Differential Reaction-Rate Methods in Flow Analysis

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Abstract: Simultaneous determinations exploiting the rates of reactions of different analytes with a common reagent, often referred to as differential kinetic analysis, is efficiently implemented in the flow analyser. To this end, specific strategies for pumping, commuting and/or detecting have been proposed. This review critically discusses the potentialities, limitations and application ranges of the different flow systems designed to accomplish differential reaction-rate methods, with emphasis to those involving spectrophotometric and luminometric detection.

Keywords: Flow analysis, differential reaction-rate methods, differential kinetic analysis, review, simultaneous determinations.

1. INTRODUCTION

An efficient way to accomplish multi-component analysis is to exploit the different rates at which two or more chemical species interact with a common reagent system [1], and the related methods are often referred to as differential reaction-rate methods. Catalytic methods where the analytes are the catalysts and the rate of the indicator reaction is the measurement basis are also included in this context. Differential reaction-rate methods constitute themselves as an effective solution to a crucial analytical problem: the resolution of mixtures of closely related species [2].

These methods require a reproducible management of the solutions involved and a rigid timing control, and these features are inherent to flow analysis [3]. Implementation in the flow analyzer is then straightforward, as demonstrated in the landmark article by Dahl *et al*. who designed a flow-injection system for the spectrophotometric determination of magnesium and strontium [4]. The method relied on the different dissociation rates of the Mg(II) and Sr(II) trans-1,2-diaminocyclohexanetetraacetate complexes under acidic conditions; Cu(II) was used as scavenger. Since then, and especially during the eighties and nineties, the availability of flow-based analytical procedures involving differential reaction-rate methods has been increasing, and specific manifold architectures have been proposed [5].

In most applications, the required time-dependent measurements are performed on different portions of the flowing sample, which are subjected to slight different handling conditions. Variations in sample dispersion, as well as in temperature, pH or ionic strength of the reaction medium, may occur during the time interval elapsed between measurements. In these situations, the approach could be considered as a *pseudo differential kinetic analysis*. On the other hand, better adherence to IUPAC definition [1] is noted when a single portion of the sample zone is halted in the detector and the time-based variation in measurement is considered as the measurement basis. For didactic purposes, the expressions *pseudo differential kinetic analysis* and derived ones are not used in this text.

In some applications, the conditions associated to each measurement can be modified by adding different reagents, and the spectrophotometric flow-injection determination of molybdenum and tungsten in alloys [6] can be selected as an example: the sample was inserted twice and a citric acid stream was added to only one of the established sample zones in order to minimise the tungsten contribution to the analytical signal. Applications involving solid bleaching or extractions [7] and/or electrochemical detectors relying on kinetic aspects (*e.g.* anodic stripping voltammetry [8]) usually exploit an ordinary flow system for monitoring purposes, and reaction-rate methods are not exploited. These applications are then not considered in this present monograph.

The strategies carried out with the stopped-flow analyser [9,10] are relevant for monitoring fast analytical systems. These analysers are compatible with very short (down to μs) time intervals, provide effective stopped-flow mixing and include modern detectors [11]. However, they have been scarcely used in routine large scale analysis and do not constitute themselves as typical flow analysers. A deeper discussion of these analysers falls then outside the scope of this review.

2. GENERAL ASPECTS

Some conditions should be met for implementing differential reaction-rate methods:

i) The concentration of the formed chemical species to be quantified, $[P_A]$, should be proportional to the concentration of the analyte, [A] associated with that species. As the reagent is present in excess, Eq. (1) holds for the involved *pseudo* first order reaction, providing that the time interval for reaction development is restricted. Thus:

$$[P_A] = k\,[A] \quad (1)$$

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where k = *pseudo* first order rate constant [2].

ii) For two or more analytes, A_i, mutual or synergistic effects on the reaction rates should ideally be absent. Eq. (1) can then be expanded to Eqs 2 and 3:

$$[P_{A1}] + [P_{A2}] = k_{A1} [A_1] + k_{A2} [A_2] \quad (2)$$

$$\Sigma [P_i] = \Sigma (k_i [A_i]) \quad (3)$$

In general, P_{A1} is essentially similar to P_{A2} in relation to the analytical property to be measured. This means additivity of the analytical signals related to P_{A1} and P_{A2}. In some applications (*e.g.* catalytic analytical procedures), P_{A1} and P_{A2} are the same chemical species.

iii) The (k_i [A_i]) terms should be as dissimilar as possible. For good discrimination, the (k_1 [A_1]) / (k_2 [A_2]) ratio should be normally > 3; lower ratios are feasible by exploiting advanced mathematical algorithms [2].

Different approaches have been used for obtaining the analyte concentrations:

If two analyte determinations are aimed at and the (k_i [A_i]) terms are very dissimilar from each other or, in other words, if the reaction development is quantitative for one analyte and relatively slow for the other, the measurement performed immediately after reagent additions, M', reflects the concentration of one analyte whereas the temporal increase in measurement [ΔM" = f(t)] is considered for estimating the concentration of the other analyte. To this end, the slope of the (M" *vs* t) function, is usually recorded and taken into account.

If two analyte determinations are aimed at and relatively high (k_1 [A_1]) / (k_2 [A_2]) ratio are involved, two measurements (M' and M") are generally performed at different pre-set time intervals. As both analytes contribute to these measurements, two equations are obtained:

$$M' = k'_1 [A_1] + k'_2 [A_2] \quad (4)$$

$$M'' = k''_1 [A_1] + k''_2 [A_2] \quad (5)$$

where k' and k" = proportionality constants related to M' and M".

As the analyte concentrations are gathered by solving Eqs 4 and 5, the approach has been referred to as the *proportional equation method* [2].

More than two measurements performed at different elapsed times can be considered, resulting in a larger number of equations to be solved. To this end, matrix calculations are generally required. Expansion of the proportional equation method is worthwhile for improving the numeric stability [12] and/or for multi-analyte determinations [13]. The approach however has been scarcely used in flow analysis probably because of the limitations associated with the (k_i [A_i]) values.

If two or more analyte determinations are aimed at and/or the (k_i [A_i]) / (k_j [A_j]) involved ratios constitute themselves as limiting factors in kinetic discrimination, several measurements are performed and chemometric tools such as *e.g.* principal component regression [14], partial least squares [15] or artificial neural networks [16] are required. A deeper presentation of these statistical tools is outside the scope of this monograph. The reader should be oriented towards specific texts such as *e.g.* Refs [17-19].

3. IMPLEMENTATION IN FLOW ANALYSIS

For implementing differential reaction-rate methods in flow analysis, strategies involving specific conditions for pump operation (A - Table **1**), special manifold architectures (B - Table **1**) and/or a more complete exploitation of the recorded signals (C - Table **1**) have been carried out, as discussed further.

3.1. Specific Pump Operating Conditions

The fluid propeller device - usually a peristaltic or a syringe pump - is operated to permit the delivered stream to be either pumped or halted during pre-set periods [20]. Alternatively, the pump can be continuously operated and stream halting is accomplished by resorting from commutation [21].

During the GO period, the sample is inserted into the analytical path and the required reagent solutions are in-line added (Fig. **1**). When the sample zone is passing through the detector, the pump is switched off, allowing the fluid element associated with the analytical readouts to be halted inside the detector. During the STOP period, successive measurements are obtained, each one related to a given yet known time interval. The (analytical signal *vs* time) function is then gathered. Thereafter, the pump is switched on again, restarting the flow, discarding the sample zone and inserting the next sample to be similarly handled.

The manifold architecture is designed as an ordinary flow system. Special attention should be given to the dimensioning of the main reactor and of the sample inserted volume, as these parameters play an additional role, namely to minimise carry-over. The inner volume of the reactor plus the front portion of the sample zone should be enough for properly washing the analytical path before stopping the handled sample inside the flow through detector. This aspect was highlighted in the spectrophotometric determinations of chlorpyrifos and carbaryl in commercial formulations [22]. Absorbance values referred to two different reaction times and two different wavelengths were taken into account and the proportional equation method was applied. Other applications involving specific pump operating conditions, some of them exploiting other approaches for gathering the analytical results, are presented in Table **1**.

Implementation of these analytical procedures is accomplished in close adherence to IUPAC definition of differential reaction-rate methods [1], as the only parameter undergoing variations during the STOP period is the time interval available for reaction development. A noteworthy characteristic is that only one sample insertion is required. Moreover, the reagent solutions are not wasted during the STOP period. The need for successive ON/OFF pump switching that may limit the pump lifetime is however a shortcoming. In spite of the low versatility of the flow system and the possibility of the analytical signal surpass the concentration dynamic range, flow systems relying on ON/OFF pump switching are mostly applied.

Table 1. Selected Applications

Analyte	Sample	Chemical Reaction	Detection Technique	Analytical Range or Detection Limit	Flow Analyser	Strategy	Remarks	Ref.
aniline, cyclohexylamine	commercial sweeteners	analytes reaction with 1,2-naphthoquinone-4-sulfonate	UV-Vis	4.2×10^{-6}, 8.0×10^{-6} mol L^{-1} (FIA), 3.8×10^{-6}, 1.1×10^{-5} mol L^{-1} (CFA)	FIA, CFA	B (FIA), A (CFA)	different added buffer solutions (FIA); very dissimilar (k_i [A_i]) terms (CFA); proportional equation method	[42]
ascorbic acid, L-cysteine	pharmaceutical formulations, human urine	Fe^{3+} reduction by the analytes; luminol-Fe^{2+}-O_2 reaction	CL	0.06-6, 0.4-40 μg mL^{-1}	FIA	B	variable lengths of the tubular reactor; PLS data treatment	[31]
bromate, chlorite	waters	oxidation of 3-3'-dimethoxybenzidine by Br_2 formed after analytes-bromine reaction	UV-Vis	6-160 μg L^{-1}	FIA	B	different reaction coils; proportional equation method	[43]
carbamate pesticides (propoxur, carbaryl, ethiofencarb, formetanate)	waters	reaction of phenolic compounds from analyte off-line hydrolysis with a product of PAP oxidation by periodate	UV-Vis	2-10, 1-4, 2-10, 4-20 μg mL^{-1}	CFA	A	PLS data treatment	[44]
catechol, resorcinol	synthetic solutions	analyte oxidations by hydrogen peroxide in the presence of *peroxidase*	UV-Vis	50-150, 30-180 μmol L^{-1}	rFIA	A	MLR data treatment	[45]
chlorpyrifos, carbaryl	commercial formulations	analyte degradations in alkaline-oxidative medium	UV-Vis	2.8×10^{-6}, 1.4×10^{-6} mol L^{-1}	FIA	A	proportional equation method	[22]
chlorpyrifos, carbaryl	commercial formulations	analyte degradations in alkaline-oxidative medium	UV-Vis	$4.13\text{-}33.04 \times 10^{-5}$, $2.94\text{-}44.05 \times 10^{-5}$ mol L^{-1}	FIA	A	PLS-1 and PLS-2 data treatment	[46]
Co(II), Cu(II)	spring waters	analytes-catalyzed reaction of luminol with H_2O_2	CL	0.0010-0.0600, 0.80-10.0 mg mL^{-1}	FIA	B	multi-site detection; PLS data treatment	[47]
Co(II), Cu(II), Fe(III), Ni(II), Zn(II)	synthetic solutions	displacement reaction (analyte-NTA yielding analyte-PAR complexes)	UV-Vis	0-200, 0-200, 0-800 0-400, 0-500, ng mL^{-1}	FIA	A	temporal and spectral information added to PLS and PCR for data treatment	[48]
Co(II), Ni(II)	synthetic solutions	analyte complexations with 2-hydroxybenzaldehyde thiosemicarbazone	UV-Vis	10-60 μg mL^{-1} (each analyte)	FIA	B	comparison of three manifold architectures; proportional equation method	[27]
Co(II), Ni(II)	synthetic solutions	displacement reaction (analyte-PSAA yielding analyte-NTA complexes)	UV-Vis	1/12 < conc. ratio < 10/1 for 0.5 μg mL Co or Ni	FIA	A	proportional equation method	[49]
Co(II), Ni(II)	natural waters, soil extracts	displacement reaction (analyte-citrate yielding analyte-PAR complexes)	UV-Vis	0.20, 0.14 mg L^{-1}	SIA	B	single sample insertion; zone slicing; two analytical paths for two sample residence times	[36]
Co(II), Ni(II)	synthetic solutions	analyte complexation with 2-hydroxybenzaldehyde thiosemicarbazone	UV-Vis	5.0-50.0 μg mL^{-1} (each analyte)	FIA	B	simultaneous insertion of two sample aliquots into a single-line flow system; proportional equation method	[28]
Co(II), Ni(II)	synthetic solutions	analyte complexation with 2-hydroxybenzaldehyde thiosemicarbazone	UV-Vis	5.0-50.0 μg mL^{-1} (each analyte)	FIA	C	large sample volume insertion, resulting in two colored zones; proportional equation method	[39]

(Table 1) contd…..

Analyte	Sample	Chemical Reaction	Detection Technique	Analytical Range or Detection Limit	Flow Analyser	Strategy	Remarks	Ref.
Co(II), Ni(II)	synthetic solutions	displacement reaction (analyte-citrate yielding analyte-PAR complexes)	UV-Vis	0-8 ppm	FIA	B	zone splitting; different temperature conditions; double path cell; proportional equation method	[50]
cobalt, nickel	steels	displacement reaction [Co(II) and Ni(II)-citrate to Co(II) and Ni(II)-PAR]	UV-Vis	0.00-5.00, 0.00-1.00 mg mL^{-1}	FIA	B	reactor replacement after every sample insertion; proportional equation method	[30]
Cu(II), Ni(II)	electroplating baths	analyte-catalysed reduction of resazurin by sulfide under alkaline conditions	UV-Vis	0.5-6, 1-15 mg L^{-1}	FIA	A	ANN data treatment	[16]
Cu(II), Ni(II)	plant digests	analyte reactions with Br-PADAP	UV-Vis	0.01, 0.04 mg L^{-1}	FIA	B	multi-site detection; proportional equation method	[35]
copper, zinc	brass	analyte reactions with Zincon	UV-Vis	not relevant	FIA	A	proportional equation method	[51]
Cu(II), Zn(II)	plant digests	decomplexation of cyanide-analyte complexes by Zincon	UV-Vis	0.05, 0.04 mg L^{-1}	MCFA	B	computer-controlled sample splitting; proportional equation method	[25]
Cu(II), Zn(II)	vitaminic formulations	displacement reactions (analyte-aminopolycarboxylates yielding analyte-Zincon complexes)	UV-Vis	0.2-3.5, 0.2-9.7 µg mL^{-1}	FIA	A	proportional equation method	[29]
Cu(II), Zn(II)	pharmaceutical preparations	displacement reactions [analyte-aminopolycarboxylates yielding analyte-Zincon (or analyte-PAR) complexes]	UV-Vis	0.03 µg mL^{-1} (each analyte)	FIA	A/B	dual sample insertion into convergent carrier streams; zone stopping at the detector; proportional equation method	[52]
Eu(II), Ce(III)	Ba-Y-F fluorescent material	analyte-catalyzed iodide oxidation by Cr(VI)	UV-Vis	0.015, 0.010 µg mL^{-1}	FIA	A	proportional equation method	[53]
Fe(II), Ni(II), Zn(II)	synthetic solutions	analyte reaction / retention as coloured complexes with TAN	SPS	0.040-0.20 mg L^{-1} (for all analytes)	FIA	B	TAN immobilized on a C_{18} bonded silica support; PLS data treatment	[54]
Fe(III), Co(II)	synthetic solutions	displacement reaction (analytes-EGTA yielding analytes-PAR complexes)	UV-Vis	2.0-25.0 µg mL^{-1}	FIA	B	closed loop configuration; iterative detections; data treatment by logarithmic extrapolation or single-point approaches	[37]
Fe(III), Co(II)	synthetic solutions	displacement reaction (analytes-EGTA yielding analytes-PAR complexes)	UV-Vis	NA	FIA	B	comparison of two manifold architectures; proportional equation method	[55]
Fe(III), Co(II), Zn(II)	synthetic solutions	displacement reaction (analytes-EGTA yielding analytes-PAR complexes)	UV-Vis	0.00-5.38, 0.00-4.60, 0.00-5.17 mg L^{-1}	FIA	A	PCR, PLS and ANN data treatment	[56]
Fe(III), Co(II), Zn(II)	synthetic solutions	displacement reaction (analytes-PAN-4S yielding analytes-EDTA complexes)	UV-Vis	NA	FIA	A	PLS data treatment	[57]

(Table 1) contd…..

Analyte	Sample	Chemical Reaction	Detection Technique	Analytical Range or Detection Limit	Flow Analyser	Strategy	Remarks	Ref.
Fe(III), Co(II), Zn(II)	synthetic solutions	displacement reaction (analytes-EGTA yielding analytes-PAR complexes)	UV-Vis	2.5-7.0, 2.0-8.0, 1.5-11.5 mg L^{-1}	FIA	A	PLS data treatment	[58]
Fe(III), total iron	synthetic solutions	UV-assisted Fe(II) oxidation to Fe(III); Tiron as the colour forming reagent	UV-Vis	4-80 µg mL^{-1} Fe(III); NA for Fe(II)	FIA	B	two flow cells aligned with the optical path or sample recycling	[32]
iron, silver, manganese	Al or Cu alloys	analyte-catalyzed oxidation of Rhodamine B by periodate; 1,10-phenanthroline as activator	UV-Vis	20-160 ng mL^{-1} (each analyte)	FIA	A	use of the Kalman filter	[59]
iron, titanium, vanadium	Al alloys	analytes-catalyzed iodide oxidation by Cr(VI)	UV-Vis	0.012, 0.020, 0.018 µg mL^{-1}	FIA	A	Jones reducing agent for yielding Fe(II), Ti(III) and V(IV)	[13]
iron, vanadium	alloys	analytes-catalyzed iodide oxidation by Cr(VI)	UV-Vis	10.70-14.70, 7.50-11.50 mg L^{-1}	MPFA	C	Jones reducing agent for yielding Fe(II) and V(IV); PLS data treatment	[15]
iron, vanadium	alloys	analytes-catalyzed iodide oxidation by Cr(VI)	UV-Vis	8.0-10.0, 6.0-8.0 mg L^{-1}	MPFA	C	Jones reducing agent for yielding Fe(II) and V(IV); improved measurement repeatability by selecting maximal and minimal local absorbance values; PLS data treatment	[41]
furfural, vanillin	synthetic solutions	analyte reactions with *p*-aminophenol	UV-Vis	0.5-4.0 µg mL^{-1} (each analyte)	FIA	B	stream splitting / merging; proportional equation method	[26]
Ga(III), Al(III)	synthetic solutions	reactions with PAR under slight alkaline conditions	UV-Vis	l-5, 20-100 mg L^{-1}	FIA	A	PCR data treatment	[14]
Hg(II), Ag(I)	tap waters, wastewaters	analyte-catalyzed reaction of hexacyanoferrate(II) with α,α'-bipyridyl; thiourea as activator	UV-Vis	0.5, 1.0 ng mL^{-1}	FIA	A	proportional equation method	[60]
lanthanides (binary mixture)	synthetic solutions	displacement reactions [analyte-carboxynitrazo (or chlorophosphonazo-III) yielding analyte-EDTA (or TTGA) complexes]	UV-Vis	10^{-6} mol L^{-1} (magnitude order)	FIA	A	proportional equation method	[61]
levodopa, benserazide	pharmaceutical formulations	analyte oxidations by periodate	UV-Vis	4.1 x 10^{-4}-2.03 x 10^{-3}, 8.5 x 10^{-5}-4.25 x 10^{-4} mol L^{-1}	FIA	A	ANN data treatment	[62]
L-phenylalanine (L-Phe), L-tryptophan, L-methionine, L-leucine	synthetic solutions	reactions with L-amino acid oxidase / Trinder	UV-Vis	0.8-2.0 x 10^{-4} mol L^{-1} (L-Phe), 1.0-5.0 x 10^{-4} mol L^{-1} (other amino acids)	SFA	A	determination of binary mixtures of L-amino acids; proportional equation method	[63]
L-phenylalanine, L-methionine	synthetic solutions	reactions with L-amino acid oxidase / Trinder	UV-Vis	0.5-2.0 x 10^{-4}, 1.0-5.0 x 10^{-4} mol L^{-1}	SFA	B	comparison of flow reversal and flow recycling; proportional equation method	[38]
methanol, ethanol	synthetic solutions	reactions of aldehydes (formed after interaction with *alcohol oxidase*) with *p*-rosaniline / sulfite	UV-Vis	10-60, 10-300 µg mL^{-1}	FIA	A	enzyme immobilized on controlled-pore glass; proportional equation method	[64]

(Table 1) contd…..

Analyte	Sample	Chemical Reaction	Detection Technique	Analytical Range or Detection Limit	Flow Analyser	Strategy	Remarks	Ref.
Mg(II), Ca(II)	synthetic solutions	dissociations of the analytes-cryptand (2.2.1) complexes; sodium ions as scavenger	UV-Vis	2.00 x 10^{-4}-1.00 x 10^{-3} mol L^{-1} (each analyte)	FIA	B	two serial flow-through detectors; proportional equation method	[33]
Mg(II), Ca(II)	synthetic solutions	dissociations of the analytes-cryptand (2.2.2) complexes; reaction of the released analytes with phthalein complexone	UV-Vis	4.00-20.00 x 10^{-5} mol L^{-1} (each analyte)	FIA	A	MLR data treatment	[65]
Mg(II), Sr(II)	synthetic solutions	dissociations of the analytes-CDTA complexes; cupric ions as scavenger	UV-Vis	2.00 x 10^{-4}-1.60 x 10^{-3} mol L^{-1} (each analyte)	FIA	B	two serial flow-through detectors; proportional equation method	[4]
Mg(II), Sr(II)	synthetic solutions	dissociation of the analytes-cryptand (2.2.2) complexes; potassium ion as scavenger	UV-Vis	4.00 x 10^{-4}-2.00 x 10^{-3} mol L^{-1} (each analyte)	FIA	B	two serial detectors or two sample aliquots inserted into converging carrier streams; proportional equation method; applicable also to Sr(II) and Ca(II) determinations	[66]
Mn(II), Fe(III)	synthetic solutions	analyte-catalyzed oxidations of salicylaldehyde thiosemicarbazone by hydrogen peroxide	F	40-600, 40-500 ng mL^{-1}	FIA	B	stream splitting / merging; simplex optimization; proportional equation method	[67]
organophosphorus pesticides (omethoate, dichlorvos, dipterex)	vegetables	analyte oxidations by peroxodisulphate; yielded orthophosphate reacts with molybdate / vanadate; yielded vanadomolybdophosphoric acid oxidizes luminol	CL	< 1 x 10^{-8} g mL^{-1}	CFA	A	UV-radiation assisted analytes oxidation; ANN data treatment	[68]
phenolic compounds (resorcinol, *m*-aminophenol, *o*-cresol, phenol, *m*-cresol)	waters	analyte reactions with a product of PAP oxidation by periodate	UV-Vis	2-9 µg mL^{-1}	CFA	A	PLS data treatment	[69]
pyridoxal, pyridoxal 5-phosphate	synthetic solutions	analyte oxidations in the presence of cyanide	F	2.5 x 10^{-8}-1.0 x 10^{-4} mol L^{-1} (each analyte)	FIA	B	stream splitting / merging; proportional equation method	[70]
rifampicin, isoniazid	combined pharmaceutical formulations	oxidations by N-bromosuccinimide under alkaline conditions	CL	0.09-5.0, 0.08-10.0 µg mL^{-1}	CFA	A	ANN data treatment	[71]
silicate, phosphate	natural waters	oxidation of thiamine by the heteropoly acids formed at different rates	F	30-600 ng mL^{-1} (each analyte)	FIA	A	proportional equation method	[72]
uranium, vanadium	phosphate ores	analytes-catalyzed iodide oxidation by Cr(VI)	UV-Vis	0-3.6, 0-2.5 µg mL^{-1}	FIA	A	proportional equation method	[73]
Zn(II), Hg(II)	synthetic solutions	reactions with 5,10,15,20-tetrakis-(3-chloro-4-sulfophenyl)porphine	UV-Vis	0-3.0, 0- 2.0 µg mL^{-1}	FIA	A	zone merging; proportional equation method	[74]

UV-Vis = spectrophotometry; SPS = solid phase spectrometry; CL = chemiluminescence; F = fluorimetry; Br-PADAP = 2-(5-bromo-2-pyridylazo)-5-diethylaminophenol; CDTA = *trans*-1,2-diaminocyclohexanetetraacetic acid; EDTA = ethylenediamino tetraacetic acid; EGTA = ethylene glycol tetraacetic acid; NTA = nitrilotriacetic acid; PAN-4S = 1-(2-pyridylazo)-2-naphthol-4-sulfonic acid; PAP = *p*-aminophenol; PAR = 4-(2-pyridylazo)resorcinol; PSAA = 2-(5-bromo-2-pyridylazo)-5-(N-propyl-N-sulfopropylamino) aniline; TAN = 1-(2-thiazolylazo)-2-naphthol; TTGA = triethylentetramine hexaacetate; SFA = segmented flow injection analyser; FIA = flow injection analyser; rFIA = reversal flow injection analyser; SIA = sequential injection analyser; MCFA = multi-commuted flow analyser; MPFA = multi-pumping flow analyser; CFA = unsegmented continuous flow analyser; A = specific pump operating conditions (see 3.1); B = specific manifold architecture (see 3.2); C = more complete exploitation of the recorded signals (see 3.3); ANN = artificial neural networks; MLR = multiple linear regression; PCR = principal component regression; PLS = partial least squares; NA = not available information.

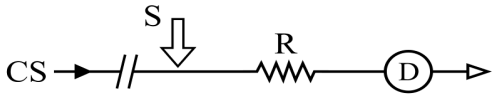

Fig. (1). Didactic representation of a typical flow system exploiting zone stopping. S = sample; CS = reagent carrier stream; R = reactor; D = detector; solid arrows = sites where pumping is applied; ‖ = intermittent pumping. For setting up the manifold, see ref. [3].

It should be recalled that the feasibility of zone stopping at the detector without switching the pump on was recently demonstrated [23], and exploitation of this possibility to implement differential reaction-rate methods in flow analysis is recommended.

3.2. Specific Manifold Architectures

As a consequence of the high versatility of the flow system, different strategies for implementing reaction-rate methods exploiting specific manifold architectures have been proposed, as discussed further.

3.2.1. Stream splitting

The main carrier stream is split, promoting the division of the sample zone; each portion of the sample zone is thereafter transported by a different emergent stream. The emergent streams can be merged together before reaching a single detector or, otherwise, directed towards different detectors.

Regarding stream splitting / stream merging, the sample is inserted into the carrier stream, and the originated sample zone flows through the confluence site b (Fig. **2**, upper) where the split process takes place. The resulting emergent streams flow through two parallel reactors. As the splitting process is generally determined by the hydrodynamic pressures involved [24], most of the sample carrier stream with the larger sample portion flows through the shorter reactor, whereas the smaller sample portion flows more slowly through the longer reactor. Higher versatility can be attained by placing a computer controlled three-way valve at point b (Fig. **2**, upper) to govern the splitting process [25]. At the next confluence site c, the emergent streams leaving the reactors are merged together. As a consequence of the asynchronous zone merging, the sample portion handled in the shorter reactor reaches the detector before the other portion. Due to the zone overlap involved, a complex sample zone is established and monitored. The resulting concentration / time function is characterised by two maximum values. As these values are associated to two mean sample residence times, differential reaction-rate analytical methods are straightforwardly implemented, as demonstrated in the spectrophotometric flow-injection determination of furfural and vanillin involving two peak height measurements [26]. It should be mentioned that better sensitivity can be attained in flow systems with stream splitting / merging by resorting from the confluence configuration: the sample is inserted into a chemically inert carrier stream and the reagent is added by confluence.

In flow systems designed without stream recombination, the emergent streams should be directed towards different detectors (Fig. **2**, lower). As both portions of the sample zone are independently handled in parallel channels, sampling rate is improved, as emphasised by Fernandez *et al.* who compared three manifold architectures for the spectrophotometric determination of cobalt and nickel [27]. The need for two separated detectors can be avoided by letting the separated emergent streams to flow though the analytical and reference cuvettes of a double-beam spectrophotometer; as a consequence of the dominance of single beam instruments in the market, this possibility has been scarcely exploited.

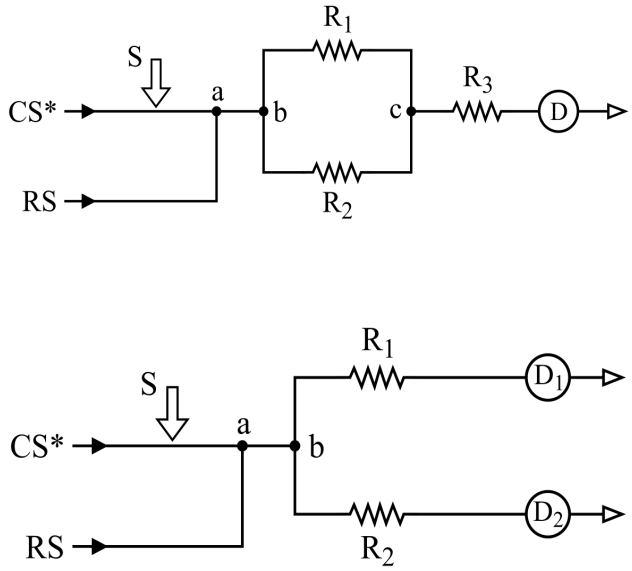

Fig. (2). Didactic representation of flow systems exploiting stream splitting with (upper|) or without (lower) stream merging. S = sample; CS* = chemically inert carrier stream; RS = reagent stream; a, b, c = confluence sites; R_i = reactors; D = detector; solid arrows = sites where pumping is applied. For setting up the manifold, see ref. [3].

3.2.2. Dual Sample Insertion

Two sample aliquots are simultaneously inserted, originating two sample zones. These aliquots can be inserted into a single carrier stream (Fig. **3**, upper) and difference in mean sample residence time into the analytical path is governed by the path length, as both aliquots are inserted at different distances from the detector. This manifold architecture results in a single system, as demonstrated into the determination of Co(II) and Ni(II) relying on two serial injection valves [28].

Alternatively, the sample aliquots can be inserted into convergent carrier streams (Fig. **3**, lower). Although more complex, the system is characterized by enhanced versatility, as the carrier stream flow rates can be modified at will, and the spectrophotometric determination of Cu(II) and Zn(II) in pharmaceutical preparations [29] can be selected as a typical application.

3.2.3. Reactor Replacement

The sample aliquot is inserted and the sample zone flows through a relocating reactor. Thereafter, next aliquot is inserted and handled inside a different reactor (Fig. **4**). In this way, different sample mean resident times are attained.

The approach is efficiently accomplished by exploiting commutation, as originally demonstrated in the analysis of

metals [30]. Two different reactors were attached in the central sliding bar of the injector-commuter, so that reactor displacement took place simultaneously with every sample insertion.

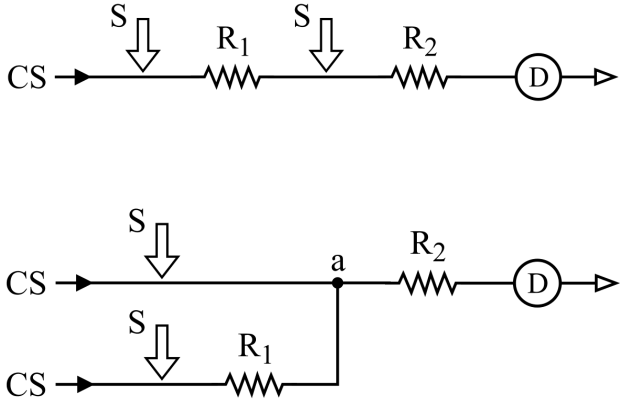

Fig. (3). Didactic representation of flow systems exploiting two sample insertions into a single carrier stream (upper) or into convergent (lower) carrier streams. Symbols as in Figs. (**1**, **2**). For setting up the manifold, see ref. [3].

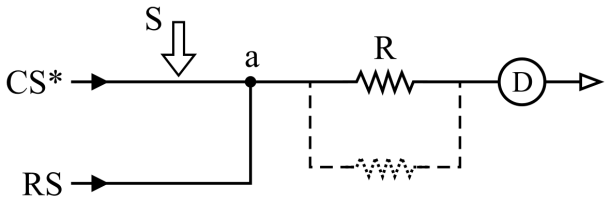

Fig. (4). Didactic representation of a flow system exploiting reactor relocation. Traced lines = alternative reactor position; other symbols as in Figs. (**1**, **2**). For setting up the manifold, see ref. [3].

The innovation can be also implemented without exploiting commutation, as demonstrated in the chemiluminescent determination of ascorbic acid and cysteine in human urine [31]. Kinetic discrimination relied on the rate of ferric ion reduction taking place prior to the sampling loop. In this way, reactor could be manually replaced without the drawbacks associated with repetitive manifold modifications.

3.2.4. Multi-Site Detection

The sample aliquot is inserted once and monitored at two different manifold sites.

Initial applications [4] utilized two sequentially positioned flow-through cuvettes (Fig. **5**, upper). The need for two detectors can be avoided by resorting from a double beam spectrophotometer (see above), or two flow cells aligned in the same optical beam [32]. A noteworthy feature of this manifold architecture is that the portions of the analytical path after first monitoring site can be heated in order to improve the kinetic discrimination [33]

An advanced manifold can be designed by exploiting multi-commutation in order to permit a single detector to sight at different manifold sites (Fig. **5**, lower). The innovation was named as *multi-site detection* [34]. The flow cell is connected to the central sliding bar of an injector-commuter and displacement of this bar moves the detector between two sites of the analytical path. The innovation was exploited in the determination of copper and nickel in plant digests [35]. As the complexation of Ni(II) by the color-forming reagent was relatively slow, the reactor between the monitoring sites was immersed in a warm water bath.

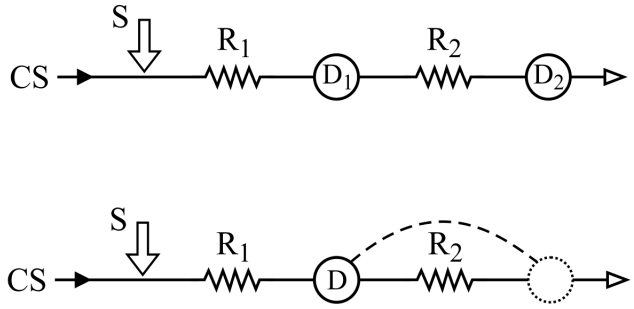

Fig. (5). Didactic representation of flow systems exploiting multi-site detection with separated (upper) or relocating (lower) detectors. Traced lines = alternative detector position; other symbols as in Figs. (**1**, **2**). For setting up the manifold, see ref. [3].

3.2.5. Other Possibilities

Other specific manifold architectures exploiting the high versatility of the flow analyzer have been proposed for implementing differential reaction-rate methods.

An interesting approach is to take advantage of sample slicing. One portion of the handled sample zone is stopped into the analytical path whereas the other flows directly towards detection; after a pre-selected time interval, the retained portion is also allowed to flow towards detection; two peaks corresponding to two mean sample residence times are then recorded. The innovation was originally implemented in a sequential injection system and the main rotary valve governed the slicing process, allowing the spectrophotometric determinations of cobalt and nickel in natural waters and soil extracts [36].

Alternatively, flow recycling can be exploited in order to permit the sample zone to be monitored several times under different residence times. The sample is inserted into the main carrier stream and directed towards detection (Fig. **6**); thereafter a strategically positioned four-way valve is switched in order to permit the sample zone to recycle, thus to pass several times through the detector; next valve switching directs sample zone towards waste. This specific architecture of the manifold has been considered as a *closed loop configuration*, and the determination of Fe(III) and Co(II)in synthetic solutions involving iterative detection by multiple passage of the sample zone through the detector [37] can be selected as a good example to illustrate this potentiality.

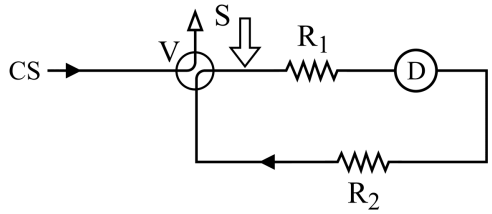

Fig. (6). Didactic representation of a flow system with sample recycling. V = four-way stream directing valve; other symbols as in Figs. (**1**, **2**). For setting up the manifold, see ref. [3].

Regarding segmented flow analysis, different manifold architectures for accomplishing flow reversals or flow recycling were critically compared in relation to the spectrophotometric determinations of L-phenylalanine and L-methionine [38], and good analytical figures of merit were reported for both architectures.

3.3. Deeper Exploitation of the Recorded Signals

A deeper exploitation of the recorded signals is performed, allowing the design of a single-line flow system without ON/OFF pump switching, similar to that in Fig. (**1**) however without zone stopping. Initial attempts to exploit this possibility involved the insertion of a large sample volume into a continuously flowing reagent carrier stream. With a too large sample zone, the analyte / reagent interactions occur predominantly at its front and trailing portions. Passage of the sample zone through the detector results therefore in two peaked signals each one characterized by a different mean sample residence time. The potentialities of this innovation were highlighted in the spectrophotometric flow injection determination of cobalt and nickel exploiting the different rates of analyte complex-ations with 2-hydroxybenzaldehyde thiosemicarbazone [39].

This innovation was improved by considering multiple measurements performed along the entire flowing sample. Each measurement refers to a given sample residence time, a given sample dispersion and a given sample / reagent volumetric ratio; this is equivalent to exploit multiple pseudo detectors. With multiple data related to different temporal and volumetric conditions, reaction rate methods involving multivariate calibration are straightforwardly implemented, as initially demonstrated in the spectrophotometric determination of iron and vanadium in alloys. The method exploited the influence of Fe(II) and V(IV) on the rate of iodide oxidation by Cr(VI) under acidic conditions; the Jones reducing agent was then needed. Data treatment involved the PLS algorithm.

The analytical procedure was recently improved by avoiding the measurements related to regions of the sample zone with pronounced concentration gradients, as these measurements are intrinsically less reproducible [40]. To this end, different sample aliquots were sequentially inserted into the reagent carrier stream [41], and the resulting zones underwent severe overlap yielding a complex sample zone with regions of maximal and minimal local concentrations. Precise absorbance values associated to these regions were attained.

4. APPLICATIONS

Analysis of Table **1** reveals that most applications of differential reaction-rate methods in flow analysis refer to the determination of two (or three) metals or similar organic compounds by spectrophotometry, fluorimetry or chemi-luminescence. The potentialities of analytical techniques, especially in simultaneous / sequential determinations, are expanded when implemented in flow analysis, and this aspect is more pronounced in relation to the above mentioned techniques.

The $(k_1\ [A_1])\ /\ (k_2\ [A_2])$ ratio constitutes itself in a limiting factor on the applications of reaction-rate methods, and this limitation is lessened in flow analysis, as the reproducible sample handling, especially timing, is inherent to the analyser.

The number of applications has however decreased in recent years, and two aspects can be highlighted in this context.

- most of the commercially available flow analyzers do not offer facilities for easy implementing differential reaction-rate methods. Consequently most of the users are working in taylor-made systems, normaly in academic laboratories.
- stopped-flow mixing permits an efficient exploitation of ultrafast reactions. However, the required instrumentation is less suitable for large-scale routine analysis.

One expects therefore that this review incentives authors towards a renaissance of this important topic in flow analysis.

5. TRENDS

Implementation of differential reaction-rate method in the flow analyser does not modify the general tendencies of flow analysis, especially in regard to downsizing, reduction of waste generation, thus matching the Green Chemistry concept, portability and suitability for routine, often *in situ,* analyses. One expects an increased exploitation of other kinetic processes such as sequential extractions, sequential sampling, sequential injection chromatography with monolithic columns, etc.

The potentialities of in-line determinations relying on different reaction rates are increased by exploiting different sample handling conditions involving *e.g.* addition of optional reagents, inter-change of manifold components, use of external energy (heating, UV or ultrasound irradiation) for assisting the analyte discrimination, etc, and these conditions are better established by resorting from concentration-oriented feed-back mechanisms. These tendencies will certainly come true, and preparation of a review article on this theme is highly recommended. Moreover, with the present development of multi-commutation [21], implementation of differential reaction-rate methods in flow analysis will certainly experiment a renaissance.

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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