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CLASSIFICATION AND DEFINITION OF ANALYTICAL METHODS BASED ON FLOWING MEDIA

(IUPAC Recommendations 1994)

Prepared for publication by

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Classification and definition of analytical methods based on flowing media (IUPAC Recommendations 1994)

ABSTRACT

The aim of this report is to classify analytical methods based on flowing media and to define (standardize) terminology. After the classification and a discussion of terms describing the systems and component parts, a section is devoted to terms describing the performance of flow systems. The list of terms included is restricted to the most relevant ones; especially 'self-explanatory' terms are left out. It is emphasised that the usage of terms or expressions that not adequately describe the processes or procedures involved should be strongly discouraged.

Although belonging to the category of methods based on flowing media, chromatographic methods are not comprised in the present document. However, care has been taken that the present text is not in conflict with definitions in that domain.

In documents in which flow methods are described, it should be clearly indicated how the sample and/or reagent is introduced and how the sample zone is transported. When introducing new techniques in the field, or variants of existing techniques, it is strongly recommended that descriptive terms rather than trivial or elaborate names are used.

INTRODUCTION

The growing need for automation of analytical procedures is caused by the significant increase in the numbers of laboratory samples to be analysed, e.g. in the fields of clinical chemistry and environmental analysis, and by the demand for fast and reliable techniques that can operate 24 hours a day, as is often required in process control. In spite of all the efforts to develop selective and sensitive sensors which can directly determine the concentration of an analyte in a *test sample* (for nomenclature with regard to sampling see ref.[1]), the great variety of analytes and the complexity of most of the products analysed make it highly improbable that such sensors, other than those for the most common compounds, will be available in the near future. Hence, separation and/or chemical conversion remain essential steps in most quantitative analytical procedures. In these cases, automation of analytical procedures implies automation of processing of the test samples. Because most separations and chemical conversions are normally done in the liquid phase, it was a logical, but nevertheless ingenious, concept of Skeggs [2,3] to perform the necessary processes on the analyte in a flowing stream which transports a test portion from a point of introduction to a detection unit. This approach has been denoted as (segmented) Continuous Flow Analysis (CFA).

For about 20 years it was taken for granted that air-segmentation, *e.g.* dividing the flowing stream into regular and small compartments separated by air bubbles, was the method of choice to avoid broadening of a discrete analyte zone (often called *sample dispersion*) on its way from the point of test portion introduction towards the detector.

In analogy to usage in process technology, where transport without zone broadening is denoted as 'plug flow', the sample zone is often denoted by the term 'plug'. Although some publications at the end of the sixties and the beginning of the seventies had already dealt with procedures in which segmentation was not applied (*e.g.*ref.[4]), it was not until the mid-seventies that it became generally accepted that segmentation could be omitted by using flow systems of appropriate dimensions, and by employing suitable flow rates, thus simplifying the whole analytical system and increasing the number of test samples that could be analysed per unit time (often denoted as *sampling frequency* or *sample frequency*). This approach became known as Flow Injection Analysis (FIA). At present the term flow injection (FI) is also used in conjunction with special analytical techniques such as flow injection potentiometry, flow injection amperometry, flow injection spectrophotometry, *etc.*.
Sampling systems which can be considered as intermediate between CFA and FIA have also been described. One of them is the Monosegmented Continuous Flow Analysis (MCFA) in which the whole injected test portion is intercalated between two air bubbles [5].
Essentially independently from these procedures, which were developed and applied within analytical laboratories, process analytical methods have been developed based on flowing media where a continuous stream of solution containing the analyte and one or more reagent streams were intermixed and processed before reaching the detection unit. These methods are sometimes described as Continuous Monitoring Systems. It should be noted that CFA and FIA are also widely used in process analytical chemistry.

The development of the various techniques and procedures have followed essentially independent pathways, each accompanied by the introduction of their own terminology. This has led to confusion, ambiguity and misunderstanding, particularly, where the various terms used in the different flow methods are not in accord with older, well-established terms and concepts used in other fields of analytical chemistry, such as chromatography, or in related branches of science, such as chemical engineering.

This report is not supposed to give a (full) description of flow methods of analysis and its component parts, but aims at the classification of analytical methods based on flowing media and the definition (standardization) of the relevant terminology. Its purpose is not to account for all the terms used, hence, self-explanatory terms are excluded. The introduction and usage of names, or expressions which do not adequately describe what occurs, is strongly discouraged. Therefore such names and expressions are also excluded from this report. An example of this latter category is the term 'reverse flow injection analysis' which may suggest that the direction of flow is reversed whereas in fact the reagent is injected into the continuous analyte stream instead of the 'normal' procedure in which a test portion is injected in a continuous reagent stream.
Although also based on flowing media, chromatography as such and typical chromatographic terms will not be considered herein. However, there are certain domains where 'flow' methods and chromatographic methods show a considerable degree of overlap; therefore care has been taken that ambiguity is avoided in these cases.
Attention is given to the classification of, and terms for, the various methods of analysis, to the description of some of the most characteristic systems and their important component parts and, finally, to some important parameters that describe the behaviour of

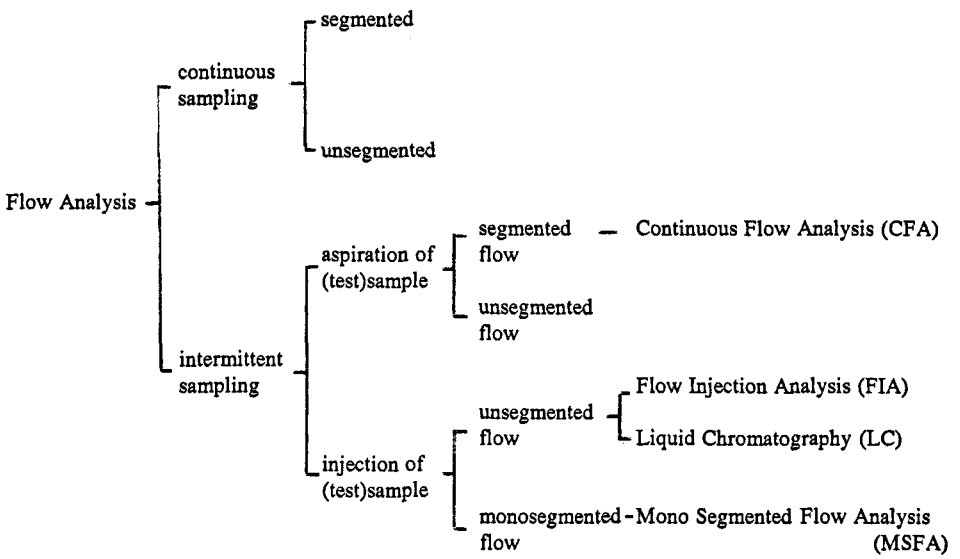
the system as a whole as well as their component parts. Because standardization and harmonization should be of help in avoiding ambiguity and in improving mutual understanding, and should not hamper the introduction of new concepts and developments, it was decided to focus on the current most important systems and aspects.

CLASSIFICATION OF ANALYTICAL METHODS BASED ON FLOWING MEDIA

Flow analysis is recommended as the generic name for all analytical methods that are based on the introduction and processing of test samples in flowing media. A primary classification can be based on two aspects:

* the way the test portion is introduced, *i.e.* continuously or intermittently/discretely, and
* the basic character of the flowing media, *i.e.* either segmented, unsegmented or monosegmented where segmentation is primarily considered as being applied for the purpose of preventing intermixing of successive analyte zones.

This leads to the following classification tree:



Classification scheme of flow methods of analysis

In principle it would be possible to introduce a more logical and descriptive system of terms with acronyms to match the various analytical procedures according to the classification scheme presented above. For instance, Flow Injection Analysis could be properly described as 'unsegmented flow system with injection of (test)sample' or 'unsegmented flow system with injection of reagent', and Continuous Flow Analysis may be denoted as 'segmented flow system with aspiration of (test)sample'. A flow injection system based on merging zones of analyte and reagent solution can be indicated as

'unsegmented flow system with injection of (test)sample and reagent'. A process monitor with a constant speed of (test)sample and based on the continuous flow analysis principle could be indicated as 'segmented flow system with continuous sampling'. This approach to classification and nomenclature has the additional advantage of being easliy expanded; thus the nature of the segmenting medium can be easily added (gas/air/nitrogen/.. segmented flow system...). Also a system for liquid/liquid extraction can be conveniently incorporated, *e.g.* (toluene) segmented flow extraction system with sample injection.

A forced introduction of this terminology would violate, however, the historical developments and current usage of terms, and its general acceptance in the shorter term may be questioned. Well-established terms like CIA and FIA may still be used but they should be restricted to the specific cases indicated above. Nevertheless, the names derived by the use of the structured approach presented above have to be recommended above all other types of names.

Summarizing: Flow analytical systems should be characterized by indicating the type of flow (segmented or unsegmented), the way the (test)sample is introduced (aspiration or injection) and when injection is used whether the (test)sample or the reagent is injected. For segmented flow methods, further clarification should be given when, for example, the type of segmenting medium is not air.

TERMS DESCRIBING THE SYSTEM AND COMPONENT PARTS

The heart of most flow systems is the part of the system between the introduction of the (test)sample and the detector or detection system. When this part simply consists of a conduit (tube or pipe) intended to transport an unaltered test portion from the point of injection towards the detector, and the analyte concentration is within the working range of that detector, dispersion of the analyte zone often has to be minimized because it merely results in dilution of the (test)sample and introduces an extra contribution to the response time and reduces the signal/peak height in procedures in which small and discrete analyte zones are used. In most analytical procedures, however, some kind of reaction with the analyte or another type of pretreatment of the matrix (*e.g.* buffering) has to be accomplished. In these instances the test sample has to be mixed with the carrier solution or other solution(s) containing buffer, reagent, *etc.*. This always leads to dilution of the analyte, and for discrete test portions, in broadening of the analyte zone. The part of the manifold where the process is supposed to occur is called the *reactor*. When only mixing has to be accomplished it is also possible to refer to this mixing action only, *e.g.* *mixing coil*. Various types of reactors/mixing devices can be distinguished:

- **Coiled reactor/mixing coil.** This is an open tube which is coiled in order to enhance radial homogenization in unsegmented streams and thus to achieve intimate mixing of analyte and, for instance, reagent or buffer. Here an effect is exploited known as 'secondary flow', *i.e.* a circulation between the centre of the tube and the walls perpendicular to the direction of the main flow caused by centripetal forces. The extent of mixing depends on the *aspect ratio* (ratio of tube diameter to coil diameter).
- **Packed bed reactor.** This reactor consists of a tube filled with small particles.The dispersion is much less than for coiled open tubes and is similar to that of chromatographic columns. The dispersion can be described by the same parameters as

used in chromatography such as *Height Equivalent to a Theoretical Plate* (HETP), *plate number* or *column efficiency*.

■ **Single Bead String Reactor (SBSR).** This is a tube packed with particles (spheres) having a diameter that is a little bit larger than one half of the tube diameter; in such a tube the particles have a regular arrangement [6,7]. The dispersion in this type of reactor is less than in the coiled reactor but not as low as for a packed bed reactor. The advantage over packed bed reactors is that SBSRs have a much smaller pressure drop which allows the use of simple peristaltic pumps.

■ **Knitted or knotted reactor.** This type of reactor consists of an open tube which is tightly knitted or knotted to ensure the presence of sharp bends [8]. Thus high local aspect ratios and enhanced radial mixing are realized. The performance is of the same order of magnitude as the single bead string reactor.

■ **Mixing chamber.** This consists of a small chamber in which entering solutions are thoroughly mixed by the action of centripetal forces, usually assisted by a stirring device (usually a small magnetic stirring bar)[9]. The behaviour can be approximated by a model of a single 'ideally stirred tank' *i.e.* the concentration at the outlet exhibits an exponential response to a stepwise change of incoming concentrations.

Various types of specific modules can be incorporated in the manifolds, *e.g.* extraction units, dialysis units, (gas)diffusion membrane units. Generally, the terms used for such modules are self-explanatory and don't require formal standardization.

■ **Introduction of (test)samples**

With regard to the system of analyte introduction, it has to be emphasized that, particularly in the case of injection, the shape of the sample zone moving through the system depends on the manner of injection. For instance, when an injection valve is used, the shape of the analyte zone after injection is approximately rectangular whereas in the case of introduction by means of a syringe, the contents of which are gradually expelled, the front of the zone is parabolic in shape, whilst the back is virtually flat (sometimes this is called 'time(d) injection', but 'syringe injection' may be a better expression) (Fig.1)[10].

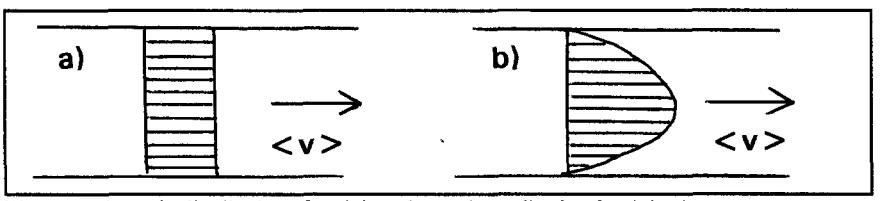


Fig.1 Schematic distribution of an injected zone immediately after injection;
a) ideal valve injection
b) 'time(d) injection' or 'syringe injection'

As long as the volume of the test portion is small in comparison to the volume of the whole system, the mode of injection does not significantly affect the final response. This is particularly true when the system contains elements or modules that themselves contribute significantly to the broadening of the analyte zone. However, the mode of injection should always be clearly indicated.

Aspiration was originally used for systems where the size of the test portion was less critical such as in segmented flow analysis with large test portions. Here the data are recorded at the moment when the signal has effectively attained steady state. However, in modern instruments based on the same principle, the reproducibility of aspiration is sufficient to allow the use of small test portions, which leads to peak-shaped signals similar to those from systems using injection of the analyte.

■ **Detection**

The method of detection influences the detector signal. Some detectors may indicate the concentration averaged over the cross section during a certain period of time comparable to the measuring of fractions collected in column chromatography (*cup-mixing detector*). Others, such as photometric transmission detectors may measure the mean concentration over the pathway (*mean value detector*), or the concentration in contact with the sensing surface of the detector. A potentiometric detector, where the active surface is parallel to the direction of the stream, is an example of the latter category. Because the method of detection can determine to a great extent the shape of the final signal recorded, it is of importance to state unambiguously the method of detection.

With respect to the evaluation of the signal, the peak height or the height at a certain fixed time, the peak area and the time between two preset signal values can be used. The most appropriate choice depends on the problem at hand.

TERMS DESCRIBING PERFORMANCE OF FLOW SYSTEMS

When introduced, not all fluid elements in the injected test portion take the same time to reach the detector; there is a certain residence-time distribution. This phenomenon is called *dispersion*. The degree of dispersion is one of the main aspects in describing the performance of a flow system because it determines the degree of dilution and the degree of mixing, as well as the frequency with which (test)samples can be introduced without affecting the signal of preceding (test)samples.

Depending on the model adopted, several expressions can be used to describe the dispersion of the analyte zone. In chromatography, in general, the Height Equivalent of a Theoretical Plate (HETP), the number of plates or column efficiency are used; in chemical engineering a tanks-in-series model is often adopted where the number of tanks decisively affects the performance. The number of tanks can be directly related to the dimensionless Péclet number ($Pe = \langle v \rangle x / \mathbb{D}$, where $\langle v \rangle$ is the mean linear velocity, x a chartacteristic length such as the tube length or tube diameter and $\mathbb{D}$ is the dispersion coefficient as defined in the field of chemical engineering). These approaches have also been introduced in the description of analytical flow systems [11]. Several authors have presented numerical solutions for the convective-diffusion equation underlying dispersion in straight tubes. These results give a better insight into the real spatial distribution of the analyte when the zone is passing through the tube [12,13].

For analytical applications it may be desirable to have a characteristic quantity that readily describes the concentrations of the analyte in the test portion before and after the dispersion process has taken place in that element of fluid that yields the analytical read-out [14]. In the literature on segmented flow analysis the ratio of these two concentrations has also been decribed as dispersion coefficient. In cases where the signal height is linearly proportional to the concentration, the ratio of the actual signal height to the maximum signal height when no dispersion would have taken place (experimentally obtained with very large sample volumes) can also be taken. The term 'dispersion

coefficient' is now widely accepted in flow injection analysis. This is unfortunate because the actual decrease in concentration is not only due to pure dispersion but also to dilution when a carrier stream containg the analyte zone merges with other streams and because the term has been defined previously in chemical engineering in transport equations in an analogous way to diffusion coefficients in Fick's law. In flow analysis it would, therefore, be more appropriate to use terms such as 'dimensionless' or 'reduced' peak/signal height instead of dispersion coefficient, but again proliferation of the term has been such that it will be virtually impossible to change the use of the term. As long as it is absolutely clear from the context what is meant this will not cause too many problems. However, one must be aware of this discrepancy when discussing analytical flow methods with chemical engineers.

Where the above mentioned expressions describing the performance have a more or less direct relation to the physical reality, it is also possible to characterize the signal in purely mathematical or statistical terms such as first, second, third moments *,etc.* representing the mean, the standard deviation and the asymmetry of a signal, respectively.

Finally attention has to be paid to the term 'sampling frequency' or 'sample frequency'. In most scientific reports on flow methods these terms are related to the frequency with which subsequent test portions can be injected without being affected by preceding signals. One has to realize that this is not equivalent to the number of (test)samples that can be analysed per unit time, because in practical analysis a regular calibration with standard samples is needed and every now and then systems may need cleaning by introduction of washing solutions; moreover it is quite ususal to perform a repetitive introduction of test portions and take the average as the result of the analysis. All such factors make that the number of (test)samples that can practically dealt with may be lower by at least a factor 4.

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