurements have issued many documents, guidelines and the like which include definitions and discussions of selectivity in analytical chemistry. Some of these documents diverge in their definitions of selectivity.

Clinical chemistry is a very important special field where analytical methods are used. While this is a limited context for analytical chemistry it is very relevant for selectivity considerations because clinical measurements are literally of vital importance. Interestingly, the clinical chemistry literature only rarely uses the idea of selectivity. Instead, they speak of interferences. In contrast to the chemical literature interferences include besides, the effects of particular chemicals also the effects of more generic sample properties, like haemolysis or lipemia, and even factors like carryover between samples.

In the analytical chemistry literature there are two focuses of selectivity discussions:

1. Selectivity of fully developed methods (*e.g.*, methods ready for validation or validated)
2. Selectivity of tools and techniques, like a sensor, a separation technique, *etc*.

Fully developed methods may be directed towards the determination of a single analyte or

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they can be multianalyte methods. The latter may be either simple juxtapositions of independent methods for each analyte or they can be "multivariate" methods, where each measured quantity (for example absorbances at different wavelength values) is influenced (at least in principle) by each analyte. Selectivity considerations for multivariate methods are amply found in the chemometric literature. These chemometric discussions are usually limited to multilinear responses, *i.e.*, when the measured values on each channel (*e.g.*, at each wavelength) are homogeneous linear functions of the analyte concentrations. Note that in some cases multivariate methods are used to determine the concentration of a single analyte only. In such cases the multivariate response is used only to eliminate the effects of the other components.

In this paper these introductory statements are given many illustrations from the literature. This will be followed by an analysis which can hopefully lead further in clarifying the concept of selectivity in analytical chemistry.

THE WORD "SELECTIVITY"

Selectivity is a commonly used word even outside of analytical chemistry. The word 'selectivity' originates from Latin 'selego', meaning 'to choose' or 'to select',[1] but it is difficult to find definitions that refer to chemical topics. Selective is defined as "tending to choose carefully"[2] and selectivity as "the state or quality of being selective."[3] By combination of the foregoing, selectivity should be "the state of choosing carefully". As discussed by Jörgen Vessman *et al.*,[4] this interpretation would perfectly suit the use of the term in analytical chemistry where selection is a key issue. In the analytical chemical literature the term selectivity is very often combined with words such as adjustment, generation, tuning, optimization, modifying, enhancing, and coefficients or constants. Methods may show good selectivity, or even high, excellent or extreme selectivity. The use of these expressions indicates that selectivity is something that can be graded or even expressed in a quantitative manner.

IUPAC recommends the following definition for selectivity in analytical chemistry: "Selectivity refers to the extent to which the method can be used to determine particular analytes in mixtures or matrices without interferences from other components of similar behavior."[5] This definition will be used here for comparison with the other definitions that follow.

Specificity is a word having similar meaning to selectivity. There has been much controversy about the distinction between these two words. The IUPAC recommendation from 2001[6] discourages the use of the term specificity for the idea of selectivity. They consider specificity only as the ultimate of selectivity.

SELECTIVITY IN ANALYTICAL CHEMISTRY TEXTBOOKS

The treatment of the concept of selectivity in analytical chemistry textbooks is usually only marginal. In the index of such textbooks only a few occurrences of the word selectivity are listed and these are mostly related to some particular techniques, like ion selective electrodes. In many textbooks one can find some definition of selectivity but these are quite different from textbook to textbook.

Douglas A. Skoog *et al.* in "Fundamentals of Analytical Chemistry"[7] give the definition just in glossary: "Selectivity – the tendency for a reagent or an instrumental method to react with or respond similarly to only a few species."

Daniel C. Harris in "Quantitative Chemical Analysis"[8] equates selectivity with specificity: "Selectivity (also called specificity) means being able to distinguish analyte from other species in the sample (avoiding interference)."

David C. Harvey in "Modern Analytical Chemistry"[9] defines selectivity as "a measure of a method's freedom from interferences as defined by the method's selectivity coefficient." This definition seems to imply that for every analytical method selectivity coefficients exist which can be defined in an unambiguous way.

In the fifth edition of Gary D. Christian's Analytical Chemistry textbook[10] a method is called specific "when the analyte alone is responsible for the signal that is measured." According to the author "a clear distinction should be made between the terms specific and selective. A specific reaction or test is one that occurs only with the substance of interest, while a selective reaction or test is one that can occur with other substances but exhibits a degree of preference for the substance of interest.

Few reactions are specific, but many exhibit selectivity." Note that the expression: "exhibits a degree of preference" allows even very slight preferences. If the analyte and an interfering compound are both present in a sample at similar concentration, then a slight preference is not sufficient for selective determination of the analyte. In such a case the test would not be selective in the sense of the IUPAC 2001 definition.

In the sixth edition of Christian's textbook[11] beyond the cited section of the previous edition another one has been added in a different chapter where selectivity has been defined as "the extent that the method can measure the analyte of interest in the matrices of the samples being analyzed without interference from the matrix (including other analytes)." Here the IUPAC 2001 definition, which was published between the two editions of the book, has been used, but without the limitation to interferences from "other components of similar behavior".

According to the first edition of "Analytical chemistry", by Robert Kellner *et al.*,[12] "Selectivity gives an indication of how strongly the result is affected by other components in the sample. In various methods different factors are used to assess this selectivity in a quantitative way." In addition, it is proposed that the use of specificity should be avoided. However, irrespective of this, there is a lack of consistency in the book and among the figures of merit; even though the avoidance was suggested, specificity is used in parallel. The second edition of this textbook from 2004[13] differs substantially from the first. In this edition M. Valcarcel wrote the chapter dealing with the figures of merit. Here two full pages deal with selectivity and many important statements are made. The definition of selectivity is a bit confusing, however. Selectivity "is defined as the ability of a method to produce signals (and results) that are exclusively dependent on the analyte in the sample. Specificity is, in general, the property of analytical methods that expresses the ultimate selectivity level or the absolute absence of interferences. A lack of selectivity is caused by so-called 'interferences', which are perturbations arising from the sample that alter one, some, or all the steps of the analytical process. Selectivity can only be ascribed to an analytical process for a particular sample-analyte pair." Probably more explanation would be needed to rationalize these definitions.

SELECTIVITY AS DEFINED BY DIFFERENT ORGANIZATIONS AND AGENCIES

Several organizations and agencies have issued documents where analytical selectivity has been defined explicitly or implicitly. Most notable are the recommendations of IUPAC. There are two such recommendations, one from 1983[5] and one from 2001.[6]

The IUPAC 1983 recommendations make some important statements. Already in the introduction it is stressed that "all terms discussed below and all propositions with respect to their use can only be applied to completely described methods of analysis, including sampling and data handling." In this document the definition of selectivity is based on the definition of interference. "An interfering substance for an analytical procedure is one that causes a predeterminate error in the analytical result." The meaning of "predeterminate error" is explained somewhat later: "In the case of a quantitative method of analysis the allowable magnitude of the systematic error should be fixed beforehand…". One may deduce from these statements (with a little extrapolation) that interference is caused by one or more interfering substances and that the presence of interference is detected by the systematic error exceeding a predetermined limit. It is also correctly added later in this document that "the extent of an interference is not necessarily proportional to the concentration or the content of the interferent in the sample and that the effect of the presence of several interferents is not always additive. Synergistic, as well as compensating effects, may occur." The problem with the IUPAC 1983 definition of interference is that a substance as such cannot cause a systematic error. One has to say also something about the concentrations. This has been recognized by adding the following remark: "… whether or not a substance interferes depends on the amount of the interferent and that of the analyte in the sample." The definition of selectivity in this document appears to be somewhat vague. The authors discourage analytical chemists from trying to use numerical quantities for characterizing selectivity. They recommend to use the words selective and selectivity only in a qualitative sense to characterize the extent to which the determination of a substance according to a given procedure is subject to interferences. This "qualitative characterization" is a rather weak (or

at least insufficiently explained) point in this recommendation. It reminds one of what Lord Kelvin has said: "when you can measure what you are speaking about, and express it in numbers, you know something about it; but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meager and unsatisfactory kind."[14] The quantitative use of the word selectivity is only recommended in the IUPAC 1983 document in combinations like selectivity factor (in ion exchange) or selectivity coefficient (of ion selective electrodes). The IUPAC 2001 recommendation defines selectivity in the following way: "Selectivity refers to the extent to which the method can be used to determine particular analytes in mixtures or matrices without interferences from other components of similar behavior." It is added that "…practical ways of calculating or quantifying selectivity will be dealt with in a future project." Thus the IUPAC 2001 recommendation reduces the range of interferents to components of similar behavior to the analyte, and it recognizes the difficulty of qualitative characterization in the IUPAC 1983 recommendation.

The definition by WELAC (Western European Laboratory Accreditation Cooperation)[15] is similar to the IUPAC 1983 definition "Selectivity of a method refers to the extent to which it can determine particular analyte(s) in a complex mixture without interference from other components in the mixture. A method which is perfectly selective for an analyte or group of analytes is said to be specific."

A number of other organizations have defined selectivity differently from IUPAC. These definitions relate also to completely described methods of analysis but they consider them selective only when no interference is apparent in typical samples. Thus for these organizations the differentiation between selectivity and specificity is irrelevant and the two terms are sometimes used interchangeably. A few examples for these definitions are shown below.

In 2001 the definition of selectivity by the U.S. Department of Health and Human Services (HHS), Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), and Center for Veterinary Medicine (CVM) said:[16] "Selectivity is the ability of an analytical method to differentiate and quantify the analyte in the presence of other components in the sample. For selectivity, analyses of blank samples of the appropriate biological matrix (plasma, urine, or other matrix) should be obtained from at least six sources. Each blank sample should be tested for interference, and selectivity should be ensured at the lower limit of quantification (LLOQ). Potential interfering substances in a biological matrix include endogenous matrix components, metabolites, decomposition products, and in the actual study, concomitant medication and other exogenous xenobiotics. If the method is intended to quantify more than one analyte, each analyte should be tested to ensure that there is no interference." The same document later uses the word specificity interchangeably with selectivity.

An explanation of the above selectivity definition was written by Surendra Bansal and Anthony DeStefano.[17] "Selectivity or specificity should be assessed to show that the intended analytes are measured and that their quantitation is not affected by the presence of the biological matrix, known metabolites, degradation products, or co-administered drugs. Specificity should be determined for each analyte in the assay. Selectivity determination depends on the type of the assay… In assays, wherein the intrinsic selectivity is low (*e.g.* HPLC or GC with detection other than MS), it is necessary to confirm, using blank matrices from at least six independent sources, that the biological matrix will not interfere significantly with the assay. The same matrix as in samples should be used whenever possible. A proxy matrix is allowed if the sample matrix is of limited availability. The blank matrix should not produce any significant interference at the retention time of the analytes. For chromatographic assays, the peak response in the blank matrix at the retention time of analyte(s) should be no more than 20% of the response for the lower limit of quantitation (LLOQ) sample."

The European Medicines Agency (EMEA) and Committee for Medicinal Products for Human Use (CHMP) issued the following definition in 2011:[18] "the analytical method should be able to differentiate the analyte(s) of interest and internal standard (IS) from endogenous components in the matrix or other components in the sample. Selectivity should be proved using at least six individual sources of the appropriate blank matrix, which are individually analyzed and evaluated for interference. Use of fewer sources is acceptable in case of rare matrices. Normally, absence of interfering components is accepted where the response is less than 20% of the lower limit of

quantification for the analyte and 5% for the internal standard. It may also be necessary to investigate the extent of any interference caused by metabolites of the drug(s), interference from degradation products formed during sample preparation, and interference from possible co-administered medications."

One of the latest definitions was published by EURACHEM in "Terminology in Analytical Measurements; Introduction to VIM3"[19] in 2011 and by Joint Committee for Guides in Metrology (JCGM) in "International vocabulary of Metrology – Basic and general concepts and associated terms (VIM)."[20] Within part 'selectivity of a measuring system' selectivity is defined as "property of a measuring system, used with a specified measurement procedure, whereby it provides measured quantity values for one or more measurands such that the values of each measurand are independent of other measurands or other quantities in the phenomenon, body, or substance being investigated." This definition relates to a much wider field than analytical chemistry as shown by the appended examples and notes. Some of these are cited here for illustration.

"EXAMPLE 1. Capability of a measuring system including a mass spectrometer to measure the ion current ratio generated by two specified compounds without disturbance by other specified sources of electric current;

EXAMPLE 4. Capability of a measuring system for ionizing radiation to respond to a given radiation to be measured in the presence of concomitant radiation;

EXAMPLE 5. Capability of a measuring system to measure the amount-of-substance concentration of creatininium in blood plasma by a Jaffé procedure without being influenced by the glucose, urate, ketone, and protein concentrations;

EXAMPLE 6. Capability of a mass spectrometer to measure the amount-of-substance abundance of the ^{28}Si isotope and of the ^{30}Si isotope in silicon from a geological deposit without influence between the two, or from the ^{29}Si isotope.

NOTE 3. In chemistry, selectivity of a measuring system is usually obtained for quantities with selected components in concentrations within stated intervals."

In clinical chemistry the possibility of any kind of interference is of utmost importance. For example, an extensive guideline (107 pages) was published in 2005 dealing only with interference testing. This guideline uses only the term specificity; selectivity is not mentioned at all.[21] The general (metrological) definition of specificity is stated in this guideline as the "ability of a test or procedure to correctly identify or quantify an entity in the presence of interfering phenomena/influence quantities". Here influence quantity is an expression used equivalently with interfering substance or interferent. Analytical specificity is defined on the basis of ISO 17511 as "ability of a measurement procedure to measure solely the measurand." These definitions are in accord with IUPAC meaning of specificity, although IUPAC does not recommend the use of this term. The definition of interference is particularly notable in this guideline: "interference – in *Clinical Chemistry*, a cause of clinically significant bias in the measured analyte concentration due to the effect of another component or property of the sample." Only a clinically significant bias is considered as interference effect and interference is not limited to components but extended also to sample properties.

CITAC (The Cooperation on International Traceability in Analytical Chemistry) and EURACHEM (A Focus for Analytical Chemistry in Europe) defined selectivity in "Guide to Quality in Analytical Chemistry. An Aid to Accreditation" published in 2002.[22] The same definition is proposed by the UNODC (United Nations Office on Drugs and Crime) in 2009:[23] "Selectivity of a method refers to the extent to which it can determine particular analyte(s) in a complex mixture without interference from the other components in the mixture. A method which is selective for an analyte or group of analytes is said to be specific. The applicability of the method should be studied using various samples, ranging from pure measurement standards to mixtures with complex matrices. In each case the recovery of the analyte(s) of interest should be determined and the influences of suspected interferences duly stated. Any restrictions in the applicability of the technique should be documented in the method. This work will allow a clear description of the measurand to be made." The given definition of selectivity is actually expanded from the WELAC definition from 1993.[15] The problem with this definition is with defining selectivity first as an extent but then equating it with specificity. The advantage of this text is that it gives a general recipe for testing specificity.

CHEMOMETRIC SELECTIVITY IDEAS

Chemometry deals mainly with multivariate data analysis in chemistry. Thus chemometricians have been interested for decades in the determination of multiple analytes by measuring multiple signals. In general each signal may depend on the concentrations of all the analytes. If we have n analytes we need $m \geq n$ signals (or measurement channels). The measured value on the i-th channel can be expressed as:

$$y_i = f_i (c_1, c_2, \ldots c_n) \qquad i=1, 2, \ldots m$$

From the measurement on m channels one may obtain (with the exception of some cases) the n concentration values. If $m = n$, then inversion of the equation system is needed. If $m > n$, then the system is overdetermined (again with exception of some cases). In the case of overdetermined systems an error minimization method needs to be used, too (*e.g.*, a least squares method). The inversion is usually too complex unless all f_i functions are linear in all concentration variables, with zero intercept. Linearity means also additivity here:

$$y_i = a_{i1} \cdot c_1 + a_{i2} \cdot c_2 + \ldots + a_{in} \cdot c_n \quad i = 1, 2, \ldots m$$

In the case of such linear relationships (where the "a" factors are typically all non-negative) it is easy to express the selectivity of a particular channel's signal for the k-th component against any other component, *e.g.* for component 1:

$$\text{selectivity} = \frac{a_{ik}}{a_{i1}}$$

One could also define a selectivity for the k-th compound versus all others. Yet all these selectivities would only show the relative contributions of the k-th compound to the i-th *signal*. But in analytical chemistry we are interested in the estimated value of the *concentration* of the k-th compound and in the effects of the other compounds (or rather of the concentrations of the other compounds) on the estimated c_k value. These effects can be studied using matrix algebra and this topic is beyond our discussion here. May it suffice to mention that Heinrich Kaiser was apparently the first who thoroughly investigated this matter in the early 1970-s.[24,25] Computer technology and algorithms were still little developed and probably he did not have access to the best techniques. In any case he had limited his work to the $m = n$ case and he used a matrix inversion algorithm which required that in each line of the matrix one element should be larger than the sum of the other elements in the same line. This largest element had to be in a different column for each line. Therefore he defined selectivity in such a way that its value was 0 if this condition was fulfilled. For "fully selective" procedures (*i.e.* when every channel is sensitive to only one analyte and each analyte has a channel sensitive to it) the selectivity defined by Kaiser becomes formally infinitely high. He called a method *selective* if its selectivity value was positive. This meant that the concentration of any of the n compounds could be relatively easily obtained. In other words the analyst could freely choose the concentration to be determined. This freedom of choice was the meaning of selectivity for Kaiser. His definition was often cited later but we are not sure if it was used in praxis.

More recently many chemometricians prefer to define selectivity based on a method devised by Lorber in 1986.[26] He introduced the idea of net analytical signal. This is best understood by considering absorbance spectra. The y_i values are absorbances at wavelengths i. These absorbance values run from $i = 1$ to $i = m$ and constitute an m-vector. If we know the spectra of each compound at unit concentration (these spectra are now m-vectors) then we can consider the linear subspace defined by the respective spectrum-vectors of all compounds except for the analyte. We may then decompose the spectrum-vector of the analyte into its orthogonal projection on the subspace and a vector which is orthogonal to the subspace. This decomposition is unique. The component which is orthogonal to the subspace is called the net analytical signal of the analyte. If we measure now the spectrum of a mixture, this spectrum-vector can be decomposed in the same way. If the mixture did not contain any unknown compounds, than the net signal of the mixture will be parallel to that of the analyte and the ratio of the lengths of these two vectors will give the analyte concentration. Thus when calculating the analyte concentration we cannot use the full length of the analyte's spectrum vector, only the length of its net analytical signal vector is used. The ratio of the length of the net analyte signal to the full analyte signal may be considered a selectivity value. This topic has been discussed in detail in an IUPAC technical report in 2006.[27]

CONCLUSIONS

We have collected some of the typical pieces of literature on the analytical selectivity issue. Here we concentrated mainly on those papers which deal with the selectivity of fully developed methods. There is also a vast literature on the selectivities of particular analytical methodologies. These will be discussed elsewhere.

The papers and documents presented here have been grouped according to the approaches taken in them. Some authors – whose collective views are well represented in the IUPAC 1983[5] and the IUPAC 2001[6] recommendations – maintain the view that method selectivity can be qualitatively graded or numerically quantified and specificity is the utmost selectivity. Others – and most notably the quality assurance community – do not think of selectivity as a gradable or measurable quantity and for them only specificity exists. Chemometricians limit their discussion to multilinear systems where selectivity may be more easily quantified. Analytical chemistry textbooks usually do not seem to attribute much importance to a discussion of the selectivity of fully developed methods.

Such a wide scatter of expert opinions about a central idea of analytical chemistry is surprising and apparently requires deeper analysis. The picture would be even more complex if we had included here the selectivity of specific analytical techniques. May it suffice to mention here that in our practical work related to molecularly imprinted polymers we have encountered numerous methods for characterizing the selectivity of such polymers. These methods are often difficult or impossible to compare. A thorough analysis of all these problems is under way.

In conclusion one has to raise the question: is it possible at all to find a satisfactory general definition of analytical selectivity? Judging from the confusion in the literature one is tempted to say that the quest for the general definition and measurement of selectivity is an ill-posed problem.

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