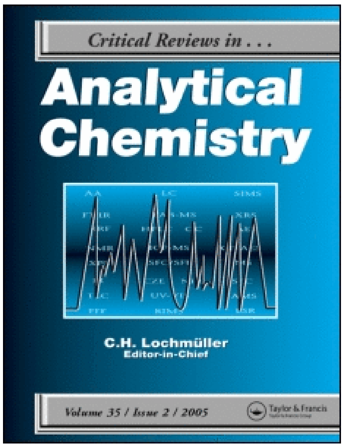

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Review and Classification of Univariate Interpolative Calibration Procedures in Flow Analysis

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Review and Classification of Univariate Interpolative Calibration Procedures in Flow Analysis

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A novel classification system introducing three main categories of the calibration methods—interpolative, extrapolative, and indicative—is suggested once more to be used in analytical chemistry. Then the univariate interpolative calibration procedures developed in the flow analysis are reviewed. In contrast to other similar reports, the present article does not present them with respect to instrumental aspects but as to how the measurement data recorded are interpreted and transformed into the analytical results. On such a basis, five groups of the calibration approaches have been specified. Finally, the particular groups of methods are compared with each other and discussed in terms of their analytical performance.

Keywords analytical calibration, analytical classification, analytical nomenclature, calibration methods, flow analysis

It is well known that analytical flow techniques reveal many advantages over conventional batch techniques, offering particularly the automation of chemical processing such as sampling, addition of reagents, dilution, preconcentration, and separation. Additionally, in the injection version, they produce an analytical signal in the form of a transient peak that is a potentially more rich source of information on the chemical system assayed than the steady-state signal typical for the conventional measurement mode. All those facilities are practically exploited in many analytical fields, including the analytical calibration.

The calibration is considered here as the reconstruction of the real dependence (calibration dependence) of the analytical signal on the concentration of a substance determined (analyte) in order to transform the signal measured for a sample assayed into the concentration of the analyte in this sample. In almost all cases, the calibration is realized in an empirical mode according to a well-defined procedure. Each calibration procedure, independently of how it is conceptually and instrumentally realized, consists of several essential stages; namely, (a) preparation of a sample and standard(s) (of well-known component concentration), (b) measurement of the analytical signals for the sample and standard(s), (c) interpretation of the measurement data (i.e., construction of the experimental calibration curve), and (d) calculation of the analytical results.

Owing to their characteristic features, the flow techniques offer a wide variety of the calibration procedures. They have been reviewed, discussed, and compared with each other in both the monographic books (1–4) and articles (5–8). However, in all those reports the procedures are presented and classified with special attention rather paid to their first two stages (i.e., as to how the sample and standards are instrumentally treated, prepared, and exposed to measurements). It has been shown there that the flow techniques are especially useful just in this area which allows the calibration to be performed in very ingenious and effective ways. As a consequence, it has been proved that the flow calibration procedures can be improved considerably in comparison with the conventional calibration procedures in terms of time, labor, and reagent consumption.

In this article, an attempt is made to review the flow calibration procedures in different manner; namely, in terms of their interpretative facilities. The suggested classification, which is certainly more essential than those met hitherto, is based on the aforementioned definition of the analytical calibration. Two main criteria are taken into consideration; namely, how the calibration dependence is *reconstructed* with the use of measurement data and how the measurement data are *transformed* into the analytical signal. It has been revealed that such an approach provides a greater chance of estimating and comparing the flow calibration procedures with respect to their analytical performance.

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MAIN CLASSIFICATION

Recently, the univariate calibration procedures developed in flow analysis were critically characterized and discussed (9). It has been stated that all of the procedures can be divided into three main categories of methods: interpolative, extrapolative, or indicative. The basic differences between those categories are schematically presented in Figure 1.

The interpolative calibration strategy (represented in batch analysis by the methods commonly named the calibration curve method or the set of standards method) is typified in that the standard solutions and the sample are prepared, treated, and measured separately from each other. As a consequence, the calibration dependence has a chance to be reconstructed in any required concentration range and the analytical result is calculated in the interpolative way (see Figure 1A).

The extrapolative strategy (represented by the standard addition method) comprises the addition of the standards into the sample and measurement of the analytical signal for total amount of the analyte. By doing so, the calibration dependence is able to be reconstructed only over the original concentration of the analyte in the sample and the analytical result has to be estimated in the extrapolative way (see Figure 1B).

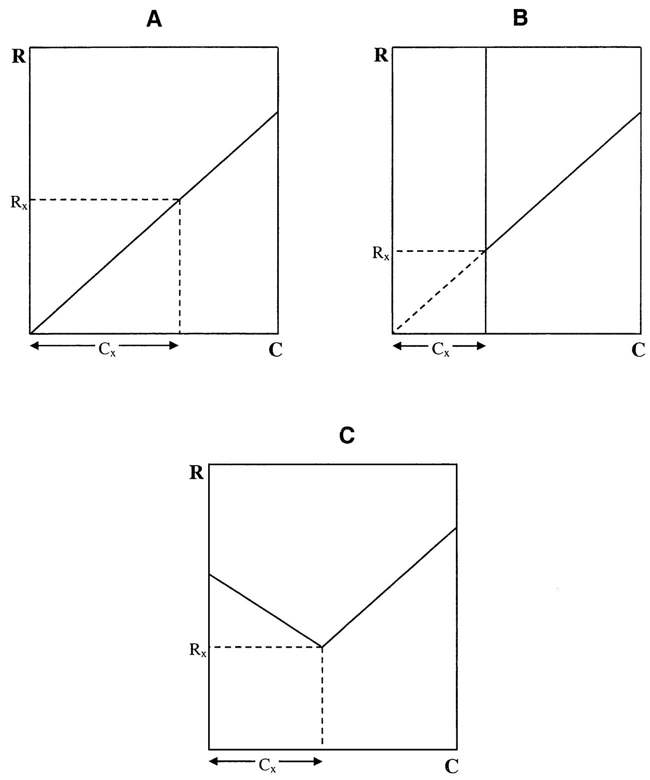

FIG. 1. Main classification of the calibration methods in analytical chemistry: In three categories of the calibration methods: interpolative (A), extrapolative (B), and indicative (C), the calibration dependence (R vs. C) is reconstructed in the form of calibration graphs (solid lines) and the signal measured for a sample (R_x) is transformed to the analyte concentration in the sample (C_x) in interpolative, extrapolative, and indicative ways, respectively.

The indicative calibration strategy comprises the titration procedures. It is performed if a titrant (i.e., a standard solution of a reactive component of well-known concentration) is successively added to a sample (or vice versa), and the analytical signals following a reaction of this component and the analyte are measured. A single signal indicating well-defined equilibrium conditions is transformed to the analyte concentration in the sample (see Figure 1c).

The present article is focused on those flow procedures which are employed for calibration by the interpolative method. The question of how the extrapolative and indicative methods are realized in the flow analysis will be a subject of separate articles.

DISCRETE RECONSTRUCTION

The calibration dependence can be considered as being reconstructed discretely if it is based on a set of several analytical signals measured one after the other for individual portions of the standard solution. In such a case, the measurement data are proposed to be transformed to the analytical signal directly or indirectly (i.e., by means of additional mathematical or experimental procedures). Either a single calibration graph or a family of calibration graphs is used for transformation process.

One-Graph Direct Transformation (DR-ODT)

In flow analysis, the calibration is commonly carried out in a traditional manner imitating the batch calibration procedure. It comprises the preparation of a set of separate standard solutions, introducing them one after the other into the flow system designed and measuring the analytical signals for each of them individually. A sample solution is treated by the same means. By doing so, a typical single calibration graph based on several experimental points is constructed and the signal measured for a sample serves for calculation of the analytical result in the interpolative way (i.e., as is shown in Figure 2).

The flow injection analysis (FIA) offers a special possibility of performing the calibration by the so-called "reverse flow technique." In this case, the standards are injected into the sample stream which flows continuously through a system (10). The signals produced after every injection are compared with the steady-state signal measured for a sample. The differences are plotted versus the analyte concentration in standards (see Figure 3), and the intercept on the concentration axis is an estimator of the analyte concentration in the sample. Such a calibration approach, called the interpolative standard addition method, has found relatively wide analytical application (11–16).

In the FIA, the signals are usually measured either in the peak-height or in peak-area mode. However, if a flow system works under the high-dispersion conditions (i.e., with a single well-stirred mixing chamber installed just before the detector), the width of the injection peak W can be mathematically connected with the analyte concentration C by:

$$W = \frac{V}{Q}\ln\left(\frac{C}{C'} - 1\right) - \frac{V}{Q}\ln(D - 1) \qquad [1]$$

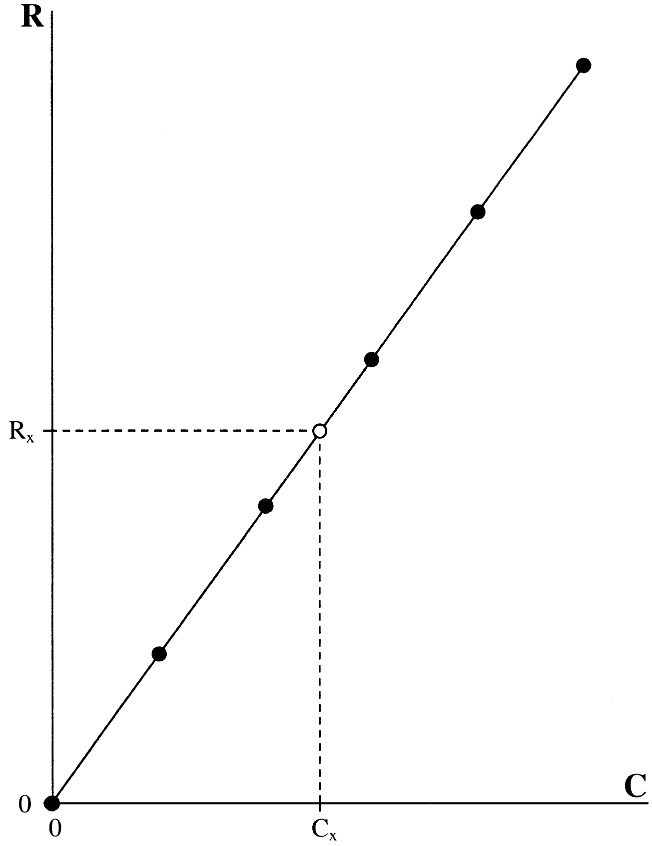

FIG. 2. Interpolative calibration performed according to the DR-ODT and DR-OIT strategies: Calibration graph (solid line) based on several experimental points serves for transformation of the signal measured for a sample (R_x) to the analyte concentration in the sample (C_x) either directly or using some indirect ways (for details see text).

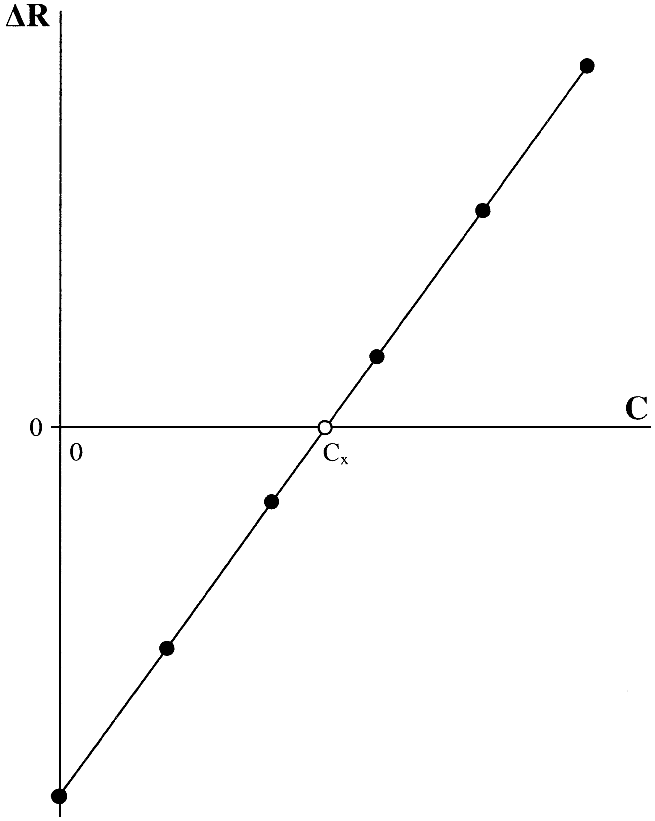

FIG. 3. Interpolative calibration performed according to the DR-ODT strategy with the use of reverse flow technique: Calibration graph (solid line) constructed by measurements of the signal difference (ΔR) and based on several experimental points serves for transformation of the zero-signal difference to the analyte concentration in the sample (C_x).

where V is the volume of the mixing chamber, Q is the flow rate through the chamber, D is the dispersion coefficient, and C' is the concentration corresponding to the signal chosen at the peak profile for peak-width measurements. The above relationship has been exploited for the calibration purposes (17, 18). Namely, the peaks produced for a set of standards were measured in the peak-width mode and the measurement data were plotted against $\ln[(C/C') - 1]$. The sample peak was measured in the same mode; hence, the width value obtained for the sample was related to the calibration graph and after some simple recalculations the analytical result was able to be estimated.

The DR-ODT calibration can be improved by using a single standard solution instead of a set of standards separately prepared. The condition is to use the flow manifold with a dedicated module allowing the standard to be successively and controllably diluted. After each step of dilution, a new standard of well-known analyte concentration is generated and exposed to measurement providing data for construction of the calibration graph. A single signal for a sample at a defined dilution degree (usually for an undiluted sample) is related to this graph.

The simplest version of such an approach has been proposed by Frary (19). In the fully automated continuous flow system coupled with the flame atomic absorption spectrometer, the peristaltic pump of a controlled flow rate delivered a single standard solution to the detector, but the difference between the pumping flow rate and the nebulizer uptake rate was compensated by aspirating diluent through a T-piece from the Mariotte bottle. With the pump running at its maximum rate nebulizer aspirated a small volume of diluent only, but as the pump was slowed the greater volume of diluent was aspirated. Thus, if the pumping rate was successively set to known values, the standard solution was controllably more and more diluted and the standards of progressively smaller analyte concentrations were able to be generated.

Another simple approach proposed the use of a loop of defined volume allowing a solution to be circulated with the aid of a pump (20). If the loop was initially filled with diluent, a standard of known volume introduced successively to it was able to be diluted controllably creating the standard solutions of desired analyte concentrations. The standard volume could be changed by a change of time and speed of the pump operation. A recirculating closed-loop manifold of a little different construction, but based on the same concept, is presented elsewhere (21, 22).

For an automatic DR-ODT calibration, the manifold for discontinuous flow analysis (DFA) was designed to allow the solutions to be mixed with each other in the flowing stream with the use of the cam-driven pump and conventional pumps (23). In the version of an incremental method, two solutions—a standard and a diluent—were involved. A constant flow rate to the detector was governed by a peristaltic pump, but the relative contribution to this rate from the standard and the diluent varies in a stepwise manner under the control of the cam-driven pump. As a consequence during the single-calibration cycle, the standard was mixed with the diluent in different well-defined ratios generating the signals in the form of plateaus.

A similar effect was able to be achieved using the fully rotary valve (FRV) (24). The FRV is a double-layer eight-channel design which, if compared with a conventional two-positional valve, is modified in such a way that the rotor, when activated, is capable not only of 45° but 360° rotation in relation to the stator. For the calibration purposes, the FRV was configured as a directive valve (25). A single standard was propelled into the FRV by four tubes and a diluent by four other ones. Both solutions were allowed to leave the FRV toward the detector by four tubes which are joined to each other. When the FRV was rotated gradually through eight particular positions, different parts of the standard were diluted by different parts of the diluent. It has been proved (25) that so many as seven standards of different well-defined analyte concentrations can be generated by this means.

One-Graph Indirect Transformation (DR-OIT)

The aforementioned calibration strategies are similar to the conventional calibration procedure in the sense that they use a set of standards of well-known analyte concentrations and the analytical signals measured for a sample can be transformed directly to the analytical result. However, the common case in flow analysis is to produce a set of different signals for local analyte concentrations which are in fact unknown. In such a situation, the crucial problem is how to find an indirect way of estimating these concentrations and making the calibration possible.

One can meet the above problem when the gradient technique is used (i.e., when the response of an analytical instrument is continuously processed for a solution of progressively changed concentrations of an analyte). The total response is then treated as a set of individual signals (measurement points) corresponding to the local analyte concentrations in the solution examined. Such a technique can be realized with the use of both continuous and injection flow systems.

An approach to obtain the calibration graph from a concentration gradient represented by a single FIA peak was suggested by Olsen et al. (26). It was assumed that each single transient signal obtained at a given delay time corresponds to a local analyte concentration in the standard zone. Hence, if a set of delay time values are considered, the calibration based on several points can be obtained from a single injection. So the calibration procedure encompassed injection of a standard solution, recording a peak, and extracting readouts from the falling part of the peak after strictly defined delay times. The same readouts were related to the calibration graph constructed separately by conventional means (i.e., by injection of a set of standards). By doing so the delay times were associated with the analyte concentrations, allowing the procedure to be used repeatedly without any additional experiments.

A lot of FIA calibration approaches exploit the possibility of using a single standard solution for generation of a set of standards in the form of separate zones. When flowing to the detector the zones are dispersed and, as a consequence, the local analyte concentrations corresponding to the maximum heights of the peaks produced are unidentified. The auxiliary factor used most often in such cases is dispersion coefficient D. It is found as the ratio of two signals obtained during the supplementary experiment for a test standard solution: a steady-state signal generated by the solution propelled continuously through an FIA system and the transient peaks produced by the solution injected and dispersed in given instrumental conditions. A local analyte concentration in every zone dispersed is then calculated taking into account the corresponding signal and the value of the dispersion coefficient.

In the FIA literature, many calibration procedures encompassing calculation of the dispersion coefficient can be found. Perhaps the oldest is that based on the zone sampling technique (27) where the solution was injected into a carrier stream and, after a predetermined time interval, a selected small portion of a dispersed zone was injected again (by another valve) into another carrier stream. By this means, a set of standards of different dispersions could be produced by changing the time interval. In another FIA system, the dispersion of a standard solution was proposed to be changed with the use of a peristaltic pump driven by a stepper motor that was actuated by pulses generated by a microcomputer (28). The same effect was achieved in the manifold allowing a standard solution to be propelled by tubes of different lengths installed between two six-way stream switching valves (29). In one more FIA system, a plug of the standard solution inserted into a carrier stream was merged with another carrier stream (30); in this case, the analyte concentrations in the standard solutions created depended on the volume injected and on the flow rates of merging streams.

A concept on how the calibration can be performed in the sequential injection analysis (SIA) technique has been presented by Baron et al. (31). The manifold employed a dilution conduit where a concentration gradient of analyte was stored. A standard solution was first aspirated into a holding coil and then a zone of the standard was transferred into a dilution conduit when it generated a concentration gradient resembling a typical FIA peak. Subsequently then, aliquots of equal volumes were withdrawn from the dilution conduit back into the holding coil to generate a calibration set of solutions of increasing concentrations. The solutions were propelled to a detector giving signals that were used for creating a calibration graph. For calibration purposes, it was sufficient to use the aliquots that spanned over the tailing part of concentration gradient. Before the method could be used as a calibration tool, the dispersion had to be defined for each aliquot taken from the dilution conduit for a given set of volume parameters.

Dispersion was also changed by varying the permeation degree of the gas analyte (ammonia) to the carrier stream (32). This effect was proved to be controlled by the flow rate of the solution examined. Thus the calibration procedure consisted of propelling a single standard solution by the permeation tube with various flow rates, producing in this way the standards of different analyte concentrations, injecting each of them, and measuring the corresponding signals. By this means, the relationship between the signals and the flow rate was able to be appointed. In this case the analyte concentrations in the standards produced was calculated not on the basis of the dispersion coefficient, but from the calibration graph constructed conventionally (i.e., with the use of a set of standards injected one after the other to the same flow system with avoidance of the permeation effect).

In the FIA analysis, there are some exceptional possibilities for transforming of an instrumental parameter by changing controllably to the analyte concentration through the means of well-defined mathematical expression. The examples of using such an approach for the DR-OIT calibration are given by Fang et al. (33) and Hernández-Córdoba et al. (34–40).

In the former case different volumes of a standard solution were suggested to be produced using controlled stepper-motor–driven peristaltic pumps and injected from a partially filling sample loop (33). It was proved that if the signals were measured for a series of well-known volumes injected, the analyte concentration C_s, corresponding to each volume V_s could be calculated from equation:

$$C_s = C_0 \cdot \left[1 - \frac{1}{2^{\frac{V_s}{V_{1/2}}}}\right] \qquad [2]$$

where C_0 is the analyte concentration in the solution introduced into the flow system and $V_{1/2}$ is the standard volume required to achieve a D value of 2 (before calibration the supplementary experiments were needed in order to estimate value $V_{1/2}$).

The flow systems designed by Hernández-Córdoba's group were dedicated to be coupled with flame atomic absorption spectrometer (34–40). In one of them a very low volume of a single standard solution was metered into the manifold by means of a peristaltic pump equipped with small bore pump tubes and turning at a low speed (34, 35). The metering time t_i had to satisfy the equation:

$$t = \frac{N}{\omega} \qquad [3]$$

where ω is the constant pump rate at which the metering stage is performed and N is an integer. It has been proved that if Condition 3 is fulfilled, the following simple relation between the initial (C_0) and produced (C_s) analyte concentrations is valid:

$$C_s = \frac{C_0}{N} \qquad [4]$$

The standard solution was measured at different N values (fixed by means of selection of appropriate T and ω values) whereas a sample was measured at a single N value. It was also found that the FIA system could be additionally calibrated by introducing a standard solution from the pump tubes of different internal radii (36, 37).

In another but very similar approach the continuous flow system was used where a peristaltic pump moved a solution to the flame atomic absorption spectrometer with variable flow rate, but the difference between the pumping flow rate and the nebulizer uptake rate was compensated by aspirating diluent through a T-piece (38–40). In this case, it was revealed that the signal-time profile obtained could be transformed to the conventional calibration graph using the following relationship:

$$C_s = \frac{C_0}{\omega \cdot r^2} \qquad [5]$$

where r is the pump tube radius. Thus a single standard solution was exposed to the measurements at different well-defined either ω or r values, whereas a sample was measured at a single value of these parameters. In Ref. (40), a sample was proposed to be transported to the detector through two tubes of different diameters in order to allow the steady-state signal to be changed toward the linear range of the calibration graph.

Several-Graph Direct Transformation (DR-SDT)

The calibration performed with the use of several calibration graphs is presented in Figure 4. In general, the graphs are constructed on the basis of the analytical signals which are measured for a set of standard solutions in well-controlled conditions defined by several different values of parameter P. If a sample is measured in the same conditions, the signals can be related to the corresponding graphs and a set of estimations (sometimes called the apparent concentrations) of the analytical result can be directly obtained.

The above strategy is represented by one of the oldest calibration approaches called the gradient dilution (26, 41). The calibration procedure involved a set of standards injected into the FIA system one after the other and the peaks obtained were synchronized with each other with respect to their base widths. The signals measured at a given defined time after the injection were believed to represent the standards being diluted to the same extent. Assuming that, the family of the calibration graphs could be constructed corresponding to particular values of delay time (as parameter P). The signals taken after the same delay time values from a single peak produced for a sample served for estimation of the analytical result by a few apparent concentrations.

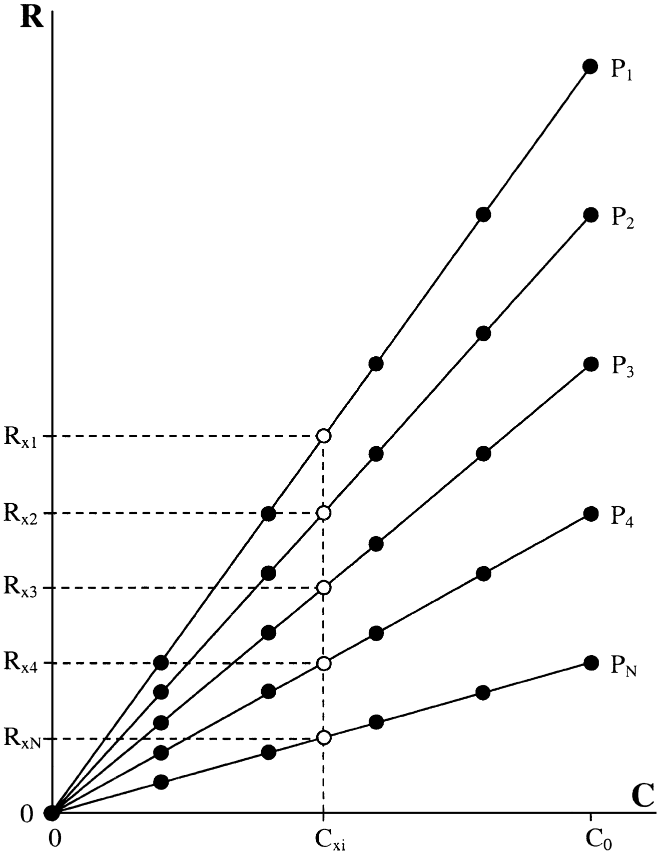

FIG. 4. Interpolative calibration performed according to the DR-SDT: Several calibration graphs (solid lines) obtained at defined instrumental parameters P_i and based on two or several experimental points serve for transformation of the signals measured at the same parameters for a sample (R_{xi}) to several estimations of the analyte concentration in the sample (C_{xi}).

In the mix-and-match calibration procedure, the FIA manifold was used for automated on-line dilution of a single standard solution introduced continuously to the flame atomic absorption spectrometer (42). It was found that, if a solution of analyte concentration C_0 flowing through the system with rate F_s was delivered to the nebulizer with rate F_0, analyte concentration C_s in the solution produced was given by:

$$C_s = \frac{C_0 \cdot F_0}{F_s} \qquad [6]$$

On this basis, it was proposed to measure a single signal for a sample undiluted and a set of signals for a stock standard solution progressively diluted. At each step of dilution (as parameter P), the linear calibration graph was constructed and the analyte concentration in the sample was calculated (taking Equation 6 into account). Dilution process was suggested to be continued until the standard signal was within 2% of the sample signal.

The DR-STD strategy can also be used in such situations (considered in the One-Graph Indirect Transformation [DR-OIT] section) where a single standard solution is used for generation of a set of standards in the form of separate zones of unknown local analyte concentrations. Instead of using some additional experimental or mathematical approaches to define the analyte concentrations, the calibration data can be interpreted in a specific direct manner. Namely, each signal measured for the standard generated under a given experimental condition (typified by parameter P) can be attributed to a single analyte concentration in the stock standard solution. By doing so, the family of two-point calibration graphs is obtained (when a set of standard solutions is used, the calibration graphs can be based on a few experimental points). If a sample is measured in at all considered values of parameter P, a set of apparent concentrations estimating the analytical result can be calculated.

The above approach is well represented by the calibration procedure developed by Tyson et al. (43). In the FIA manifold, a zone of the standard solution injected was directed to three tubes of different lengths that were merged with each other before the detector. Thus, the zone split into three subzones that reached the detector one after the other because of two reasons: different ways to the detector and their different residence times in the tubes. As a consequence, a threefold peak was produced with five characteristic measurement points of well-defined delay times (as parameters P): the three maxima and the two minima. When the sample solution was injected in the same way, five points of the sample peak were believed to be obtained at the same delay times as those of the standard peak and they could be used for estimation of the analytical result.

A similar effect was achieved with the FIA manifold where two zones of a standard solution were injected from the loops of different volumes and they were separated by a zone of water injected from an intermediate loop (44). When flowing to the detector, the standard zones overlapped each other to an extent controlled by the length and volume of the intermediate loop. A double peak was consequently obtained with one minimum and two maximum points. The measurement data stored for a standard and for a sample were interpreted as described previously.

In a more sophisticated FIA system, a calibration solution was able to be sequentially injected from several loops (45). Several zones produced in such a way overlapped strongly in the carrier stream and the multipart peak was consequently measured. In this case, a set of characteristic points (minima and maxima) taken from both the standard peak and the sample peak were taken for calibration.

Burguera et al. (46) proposed a manifold with a time-based variable volume injector that allowed intercalation of sample plugs of strictly defined volumes (parameter P) into the continuously flowing carrier stream by a fixed air pressure. The family of calibration graphs of different slopes was created after injection of the different volumes of a single prepared standard.

De la Guardia et al. (47) developed a variable-volume injector and coupled it to the flame atomic absorption spectrometer without using a peristaltic pump. Such a connection permitted the modification of the volume injected as a function of two parameters: the period of time corresponding to each pulse of the injector and the aspiration flow. It has been proved that, by working at different aspiration flow values (obtained by modifying the nebulizer position), different calibration graphs can be obtained for each pulse position.

Kościelniak et al. (48) proposed to perform the DR-SDT calibration using the FIA system with the FRV operated as the injection valve. When the valve was equipped with four loops of different volumes and it was fully rotated from the start position clockwise and inversely, as many as eight different signals were able to be produced from a single standard solution. This was so because the zones injected were dispersed differently not only due to injection of various volumes, but additionally due to different ways of transporting them from the FRV to the detector. Thus if different calibration parameters (i.e., loop volumes and distances to the detector) were taken into account, eight calibration graphs could be constructed allowing the analytical result to be estimated by the same number of apparent concentrations.

The DR-SDT calibration was also performed using the flow injection system working in accordance with the zone sampling technique (49). The family of the calibration graphs was constructed for a standard solution reinjected after several defined time volumes. In this case it was recommended to take into account only one signal for a sample (i.e., measured at one of the reinjected time volumes considered), which should be less than the highest signal obtained for a standard and great enough to ensure good sensitivity.

CONTINUOUS RECONSTRUCTION

The calibration dependence can be considered as being reconstructed continuously if the analytical signals are measured during the continuous change of the analyte concentration in a single standard solution. In such a case, the measurement data are transformed to the analytical result with the aid of a single calibration graph or by directly using a family of calibration graphs.

One-Graph Indirect Transformation (CR-OIT)

The CR-OIT calibration (schematically shown in Figure 5) is commonly realized in such a way that the calibration graph is constructed by means of the gradient technique with the use of a single standard solution and a single signal is measured for a sample solution (usually undiluted). Since the local analyte concentrations producing the transient signals are as a rule unknown, they are estimated either from mathematical expressions or on the basis of experiments performed separately. The calibration procedures can be performed with the use of continuous, discontinuous, and injection flow systems.

Tyson proposed the use of a high-dispersion continuous system providing concentration time profiles (10). Based on this concept, the method called the exponential dilution flask calibration method was developed and tested (11, 50, 51). In this approach, a single standard solution was continuously propelled through a well-stirred mixing chamber initially filled with a diluent solution and connected directly to the detector. When the measurement data were plotted against time (t), the multipoint exponential calibration graph was created. Time values could be transformed to the corresponding analyte concentrations C_s, according to the equation:

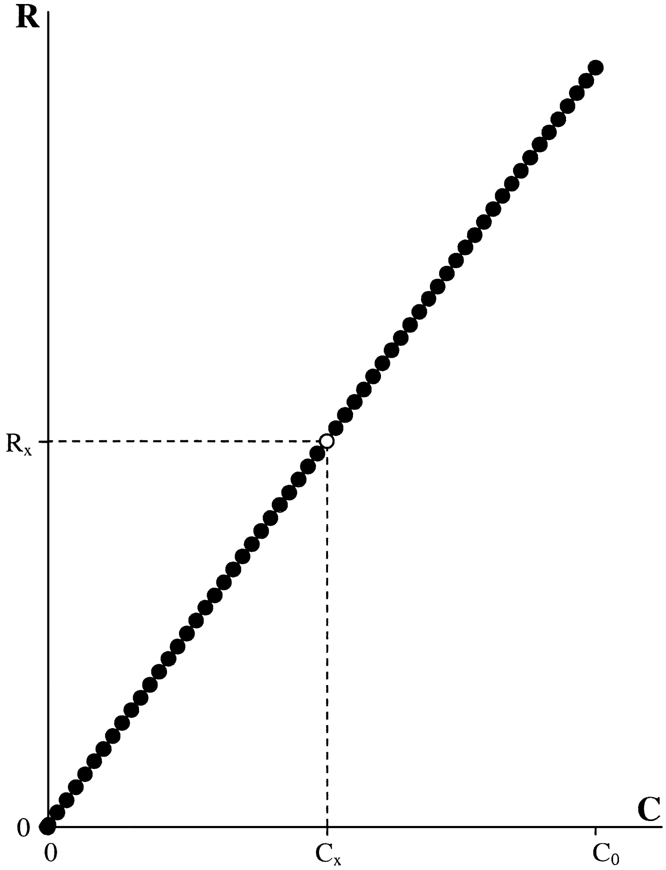

FIG. 5. Interpolative calibration performed according to the CR-OIT strategy: Calibration graph (points) based on many experimental points serves and obtained usually by dilution of a single standard solution of the analyte concentration C_0 serves for transformation of the signal measured for a sample (R_x) to the analyte concentration in the sample (C_x).

$$C_s = C_0 \cdot \left[1 - \exp\left(-\frac{Qt}{V}\right)\right] \quad [7]$$

where C_s is the analyte concentration in the standard introduced, V is the volume of the mixing chamber, and Q is the flow rate through the chamber. For the sample, the steady-state signal was measured and related to the calibration graph S versus t in order to estimate the corresponding time value. Finally, the analytical result was calculated from Equation 7.

A similar approach has been presented with the use of the FIA system (52, 53). A discrete volume of a standard solution was injected into a carrier stream and then introduced continuously to the mixing chamber. The falling part of the peak profile generated was considered for calibration purposes as the dependence between transient signals and time (t). Empirical relationship 8 was established with the use of a series of standards to make possible the transformation of the signal-time profile to the signal-concentration calibration graph:

$$C = A \cdot B^t \tag{8}$$

where A and B are empirical coefficients (A is directly proportional to the concentration of the standard injected and B depends on the manifold volume and flow rate employed).

For calibration according to the CR-OIT strategy, the manifold for discontinuous flow analysis (DFA) was also adapted (23). In this case, two standard solutions of different analyte concentrations were exceptionally used. Both solutions were mixed with each other through the use of three piston pumps working continuously in such a specific manner (optimized in the separate experiments) that the linear calibration gradient defined by low- and high-analyte concentrations in the standards was able to be generated. The fourth pump of the manifold dispensed a sample at a constant rate, which was equal to the overall flow rate of the standard solutions.

Interesting approaches belonging to the CR-OIT strategy were proposed by Hernández-Córdoba's group (54, 55). In one of them, a manifold with two variable-speed peristaltic pumps has been designed (54). One of the pumps moved a standard solution with the flow rate linearly increased in time, while the second one displaced a diluent solution with the flow decreased linearly at the same rate. In this way, both solutions merged with each other were propelled to the detector with the constant flow rate creating the concentration gradient and signal-time profile. The sample solution was pumped continuously through the manifold producing steady-state signal S_x. The analyte concentration in the sample C_x, was proposed to be calculated from the equation:

$$C_x = \frac{S_x}{S_{\text{fit}}} \cdot C_0 \tag{9}$$

where C_0 is the analyte concentration in the standard and S_{fit} is the signal obtained by the suitable treatment of the signal-time data. The three different procedures for mathematical treatment of these data (with no necessity to perform additional experiments) are proposed in order to calculate the analytical result.

In another calibration approach developed by the same group, the flow manifold designed was dedicated to be coupled with the flame atomic absorption spectrometer (55). The procedure proposed was carried out in two steps: first a standard was pumped at an increasing flow rate (from zero or a low value) until the nebulizer flow rate, and then a sample solution was pumped at a decreasing rate. The absorbance time profiles thus obtained intersected with each other at a point which permitted the analyte concentration in the sample C_x, to be calculated according to the following equation:

$$C_x = C_s \cdot \frac{t_i}{\tau - t_i} \tag{10}$$

where C_s is the analyte concentration in the standard whereas t_i and τ are the time values corresponding to the intersection point and the time necessary to reach the nebulizer uptake rate, respectively.

Multigraph Direct Transformation (CR-MDT)

In some cases, the measurement data obtained by the gradient technique for the calibration purposes can be interpreted as presented in Figure 6. Namely, when both a standard and a sample are continuously diluted in the same experimental conditions, all transient signals obtained for the standard can be attributed to the initial analyte concentration in this solution and the family of many two-point calibration graphs is constructed. When assuming that the signals measured for the sample correspond to the standard signals in terms of the dilution degree of both solutions, the sample signals can be related to the corresponding linear graphs. As a consequence, a great number of apparent concentrations is able to be obtained. If these concentrations differ from each other randomly, the final analytical result is calculated as an average value of them.

Some examples of the CR-MDT strategy realized by either an injection or continuous flow system can be found in the

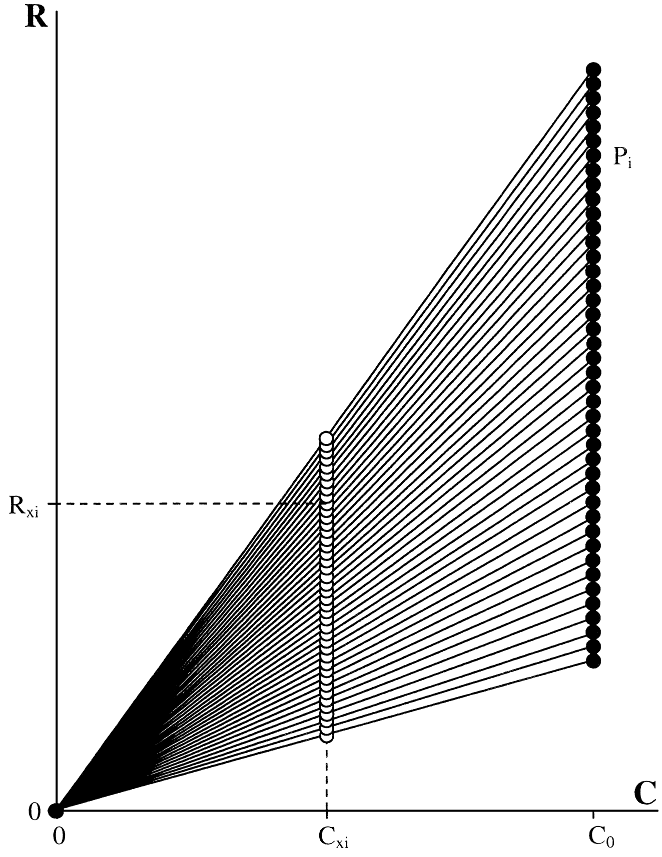

FIG. 6. Interpolative calibration performed according to the CR-MDT: Many calibration graphs (solid lines) obtained at defined instrumental parameters P_i and based on two experimental points serve for transformation of the signals measured at the same parameters for a sample (R_{xi}) to many estimations of the analyte concentration in the sample (C_{xi}).

literature. The FIA approach is represented by the calibration approach called the gradient ratio calibration method (GRCM) (56–59). In this method both calibration solutions, a standard and a sample, are injected to the flow system one after the other under low dispersion conditions. Two peaks recorded were synchronized with each other with respect to their base widths. Each two transient signals measured for a standard and for a sample at a given defined time after the injection were believed to represent both solutions being diluted to the same extent. The measurement data stored from the falling part of the peak were suggested to be taken into consideration for calibration purposes.

A specific version of the GRCM calibration method has been applied to the FIA spectrophotometric determination of total protein in blood (60). In this case, three peaks were proposed to be produced and synchronized: for the standard and sample solutions and, in addition, for a calibrating dye solution. All those peaks were analyzed point-by-point along their falling portions. It has been proved that the analytical result could be calculated on the basis of each pair of the measurement data being recorded for the dye solution at two such delay times at which the signals produced by the standard and sample solutions were equal to each other.

In Ref. (61), it has been shown how the CR-MDT strategy can be realized in the continuous flow mode. The standard and sample solutions were propelled continuously one after the other to the flame atomic absorption spectrometer being progressively diluted with water in the mixing chamber originally designed. The two sets of transient signals produced were then positioned to each other with respect to the starting time of the dilution process. As in the case of the FIA peaks, it was assumed that each two transient signals measured for both solutions at a given delay time represented them being diluted to the same extent. It has been revealed that such a simple system can serve not only for calibration purposes, but also for detection and examination of chemical interferences.

Another continuous flow system coupled with the flame atomic absorption spectrometer and enabling the same calibration approach was proposed by Hernández-Córdoba et al. (34, 62, 63). The standard and sample solutions were pumped one after the other with continuously changing flow rate while a diluent was aspirated to the nebulizer through the T-piece, which ensured the total flow to be constant. In this case, it was suggested to present the measurement data obtained in the form of two absorbance-time multipoint graphs and to calculate the analytical result C_x, from the absolute values of the slopes S_0 and S_x, of the linear portions of these curves:

$$C_x = \frac{S_x}{S_0} \cdot C_0 \qquad [11]$$

where C_0 is the analyte concentration in the standard. In fact, such a means of measurement data interpretation is equivalent to the one presented in Figure 6.

DISCUSSION

When classifying the flow interpolative calibration procedures reported in the literature to five groups of methods according to the reconstruction or transformation ways applied, the chances open for easy identification and evaluation of their analytical features and abilities.

As all the procedures considered above are realized by using the flow manifolds, they can be performed fully automatically and under control of a dedicated computer software (even if some of them are not originally proposed in such a form). For the same reason they can generally save consumption of time, work, and reagents in comparison with not only the batch calibration procedures but also with traditional flow approach (i.e., using a set of separately prepared standard solutions and measuring the analytical signals for each of them individually). Especially small amounts of reagents are required by the manifolds operated in the flow injection mode as well as those flow systems which allow the calibration data to be completed with the use of a single standard solution only.

As already mentioned, the most popular calibration approach in flow analysis is still the traditional one. Certainly, one of the reasons for this situation is simply psychological: If a common procedure is used routinely for a long time, it is very difficult to change the habit even if another attainable way is believed to be better in some respect. Therefore it can be suspected that such novel calibration approaches have a greater chance to be introduced to routine analysis, which is similar to the traditional one so much as possible at both the laboratory and interpretative stages. Considering this aspect, the procedures allowing a single calibration curve to be constructed (i.e., those belonging to the DR-ODT, DR-OIT, and CR-OIT strategies) and especially those additionally providing a chance to transform the measurement data directly (i.e., DR-ODT) certainly have an advantage over the remaining methods (i.e., DR-SDT and CR-MDT).

Almost all flow manifolds proposed for calibration purposes are able to be merged with optional detectors commonly used in the flow analysis. However, many of them have been designed with the special purpose to be connected with the flame atomic absorption spectrometers. The main task of doing so is to extend the dynamic range of just this kind of instrument (which is so often used in routine analysis), and as a consequence to increase their analytical applicability. As proved, it is possible to do either by measuring the signals in the peak width mode (17, 18) or by performing the calibration by the DR-OIT or CR-OIT strategies with the use of special manners of continuous dilution of the calibration solutions (19, 34–40, 51–53).

The majority of the calibration procedures presented can be performed with the use of a single stock standard solution. In most of them, a set of standard solutions needed to construct the calibration graph(s) is prepared by means of dilution of the stock solution. In such cases, the main problem lies in the risk of accumulation of errors in the preparation of standards. If some systematic error is committed at a particular step of dilution, it influences the accuracy of the preparation of standards further along the line. As a consequence, the calibration dependence is reconstructed erroneously and the analyte in the sample may be determined with serious inaccuracy.

Taking into account some other sources of analytical inaccuracy, the resistance of the calibration approaches to the interference effect should be considered. It is well known that in principle this effect cannot be eliminated by using the interpolative calibration methods unless some additional chemical treatment is used (i.e., the sample composition is matched in the standards or special substances are added to a sample). However, some exceptional opportunity of detecting and reducing the interference effect is offered by those procedures belonging to the CR-MTD strategy. When the sample containing the interferents is continuously diluted in the same conditions as the standard, the interference effect is expected to be progressively decreased (56, 57). As a consequence, the apparent concentrations calculated at each step of dilution are changed approaching progressively the true value of the analyte concentration in the sample. This value can be evaluated by such a manner that the apparent concentrations are presented versus signal (e.g., measured for the standard), and a function (usually nonlinear) approximating this relationship is then extrapolated to zero-value of the signal (58). However, it has been proved that in some exceptional cases the interference effect can be stable or even increase with the sample dilution causing the calibration by the CR-MTD approach to completely fail (58, 59).

As far as the interference effect is concerned, special attention should be paid to the interpolative standard addition method (11–16). Its name suggests that this calibration approach is typically extrapolative (i.e., it is able to reduce the interferences), but has an interpolative character (i.e., it is able to avoid all limitations of an extrapolative method). However, it has been theoretically and experimentally proved that the method is actually interpolative, generally requiring common additional activities in order to overcome the interferences (64).

Another general problem is with usefulness of the particular calibration approaches when the calibration dependence is nonlinear. In such a case, only procedures can be applied which allow this dependence to be reconstructed in the form of several point or multipoint calibration graphs irrespective of whether the standard solutions are prepared in a series separate from each other or are generated from a single stock solution. Thus the procedures considered are those belonging to the DR-ODT and DR-OIT, and CR-OIT, methods, but not to the remaining calibration strategies (DR-SDT and CR-MDT) that offer a set of two-point calibration graphs only.

However, one should remember that in the DR-STD and CR-MDT methods the calibration graphs are prepared at different experimental conditions; hence, it can happen that some graphs reconstruct the linear calibration dependence but other graphs correspond to the nonlinear one. It can be expected in such a case that a part of apparent concentrations would be statistically equal to each other, but the remaining concentration values should significantly differ from them. Thus, if such an effect is observed, the nonlinearity of the calibration dependence is able to be detected and the final analytical result consequently can be calculated from the apparent concentrations of the same values only. When the ability of the DR-STD and CR-MTD methods to act in the manner just mentioned is greater, the greater is the number of apparent concentrations possible to obtain in a given calibration procedure. From this point-of-view, the CR-MTD methods certainly reveal an the advantage over the DR-STD methods.

Every particular calibration approach has own specific sources of analytical errors. For instance if the measurement data cannot be transformed directly (i.e., when the procedures belonging to the DR-OIT and CR-OIT strategies are applied), the additional laboratory or mathematical activities required to find the analytical result certainly make its accuracy and precision worse. A similar problem arises when a calibration purpose is too sophisticated in terms of experimental conditions, which can in fact be difficult to reproduce to a satisfactory extent (e.g., when two injection valves need to be strictly synchronized with each other for the purpose of sampling a zone (27, 47) or when several zones overlapped with each other are the sources of measurement data (43–45, 48)). In the case of the CR-MDT procedures, the factor influencing the accuracy of the analytical results is the adjustment of the continuous signals obtained for the sample and standard solutions.

TABLE 1
The Features Revealed by the Calibration Strategies in Flow Analysis

Ability	DR-ODT	DR-OIT	DR-SDT	CR-OIT	CR-MDT
To be automated and computerized	+	+	+	+	+
To save time, work, and reagent consumption	+	+	+	+	+
To be similar to the batch calibration procedure	++	+	−	+	−
To extend the FAAS potentiality	−+	+	−	+	−
To use a single standard solution	+	+	+	+	+
To eliminate interferences	−	−	−	−	+−
To reconstruct the nonlinear calibration dependence	+	+	− +	+	+−
To extend linear range of the calibration dependence	−	−	+	−	+
To improve precision	−	−	+	−	+−

Special opportunities to improve the analytical performance are offered by the procedures allowing the calibration dependence to be reconstructed in the form of several or many calibration graphs (i.e., the DR-SDT and CR-MDT procedures). In comparison with a single graph, the family of graphs of different slopes gives a chance to transform the measurement data from a much wider range of the calibration dependence. Besides the analytical result is able to be estimated by the concentration values of different precision, which depend on both the random fluctuation of the signals and the slope of graphs used for transformation of these signals. Thus the final result can be calculated with the use of those apparent concentrations selected, which are obtained in conditions ensuring the best precision. On the other hand if a procedure of the CR-MTD strategy is used in the case of an interference effect occurring (see above), very small signals have to be taken into account for calculation of the analytical result thus making its precision very poor (57–59).

In Table 1 the features of the procedures belonging to all interpolative calibration strategies considered have been summarized.

CONCLUSIONS

When reviewing the literature related to flow analysis, a lot of interesting and ingenious concepts can be found on how the analytical calibration can be realized. No wonder, as the flow techniques create many facilities that are very useful for this purpose. However, in such a situation, one of the important and urgent problems is to make an attempt to introduce a classification of the flow calibration approaches as well as to standardize the relevant nomenclature. Such an attempt has been suggested here.

The main classification of the calibration procedures introducing three categories (namely, interpolative, extrapolative, and indicative), is submitted for consideration once more. The interpolative approaches are divided into five groups in accordance with how the calibration dependence is reconstructed to the empirical form and how the analytical signal is transformed to the analytical result in every particular case. The taxonomy proposed is opened (i.e., it allows for a possibility of including such novel calibration approaches as would be based on other general reconstruction or transformation ways than those specified above). Although it perhaps could be improved by doing some modifications and changes, it makes some desirable order in the flow calibration area.

The general conclusion is that it is worth an appeal to researchers developing new calibration proposals to pay attention not only to their instrumental and preparative aspects, but even more to the interpretation stage. Such an approach certainly would be helpful to evaluate and compare calibration approaches in terms of their essential features (i.e., of analytical performance and usefulness. Another important request is to avoid free names and expressions that sometimes can be quite wrong (like "the interpolative standard addition method"), and can lead not only to some misunderstandings but also—in extreme cases—to analytical errors.

Another problem revealed is that, despite the many advantages of various flow calibration approaches listed and discussed above, none of them can yet compete with conventional ones as far as routine analysis is concerned. Although the psychological aspect previously mentioned is certainly one of the reasons for such a situation, the fact is that alternative ways proposed are too often typified by serious drawbacks and limitations as well as being too sophisticated in terms of procedural or interpretative features. The result is that they arouse distrust and suspicion. Therefore the question of developing new calibration ideas for improved analytical performance and greater confidence in terms of routine applicability as well as to making attempts to put them into analytical practice is still a great challenge for the analysts involved in flow analysis.

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