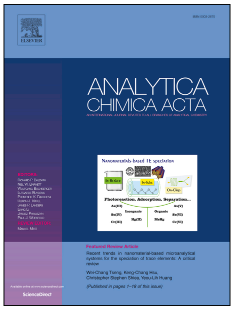

Prospects of pulsed amperometric detection in flow-based analytical systems - A Review

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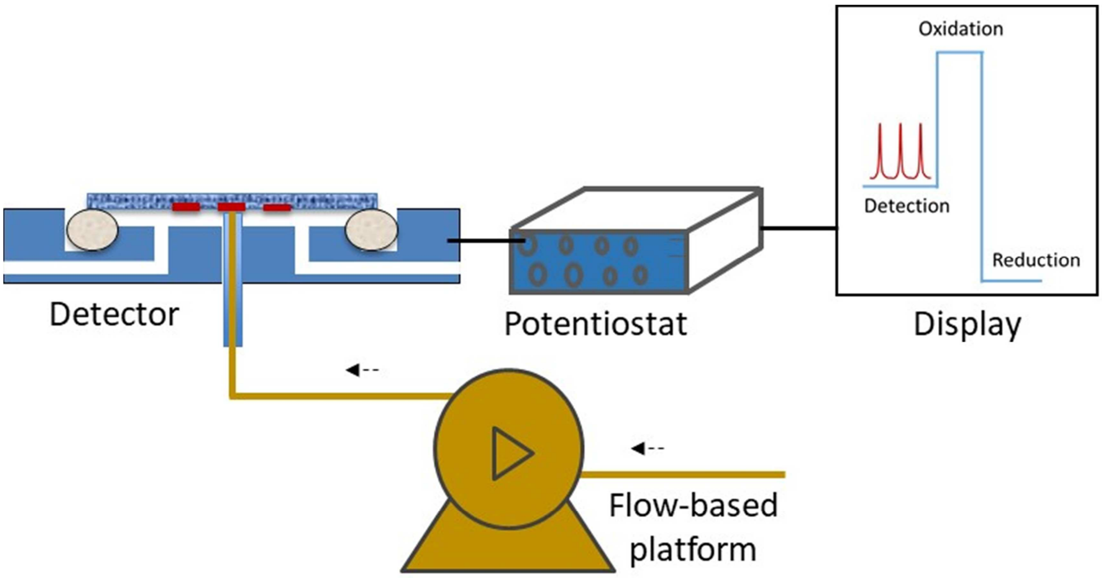
Oxidation
Detection
Reduction
Detector
Potentiostat
Display
Flow-based platform

Prospects of pulsed amperometric detection in flow-based analytical systems - A Review

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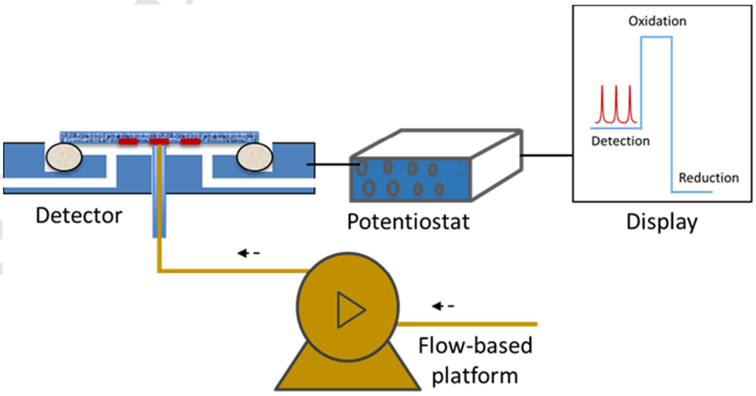
Highlights

- The fundamentals and waveform designs of pulsed amperometric detection (PAD).
- Electrochemical (EC) detector designs are commonly used for PAD.
- The technological advancement of PAD and its selected applications since 1997-2018.
- Future directions of PAD such as 3D printed EC detector, nanomaterials, multi-modal EC detection.

Graphical abstract



Abstract

Electrochemical (EC) detection techniques in flow-based analytical systems such as flow injection analysis (FIA), capillary electrophoresis (CE), and liquid chromatography (LC) have attracted continuous interest over the last three decades, leading to significant advances in EC detection of a wide range of analytes in the liquid phase. In this context, the unique advantages of pulsed amperometric detection (PAD) in terms of high sensitivity and selectivity, and electrode cleaning through the application of pulsed potential for noble metal electrodes (e.g. Au, Pt), have established PAD as an important detection technique for a variety of electrochemically active compounds. PAD is especially valuable for analytes not detectable by ultraviolet (UV) photometric detection, such as organic aliphatic compounds and carbohydrates, especially when used with miniaturised capillary and chip-based separation methods. These applications have been accomplished through advances in PAD potential waveform design, as well as through the incorporation of nanomaterials (NMs) employed as microelectrodes in PAD. PAD allows on-line pulsed potential cleaning and coupling with capillary or standard separation techniques. The NMs are largely employed in microelectrodes to speed up mass and electron transfer between electrode surfaces and to perform as reactants in EC analysis. These advances in PAD have improved the sensitive and selective EC detection of analytes, especially in biological samples with complex sample matrices, and detection of electro-inactive compounds such as aliphatic organic compounds (i.e., formic acid, acetic acid, maleic acids, and β-cyclodextrin complexes). This review addresses the fundamentals of PAD, the role of pulsed sequences in AD, the utilization of different EC detectors for PAD, technological advancements in PAD waveforms, utilisation of microelectrodes in PAD techniques, advances in the use of NMs in PAD, the applications of PAD, and prospects for EC detection, with emphasis on PAD in flow-based systems.

Keywords

Electrochemical detector
Flow-based analytical systems
Pulsed amperometric detection

Abbreviations

AD	Amperometric detection

APAD	Activated pulsed amperometric detection
CE	Capillary electrophoresis
DC	Direct current
EC	Electrochemical
FC	Flow cell
FIA	Flow injection analysis
HPAEC	High-performance anion exchange chromatography
HPLC	High-performance liquid chromatography
IPAD	Integrated pulsed amperometric detection
LC	Liquid chromatography
MPAD	Multiplex-pulsed amperometric detection
NMs	Nanomaterials
PAD	Pulsed amperometric detection
PED	Pulsed electrochemical detection
QPAD	Quadrupole pulsed amperometric detection
RDE	Rotating disk electrode
Redox	Reduction and oxidation
RPAD	Reverse pulsed amperometric detection
S/N	Signal-to-noise
SIPAD	Six-potential integrated pulsed amperometric detection
SPEs	Screen-printed electrodes
TL-FC	Thin-layer flow cell
WJ-FC	Wall-jet flow cell
ZrO_2	Zirconium dioxide

1. Introduction

The use of electrochemical (EC) detection techniques and corresponding EC detectors in flow-based analytical systems such as flow injection analysis (FIA), capillary electrophoresis (CE), and liquid chromatography (LC) has attracted the interest of analytical chemists over the last three decades [1-5]. The pioneering work of Kissinger *et al.* [6] laid the foundation for the incorporation of EC detection modes and EC detectors with flow-based analytical techniques.

EC detection is ideally suited to miniaturised analytical systems [7] due to the compatibility of EC detection techniques in general with miniaturisation, simple instrumentation, low electrical power requirements for in-field use, low cost, and robustness [8]. EC detection offers high selectivity through the proper choice of detection potential and/or electrode material [9], and high sensitivity towards electroactive compounds (a material electrically active or responsive) [10]. The versatility of EC detector designs and detection modes meets most of the requirements of flow-based analysis [11].

EC detection techniques include a variety of detection mechanisms to determine target analytes in a liquid stream such as measurement of current at fixed or variable potential or as a function of time (amperometry, voltammetry or coulometry, respectively), measurement of Nernstian potential (potentiometry) and measurement of conductivity [11]. Amongst these different EC detection techniques, amperometric detection (AD) has been widely used in flow analysis systems because of its high sensitivity [10] and instrumental simplicity [7]. However, a major disadvantage of the AD is the deposition of solution impurities or EC reaction by-products on the electrode surface. To enhance the performance of electrodes in the AD, a pulsed potential is often applied during amperometric measurements, hence the term pulsed amperometric detection (PAD) [11]. PAD has been drawing the attention of analytical researchers over the last 30 years and has become an alternative detection technique for the quantitative detection of numerous organic compounds such as carbohydrates [12]. Noble metal electrodes (e.g. Au, Pt) offer partially unsaturated d-orbitals, which enhances adsorption of the analytes (e.g. carbohydrates) on the electrode surface and subsequent detection by PAD. PAD is generally based on a triple potential waveform that facilitates potentiostatic cleaning [11] of the electrocatalytic solid anodic electrodes (e.g. C, Au, and Pt) [12] and reactivation of the electrode surface after each measurement cycle, on a time scale of milliseconds, allowing rapid measurements in dynamic systems including detection in flow-based analytical methods. Thus, PAD can be used to reduce fouling of the electrode surface that otherwise results in a loss of electrode activity over time [11].

AD in non-pulsed mode uses direct current (DC) for the detection of a variety of organic and inorganic compounds [12]. In DC amperometry, during detection in an oxidative mode using the anodic detection electrode (also designated the working electrode), many organic aromatic compounds demonstrate high electroactivity (i.e., standard reduction potentials). The high electroactivity demonstrated by aromatic compounds is attributed to inherent π-resonance, functioning to stabilise the free radical intermediates during the oxidative reactions at the electrode surface [13]. As a consequence, the activation energy barrier of the EC oxidation reaction decreases significantly, resulting in a higher rate of oxidation of the analyte at the surface of the electrode [13]. On the other hand, organic aliphatic compounds have functional group such as hydroxyl (e.g. carbohydrates, alcohols, and alditols), and hydroxyl/amine (e.g. amine, amino acids, aminosugars, aminoglycosides, peptides, and proteins) demonstrate low electroactivity (i.e., standard reduction potentials), and hence, there is no possibility of stabilization of free-radical intermediates via π-resonance. For this reason, low oxidation rates resulting from the increased activation energy barrier of EC oxidation are observed for aliphatic compounds at inert electrode surfaces during the DC amperometric-based detection process. However, the activation energy barrier of EC oxidation for organic aliphatic compounds was reported to reduce greatly when noble metal electrodes such as Pt or Au were used [13]. Hence, the adsorption of analytes on the electrode surface increases, resulting in the gradual inactivation of the electrode surface for further use [12]. In this context, PAD applies an alternate cathodic and anodic potential in a cyclic order to reactivate and maintain clean electrode surfaces and to enhance the sensitivity and reproducibility of the EC signal. Hence, aliphatic compounds can easily be detected in a sensitive manner by the use of DC amperometric techniques in pulsed mode [12]. At present, the PAD technique remains under the overarching categorisation of pulsed electrochemical detection (PED), which encompasses all waveform applications of metal electrodes for amperometric-based detection [12].

During the last two decades (1997-2018), approximately 423 journal papers, including 5 reviews on PAD have been published (see Fig. 1).

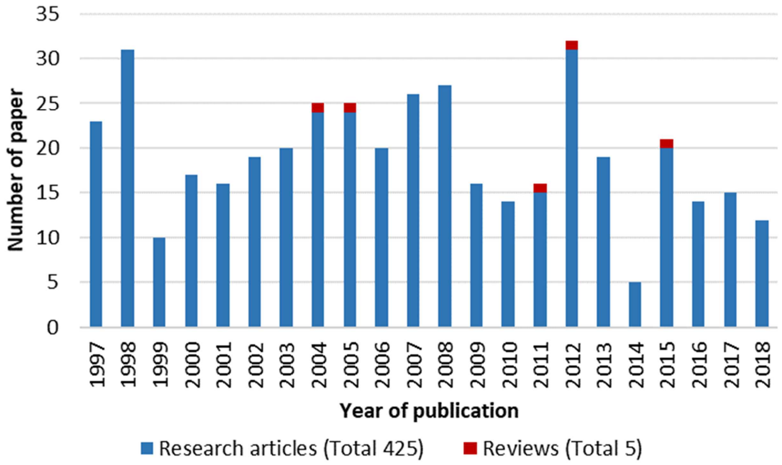


Fig. 1. Number of published articles related to PAD in flow-based systems such as CE, FIA, and LC from 1997 to 2018 (Title searched phrases: “pulsed amperometric detection” and “pulsed electrochemical detection”).

Amongst these reviews, in 2004 Jandik *et al.* [14] covered topics including developments in the area of analysis of amino acid-carbohydrate mixtures by high-performance anion exchange chromatography (HPAEC), and in 2005 LaCourse *et al.* [15] discussed the detection modes of PED and general PED waveform design at microelectrodes, and microelectrode applications in microchromatographic and electrophoretic separation techniques. In 2011, Trojanowicz [16] discussed about the PAD waveforms and microelectrode materials (such as gold, platinum, silver, and graphite) and reported their applications in liquid chromatography. Then in 2012 Corradini *et al.* [17] described HPAEC coupled with PED techniques for carbohydrate determination, in 2015 Fedorowski *et al.* [12] outlined the development of advanced waveforms of PED and the use of microsystems in combination with PED. Fedorowski *et al.* [12] also discussed advancements in PED technology, such as improvements to waveforms and microelectrodes, as well as the advanced analysis of carbohydrates including the fingerprinting of bioproducts and characterization of enzymatic processes.

As the applications of PAD in flow-based analytical systems is increasing continuously (*ca.* 67 journal articles published during the period of 2014-2018 as demonstrated in Fig. 1), it is necessary to collate recent knowledge regarding the advanced waveforms, NMs, and microelectrodes in PAD incorporated within flow-based systems. Therefore, the following sections of this review will cover the fundamentals of PAD, the role of pulsed sequences in AD, the utilization of different EC detectors, microelectrodes, NMs, technological advances in PAD, the applications of PAD to aqueous-based separation techniques, such as CE, FIA, and LC systems from 1997-2018, and future directions for EC detection, with emphasis on PAD in flow-based systems.

2. Fundamentals of PAD

2.1 Amperometric detection

Amperometric detection (AD) is a widely reported EC detection technique in CE, FIA, and LC [11]. The AD is performed using a two or three electrode EC cell, with a working electrode, a reference electrode, and an auxiliary electrode [18]. This technique is carried out by applying a constant potential to the working electrode and the resulting current is measured as a function of time. This technique is different from cyclic voltammetry (CV), which is performed by cycling the potential of a working electrode and measuring the resulting current [18]. At the surface of the working electrode, the redox (reduction and oxidation) reactions of the analytes take place by the application of a potential where the output current is proportional to the analyte's concentration [7, 19]. The mathematical expression that relates the amount of analyte oxidised or reduced at the working electrode surface to the resulting current is established according to Faraday's law (Equation 1) [7]:

$$I_t = \frac{dQ}{dt} = nF\frac{dN}{dt} \qquad (1)$$

where I_t is the yielded current at the working electrode surface at time t, Q is the charge at the working electrode surface, t is the time, n is the number of electrons transferred per mole of analyte, F is the Faraday constant (96485 C mol^{-1}), and N is number of moles of analyte oxidised or reduced [20].

2.2 Pulsing sequences in PAD

PAD utilises electrocatalytic surfaces to stabilise (mainly aliphatic) free radical intermediates. However, large amounts of catalytic activity promote the accumulation of interferents at the working electrode Pt or Au surface during the redox reaction [12]. To sustain a clean and reactive electrode surface for continuous reproducible detection a cyclic potential waveform in PAD must have at least three principal steps: (1) application of a potential to promote electrocatalytic oxidation of the analyte of interest, (2) oxidation *via* a large positive anodic potential resulting in the formation of a surface oxide, and (3) reduction to restore the activity of the electrode *via* a large negative cathodic potential, resulting in removal of the surface oxide [21].

Furthermore, for the analysis of simple carbohydrates, Neuburger and Johnson [22] established that PAD with an Au electrode in basic media resulted in a lower limit of detection and a higher sensitivity compared to PAD with a Pt electrode. Therefore, at present most PAD applications take these advantages of using an Au electrode for the detection of the target analyte of interest in basic media.

2.3 PAD detection modes

All PAD detection modes include an oxidation step i.e., a large positive anodic potential result in the formation of a surface oxide. PAD enhances the electrode reactivation, including oxide formation and its removal at the surface of the metal electrode. These mechanisms can be achieved through three detection modes as shown in Fig. 2.

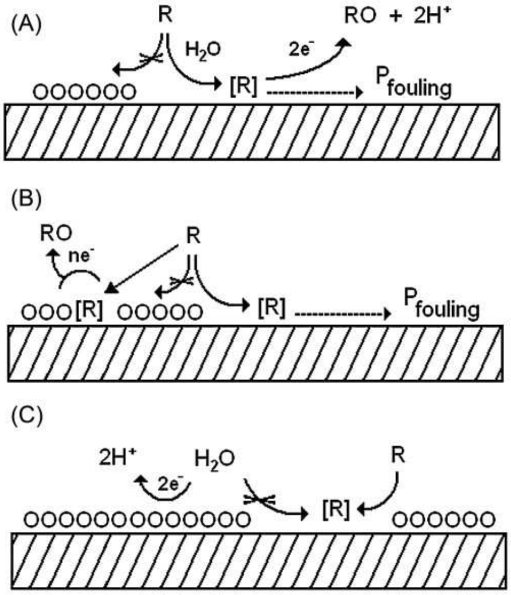


Fig. 2. Schematic diagram of the three different detection modes A, B, and C, of PAD respectively (reproduced with permission) [12]. In (A), reactant R is adsorbed on the oxide-free surface of the electrode resulting in either oxidation to RO or the fouling ($P_{fouling}$) of the electrode. In (B), R is adsorbed on the electrode surface which may result in oxidation simultaneously with the formation of surface oxide or fouling. In (C), reactant R is adsorbed on the electrode surface, suppressing oxide formation and resulting in a negative response [12].

2.3.1 Mode A: Direct detection of analytes at oxide-free surfaces

In the absence of a surface oxide, electrocatalytic noble metal electrode surfaces can adsorb organic aliphatic compounds (see Fig. 2A). Convective diffusion-based mass transport mechanisms bring the analytes to the electrode surface and the electrode drives the oxidation of the compounds with little or no concurrent formation of surface oxide. The oxidised products exit the diffusion layer and then readsorb for further oxidation or fouling of the electrode surface [12, 23]. The response from the analyte using detection mode A is larger than the baseline signal or background response [12]. This detection mode is used for the determination of carbohydrates with either Au electrode in alkaline solutions or Pt electrode in acidic solutions [13].

2.3.2 Mode B: Direct oxide-catalysed detection of analytes

This detection mode is accomplished by the concurrent formation of a surface oxide and oxidation of the analyte at a metal electrode [15]. In Fig. 2B convective diffusional mass transport brings the analytes to the electrode surface and catalytic oxidation of the compounds occurs. The primary analytical signal results from the oxidation of pre-adsorbed analytes. The products formed by the oxidation of analytes may either foul the electrode surface or leave the diffusional layer. The continuous and significant signal generated from surface oxide formation at the electrode makes a large contribution to the background signal (larger than in mode A), ultimately resulting in a decreased signal- to-noise (S/N) [12, 23]. This detection mode is used for the determination of both aliphatic amines and amino acids using Au or Pt electrodes (in alkaline solutions), and various sulfur compounds with Au (in alkaline solutions) or with Pt electrodes (in acidic solutions) [15].

2.3.3 Mode C: Indirect detection of analytes at oxide surfaces

The indirect analyses require analyte preadsorption at the electrode surface prior to analyte oxidation [24]. This detection mode (Fig. 2C) is used for electro-inactive analytes, which can interfere with the formation of surface oxides. Electro-inactive analytes suppress the baseline signal resulting from anodic currents due to surface oxide formation. This suppression generates the negative peak for the analyte due to the prevention of surface oxide formation [12, 23]. The suppression of these anodic currents presented an indirect detection scheme for PAD that was dependent on analyte adsorption. Mode C is typically applied for the detection of inorganic and sulfur-containing organic compounds [15].

3. PAD waveform design

The simplest PAD waveform, Fig. 3a [12, 13, 25] includes three different potential steps. The analyte of interest is detected by the application of the detection potential (E_{det}) at the Au or Pt electrode for a certain time (t_{det}). Then the anodic oxidative potential (E_{oxd}) is applied for a time (t_{oxd}), to produce a surface oxide on the electrode surface with simultaneous oxidative desorption of adsorbed carbonaceous materials. In the last step, a cathodic reductive potential (E_{red}) is applied to reactivate the electrode [26]. This type of waveform with detection mode A is used to determine alcohol-containing compounds such as alcohols, amino-glycosides, alditols, and carbohydrates with an Au electrode (in alkaline solutions) and a Pt electrode (under both alkaline and acidic conditions) [27-30]. The application of the PAD waveform with detection mode B was reported to produce inferior results to that with detection mode A [13].

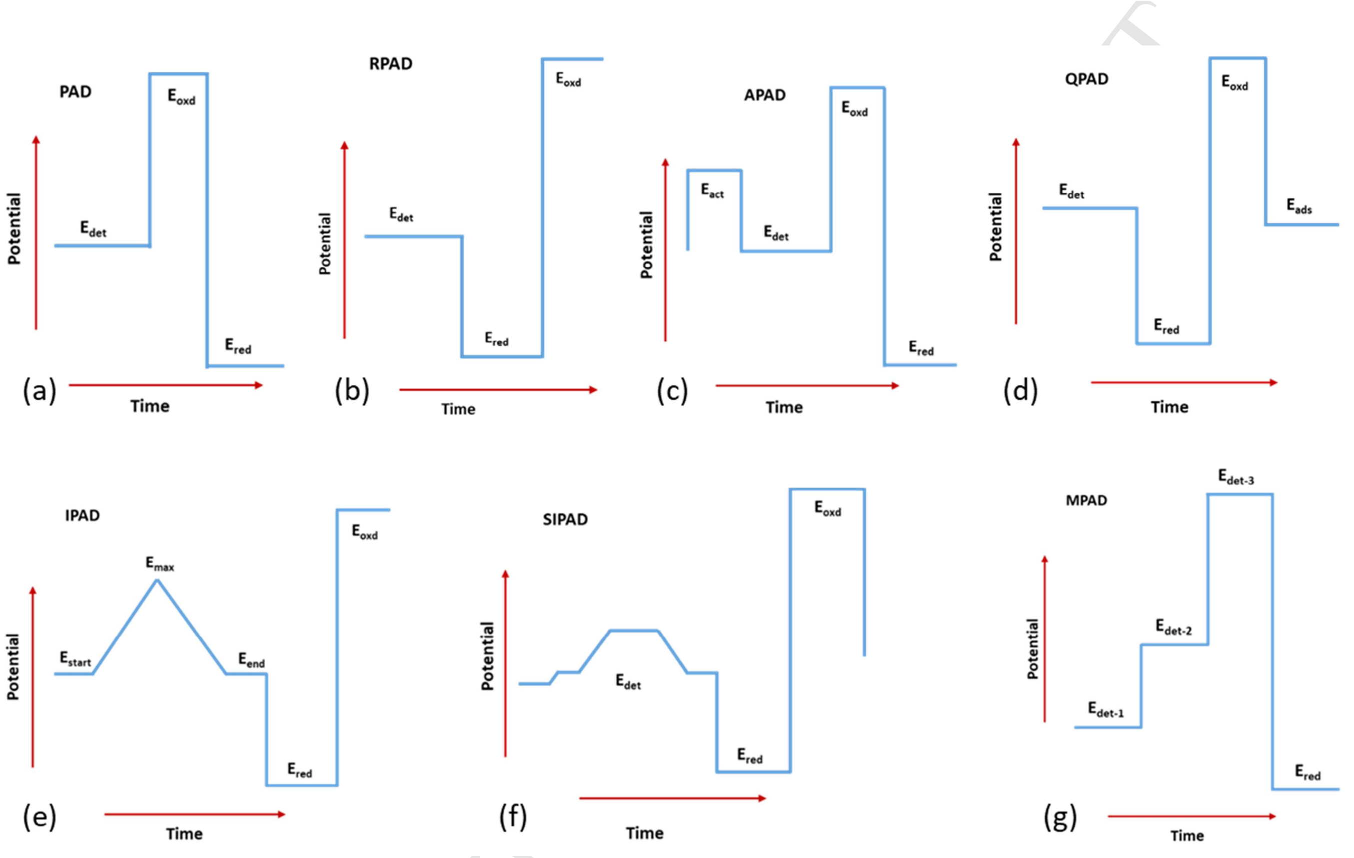


Fig. 3. Schematic diagrams of (a) PAD, (b) RPAD, (c) APAD, (d) QPAD, (e) IPAD, (f) SIPAD, and (g) MPAD waveforms. The regions of E_{act}, E_{ads}, E_{det}, E_{red}, and E_{ox} correspond to activation potential, potential to disrupt the adsorption, detection potential, reduction potential, and oxidation potential respectively (reproduced and redrawn with permission) [12, 31].

The analytical response in detection mode A is larger than the baseline signal (background response) [12]. In the detection mode B, a continuous significant current is generated by the oxide surface, contributing significantly to the background or baseline signal resulting in baseline drift [32]. To overcome this situation Gilroy [32] demonstrated that the use of a lower potential can slow down surface oxide formation and diminish its contribution to the background signal. Later on, Polta and Johnson [33] reversed the PAD waveform potential steps E_{oxd} and E_{red} to obtain similar or better result, known as reverse pulsed amperometric detection (RPAD, see Fig. 3b) [12, 13, 25]. Nevertheless, this waveform with detection mode B achieved lower baseline for the detection of sulfur compounds and poor oxidative cleaning performance [13].

Prior to applying E_{det} in RPAD, it became necessary to introduce a fourth potential pulse (E_{act}) to ensure sufficient oxidative cleaning of the electrode surface [34]. This is known as activated pulsed amperometric detection (APAD, see Fig. 3c) [12, 35]. This initial potential step accelerated the activation of the surface oxide after which switching to a low detection potential satisfied detection mode B [12]. APAD waveforms were used by Williams *et al.* [34] to determine arsenic (III), and by Johll *et al.* [36] to determine cysteine with Pt electrodes in acidic conditions.

In quadrupole pulsed amperometric detection (QPAD, Fig. 3d) [12, 37], after the detection step (E_{det}) an additional cathodic electrode surface cleaning step (E_{red}) is used to reduce each partially solvated species of Au, which finally returns to metallic Au. Then a brief potential E_{oxd} is introduced to activate the electrode surface and finally a negative potential (E_{ads}, t_{ads}) to disrupt the adsorption of the analyte on the electrode surface [38].

In integrated pulsed amperometric detection (IPAD, Fig. 3e) [12, 21], the onset of a cyclic scan precedes the oxidation of the analyte and gradually progresses with the positive scan through an oxide formation region that follows the detection by mode B. As the potential progresses out of the oxide formation region through the negative scan, the oxide background signal is rejected, whilst the analyte signal is recorded. This integrated pulsed waveform can eliminate drift and changes due to the small variations of mobile phase composition, pH, and application of gradients in chromatography [14]. IPAD with detection mode B has been utilised to determine amino acids, amines, proteins, peptides, and thiol compounds at both Au and Pt electrodes [30, 39-41].

Fedorowski *et al.* [12] and Clarke *et al.* [42] reported the utilisation of six-potential integrated pulsed amperometric detection (SIPAD, Fig. 3f) [37, 42] for the determination of amino acids and amino sugars, without any additional pre-column or post-column derivatization, in LC. In the optimisation step, the gradual erosion of gold from the surface of the electrode was reduced by incorporating a large negative potential prior to the waveform integration period. The addition of a short adsorption step in six-potential IPAD resulted in a highly efficient cycle which overcame the limitations of amino sugars and amino acids analysis.

Multiplex-pulsed amperometric detection (MPAD, Fig. 3g) [13, 38, 43] uses multiple potential pulses as a function of time to monitor the current at several applied potentials, which makes it feasible to detect different compounds, both individually and simultaneously [44, 45]. It is also used for the introduction of internal standard addition in the

FIA system with AD [46], and for increasing the selectivity of the EC method for the detection of the products of oxidation or reduction, even in the presence of interfering species [31]. Additionally, the MPAD detection mode enables the simultaneous determination of electroactive compounds that partly overlap and cannot be determined by voltammetric techniques. Besides the application of a potential pulse for analyte detection, this technique also enables the constant application of a cleaning potential pulse at the end of the cycle [45].

4. EC detector designs for PAD

The term EC detector has been mainly used in relation to amperometric or coulometric detectors. EC detectors respond only to those species which can be oxidised or reduced by the applied potential on the electrode material used in the detectors. The working electrode of these detectors is kept at a constant potential against a suitable reference electrode, and the current flowing across the working electrode is measured. Current depends on the concentration of an analyte in the carrier stream but also largely on the flow pattern of the carrier stream near the electrode. For these reasons, the design of the flow geometry is particularly important in EC detectors. Two geometries such as thin-layer FC (TL-FC, Fig. 4 (a, b)) and wall-jet FC (WJ-FC, Fig. 4 (c, d)) have been frequently utilised in EC detection [47, 48], depending on the type of the working electrode, the shape of the inlet capillary nozzle and the distance between the nozzle and the electrode surface [3-5].

In a TL-FC (Fig. 4 (a,b)) [49], the solution flows through a thin flat channel parallel to the electrode surface which is contained in one of the channel walls [3-5]. In a WJ-FC (Fig. 4 (c, d)) [49], the carrier stream exits through a small orifice into a liquid-filled space and forms a jet that impinges on the electrode surface [47, 49] and the solution is drained away from the vicinity of the electrode after contact.

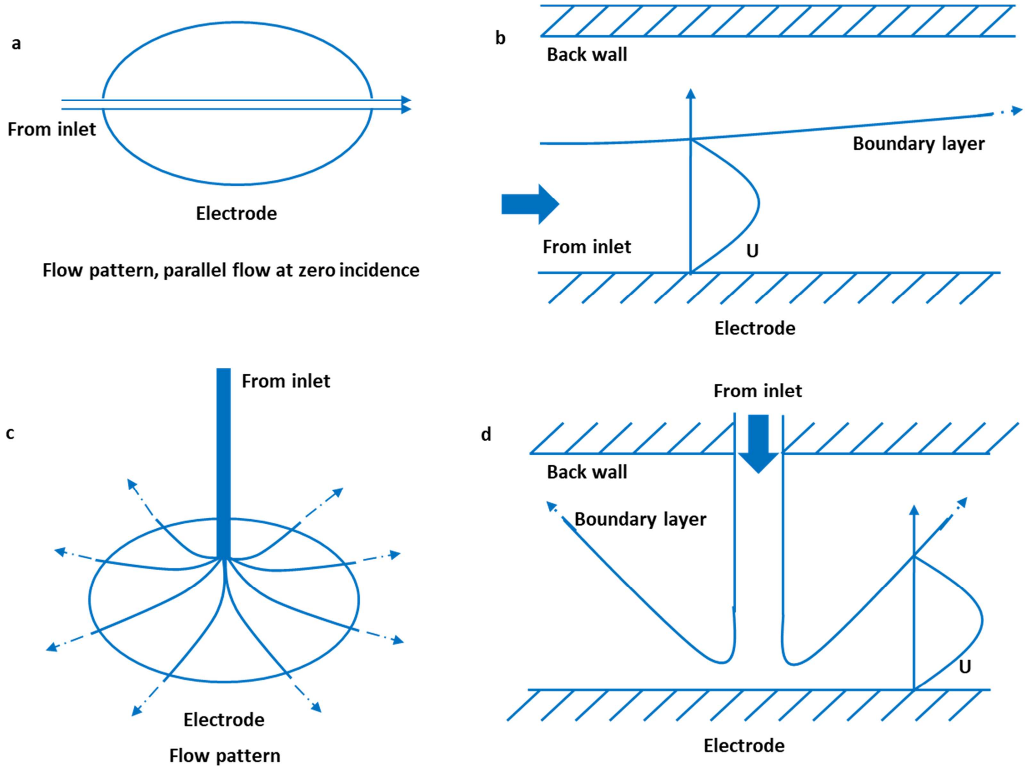


Fig. 4. Schematic diagram of flow patterns, and boundary layers: (A, B) thin layer flow cell, and (C, D) WJ-FC. U, indicates the rate of flow at the surface of the electrode, which is the radial flow velocity for the WJ-FC (reproduced and redrawn with permission) [49].

Compared with other electrode geometries, such as the tubular, the flat plate with the parallel flow at zero incidences, and the rotating disk electrode (RDE) the WJ configuration appears to be the most suitable for continuous-flow monitoring. In particular, it shows high sensitivity in the millilitre flow rate range [50, 51]. It also has several desirable features such as ease of maintenance and a simple and robust design. As shown by Albery *et al.* [52] and Gunasingham *et al.* [53], the WJ electrode affords an attractive alternative to the RDE for fundamental EC studies, despite the fact that it does not have a uniformly accessible surface. Perhaps the most useful aspect of the WJ electrode in this respect is the fact that it can be used in a continuous-flow system. The WJ electrode is an attractive configuration for EC detectors for LC on account of its high convective mass transfer characteristics [49]. It offers many useful features such as well-defined hydrodynamic properties, low void volume, good sensitivity, fast response, ease of operation, and low cost [54, 55].

5. Technical advances

5.1 Faster waveforms

The requirement of using PAD at a high frequency was necessitated by the rapid advances in CE- and LC-based flow systems. Neuburger *et al.* [56] achieved an increased S/N for carbohydrate detection by expanding the current integration time period (t_{int}) duration from 16.7 ms to 200 ms, which eliminated the noise resulting from the 60 Hz power supply. Later, LaCourse and Johnson [38] used pulsed voltammetry to optimise the PAD waveform potential and time, with the waveform frequency of 1 Hz at $\mathrm{t_{int}}$ equal to 200 ms. Additionally, Roberts *et al.* [57] succeeded in the detection of carbohydrates by increasing the waveform frequency from 0.5 to 6.2 Hz. This was accomplished by minimising the time for oxidative cleaning and reductive reactivation of the electrode surface without changing the t_{int} (200 ms) for ideal current sampling. Additionally, Jensen and Johnson [58] applied a 6.7 Hz frequency waveform by incorporating the cathodic reduction potential ideal for removing the products formed during the glucose oxidation. This waveform for detecting glucose in an LC-PAD system established a sub-picomole limit of detection (LOD) with a linear dynamic range that covered more than three orders of magnitude [12].

5.2 Microelectrodes in PAD

PAD depends on reactions at the electrode surface, which makes it suitable for use with micro-separation platforms. EC detection allows miniaturisation with technological advancements in the fabrication of microelectrodes. The diameters of microelectrodes range 0.2-5 x 10^4 µm which results in extremely small detection cell volumes without loss of detection sensitivity [15]. So, EC detection together with capillary-and standard-based separation systems offers [12] better separation efficiencies, less solvent consumption, greater mass sensitivity, higher mass transfer to the electrode, low cell resistance, and increased ability to respond to changes in applied potential [59-61]. Howell *et al.* [62] showed the benefits of utilising disk shaped 7 x 10^3 µm Au and Pt micro-voltammetric electrodes in a high resistance solution without any instrumental correction procedures to correct ohmic potential (iR) effects. Additionally, Chen *et al. [63]* employed pulsed potential at a Pt microelectrode to determine glucose, potassium ferrocyanide and various catechols in biological environments. Afterwards, initial reports of carbohydrate detection utilising an Au microelectrode in CE-PAD systems were published [64-66]. CE-IPAD utilising an Au microelectrode was first introduced by Holland *et al.* [67] and LaCourse *et al.* [68] for the determination of sulfur-containing compounds and amines. Since then, several reviews have been published about the applications and advances of PAD utilising microelectrodes combined with aqueous media based separation systems [15, 69, 70].

5.3 Disposable screen-printed electrode

In flow-through EC cells, a cheap microfabrication technique is realised by printing the working electrode onto a polymeric substance, which allows the routine use of disposable working electrodes [12]. Cheng *et al.* [71] initially described stable detection for at least one week using a disposable Au microelectrode with PAD and IPAD waveforms. Detected analytes included carbohydrates, amines and sulfur-containing compounds. Liang *et al. [72]* made a comparison between disposable and conventional Ag working electrodes for the determination of iodide using PAD waveforms. According to the report, disposable electrodes provided better results in terms of equilibration, detection limit, reproducibility, and calibration linearity. Cheng *et al*. [73] showed similar investigation results for the analysis of alcohols, aldehydes, cyanides, sulphides, sulphites, sulfoxides and ketones.

6. Applications of PAD in flow-based analytical systems

Since 1997, PAD applications have progressed due to advancements in electrode technology and potential waveforms. The applications percentage of PAD in flow-based systems from 1997 to 2018 are illustrated in Fig. 5 and Table 1. The significant applications of PAD include the determination of carbohydrates, alditols, EPA priority pollutants, amino acids, aminoglycosides, antibiotics, and biogenic amines. The remaining applications such as determination of sulfur-containing compounds, aliphatic carboxylates, nonsteroidal anti-inflammatory drugs etc.

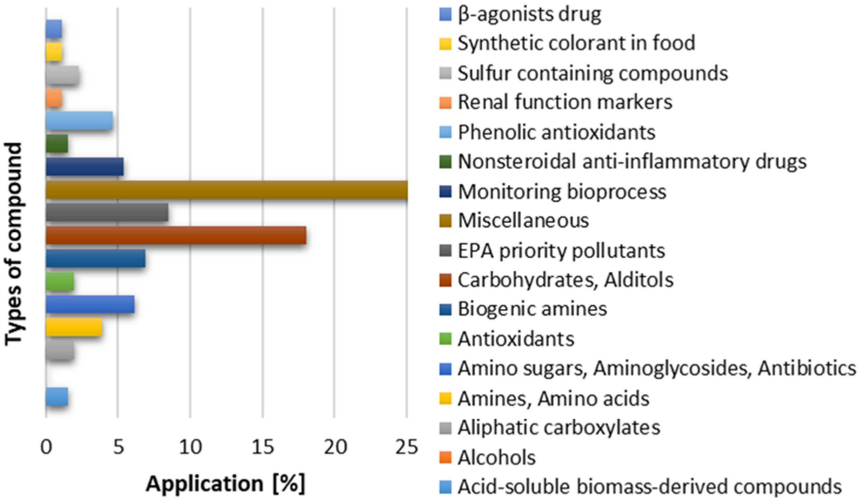


Fig. 5. Applications of PAD in flow-based systems such as CE, FIA, and LC (1997-2018).

Table 1. Selected applications of PAD in flow-based systems (1997-2018).

Year	Application	Sample matrix	Solvent; pH	Instrument	Detector	WE, RE, AE	Mode	LOD [ɥg L^{-1}]	Ref.
Amines/amino acids									
2001	Bialaphos	Urine, serum	NaOH, Na_2CO_3	HPAEC	TL-FC	Au, Ag/AgCl, Ti	IPAD	51	[74]
2001	Glufosinate	Urine, serum	NaOH, Na_2CO_3	HPAEC	TL-FC	Au, Ag/AgCl, Ti	IPAD	18	[74]
2001	Glyphosate	Urine, serum	NaOH, Na_2CO_3	HPAEC	TL-FC	Au, Ag/AgCl, Ti	IPAD	65	[74]
2002	Amino acids	Food	Water, NaOH, Na Ac; 7	HPAEC	TL-FC	Au, pH electrode	IPAD	-	[75]
2003	Amino acids	Plant litter, soil	MSA or HCl	HPAEC	TL-FC	Au, Ag/AgCl, Ti	IPAD	-	[76]
2004	Taurine	Milk	NaOH	HPAEC	TL-FC	Au, Ag/AgCl, Ti	IPAD	62	[77]
2007	4-hydroxyproline	Gelatine	NaOH; 8	HPAEC	TL-FC	Au, pH-Ag/AgCl	IPAD	10	[78]
2007	Proline	Gelatine	NaOH, Ba AC	HPAEC	TL-FC	Au, pH-Ag/AgCl	IPAD	10	[78]
2009	Amino acids	Commercial	NaOH	HPAEC	-	Au, Ag/AgCl, Pt	In. PAD	0.2-3	[24]
2009	Proteins	Commercial	NaOH	HPAEC	-	Au, Ag/AgCl, Pt	In. PAD	0.2-3	[24]
Biogenic amines									
2003	Biogenic amines	Milk	NaOH, Citrate buffer; 3.5	CE	TL-FC	Au, Ag/AgCl, Ti	PAD	20-400	[79]
2005	Histamine	Commercial	$NaClO_4$, $HClO_4$, H_2O	HPLC	-	Au-GC, Ag/AgCl, -	PAD	67	[80]
2006	Cysteine	Commercial	Na phosphate, NaOH; 10	FIA	-	Au, Ag/AgCl, Pt	PAD	60.5	[81]

2007	Agmatine	Alcoholic beverages	MSA, NaOH	CEC	-	Au, pH-Ag/AgCl, Ti	IPAD	17	[82]
2007	Biogenic amines	Meat products	MSA; 12.7	CEC	TL-FC	Au, pH-Ag/AgCl, Ti	IPAD	700-2000	[83]
2007	Cadaverine	Alcoholic beverages	MSA, NaOH	CEC	-	Au, pH-Ag/AgCl, Ti	IPAD	69	[82]
2007	Dopamine	Alcoholic beverages	MSA, NaOH	CEC	-	Au, pH-Ag/AgCl, Ti	IPAD	21	[82]
2007	Histamine	Alcoholic beverages	MSA, NaOH	CEC	-	Au, pH-Ag/AgCl, Ti	IPAD	28	[82]
2007	Phenylethylamine	Alcoholic beverages	MSA, NaOH	CEC	-	Au, pH-Ag/AgCl, Ti	IPAD	39	[82]
2007	Putrescine	Alcoholic beverages	MSA, NaOH	CEC	-	Au, pH-Ag/AgCl, Ti	IPAD	39	[82]
2007	Spermidine	Alcoholic beverages	MSA, NaOH	CEC	-	Au,pH-Ag/AgCl, Ti	IPAD	62	[82]
2007	Spermine	Alcoholic beverages	MSA, NaOH	CEC	-	Au, pH-Ag/AgCl, Ti	IPAD	36	[82]
2007	Tyramine	Alcoholic beverages	MSA, NaOH	CEC	-	Au, pH-Ag/AgCl, Ti	IPAD	73	[82]
2014	Dopamine	Commercial	KCl	-	-	rGO-GC, Ag/AgCl, Pt	PAD	107.2	[84]
2014	Dopamine	Commercial	PPB; 7	-	-	Au/rGO/GC, SCE, Pt	PAD	214.4	[84]
2018	Cysteamine	River water, serum	H_2SO_4	FIA	-	BDD, Ag/AgCl, Pt	MPAD	0.77	[85]
2018	Dopamine	Commercial	$HClO_4$, CH_3COONa	RP-HPLC	TL-FC	-	IPAD	2×10^{-5}	[86]
2018	Dopamine	River water, serum	H_2SO_4	FIA	-	BDD, Ag/AgCl, Pt	MPAD	1.5	[85]
Amino sugars/aminoglycosides/antibiotics									
1997	Kanamycin sulphate	Commercial	SOSP, SS, THF, PPB; 3	HPAEC	-	Au, Ag/AgCl, SS	PAD	150-200	[87]

1998	Netilmicin sulfate	Commercial	SOSP, SS, THF, PPB; 3	HPAEC	-	Au, Ag/AgCl, SS	PAD	200-300	[88]
2000	Galactosamine	Seawater	BA, NaOH	HPAEC	TL-FC	Au, pH-Ag/AgCl	PAD	-	[89]
2000	Glucosamine	Seawater	BA, NaOH	HPAEC	TL-FC	Au, pH-Ag/AgCl	PAD	0.18	[89]
2000	Mannosamine	Seawater	BA, NaOH	HPAEC	TL-FC	Au, pH-Ag/AgCl	PAD	0.72	[89]
2000	Tobramycin	Commercial	SOSP, SS, THF, PPB; 3	HPAEC	-	Au, Ag/AgCl, SS	PAD	80-200	[90]
2002	Lincomycin	Commercial	SOSP, SS, THF, PPB; 3	RP-LC	-	Au, Ag/AgCl, SS	PAD	35-175	[91]
2002	Spectinomycin	Commercial	PFPA, PDHP, THF; 6.25	RP-LC	TL-FC	Au, Ag/AgCl, SS	PAD	50	[92]
2003	Tetracycline	Pharmaceutical tablets	PDHP, PPA, NaOH; 2-10	FIA	TL-FC	Pt, Ag/AgCl, SS	PAD	0.01	[93]
2006	Etimicin sulfate	Commercial	OA, HFBA, ACN; 3.4	LC	-	Au, Ag/AgCl, SS	PAD	200	[94]
2006	Neomycin	Commercial	SOSP, SS, THF, PPB; 3	RP-LC	TL-FC	Au, H, C filled PTFE	PAD	-	[95]
2006	Tobramycin	Commercial	KOH	HPAEC	TL-FC	Au, pH, -	PAD	1.87	[96]
2007	Amikacin	Commercial	SOSP, SS, THF, PPB; 3	RP-LC	TL-FC	Au, H, C filled PTFE	PAD	200	[97]
2008	Amikacin	Cerebrospinal fluid	SOSP, SS, THF, PPB; 3	RP-HPLC	-	Au, H, C filled PTFE	PAD	50	[98]
2010	Netilmicin	Commercial	SOSP, SS, THF, PPB; 3	RP-LC	TL-FC	Au, H, C filled PTFE	PAD	130	[99]
2013	Micronomicin	Commercial	ACN, TFA, PFPA, NaOH; 2.6	LC	TL-FC	Au, Ag/AgCl, Ti	PAD, QPAD, SPAD	80	[100]
2015	Gentamicin	Commercial	SOSP, SS, THF, PPB; 3	HPAEC	-	Au, Ag/AgCl, SS	PAD	1000	[12]

Carbohydrates/alditols

382	2000	Galactinol	Olive plant extracts	NaOH	HPAEC	TL-FC	Au, Ag/AgCl, Ti	PAD	-	[101]
383	2000	Myo-inositol	Olive plant extracts	NaOH	HPAEC	TL-FC	Au, Ag/AgCl, Ti	PAD	-	[101]
384	2000	Raffinose	Olive plant extracts	NaOH	HPAEC	TL-FC	Au, Ag/AgCl, Ti	PAD	-	[101]
385	2000	Saccharides	Wastewater	NaOH	HPAEC	TL-FC	Au, -, -	IPAD	-	[102]
386	2004	Alkylglycosides surfactants	Detergent formulation	NaOH	RP-LC	TL-FC	Au, Ag/AgCl, SS	PAD	26	[103]
387	2004	Arylglycosides surfactants	Detergent formulation	NaOH	RP-LC	TL-FC	Au, Ag/AgCl, SS	PAD	13	[103]
388	2004	Glucose	Blood	Borate, NaOH; 9.4	CE	-	Au, Pt, Pt	PAD	0.0002	[104]
389	2004	Lactulose	Milk (Heat treated)	NaOH, $Ba(OAc)_2$	HPAEC	TL-FC	Au, pH-Ag/AgCl	PAD	411	[104]
390	2005	Glucose	Blood	NaOH	HPAEC	TL-FC	Au, Ag/AgCl, Ti	PAD	0.92	[105]
391	2005	Isomaltose	Blood	NaOH	HPAEC	TL-FC	Au, Ag/AgCl, Ti	PAD	12.90	[105]
392	2005	Levoglucsoan	Smoke samples	$Na_2B_4O_7$; 12.30	CE	TL-FC	Au, Ag/AgCl, Pt	IPAD	2707	[106]
393	2005	Maltose	Blood	NaOH	HPAEC	TL-FC	Au, Ag/AgCl, Ti	PAD	10.30	[105]
394	2005	Ribose	Blood	NaOH	HPAEC	TL-FC	Au, Ag/AgCl, Ti	PAD	7.50	[105]
395	2006	Galactosan	Biomass aerosol	NaOH	HPAEC	TL-FC	Au, -, -	IPAD	2	[107]
396	2006	Levoglucsoa	Biomass aerosol	NaOH	HPAEC	TL-FC	Au, -, -	IPAD	2	[107]
397	2006	Mannosan	Biomass aerosol	NaOH	HPAEC	TL-FC	Au, -, -	IPAD	2	[107]
398	2007	Sugar phosphates	Blood	NaOH, Na_2CO_3	HPAEC	-	Au, Ag/AgCl, SS	PAD	10-30	[108]
399	2008	Carbohydrate	Geophytes	NaOH	HPAEC	TL-FC	Au, -, -	PAD	-	[109]

400	2009	Sorbitol	Blood	NaOH	HPAEC	-	Au, Ag/AgCl, SS	PAD	0.003	[110]
401	2010	Galactose	Blood	NaOH, NaOAc, Na_2CO_3	HPAEC	-	Au, Ag/AgCl, SS	PAD	36-72	[111]
402	2014	Lactose, lactulose	Dairy products	KOH	HPAEC	-	-, pH-Ag/AgCl, -	PAD	-	[112]
403	2015	3’-sialyllactose	Commercial	NaOH	HPAEC	-	Au, PH-Ag/AgCl, -	PAD	220	[113]
404	2015	6’-sialyllactosamine	Commercial	NaOH	HPAEC	-	Au, PH-Ag/AgCl, -	PAD	100	[113]
405	2015	6’-sialyllactose	Commercial	NaOH	HPAEC	-	Au, PH-Ag/AgCl, -	PAD	30	[113]
406	2015	β-D-Glucans	Glucose	-	HPAEC	-	-	PAD	-	[114]
407	2016	Sugar	Pet food	ACN, MeOH, EtOH, water	HPAEC	-	Au, AgCl, -	PAD	-	[115]
408	2017	Arabinose	Spirulina platensis	NaOH, Na Ac, water	HPAEC	-	Au, PH-Ag/AgCl, -	PAD	0.02	[116]
409	2017	Arabinose	Astragalus residue	-	HPAEC	TL-FC	Au, Ag, -	IPAD	67	[117]
410	2017	Carbohydrate	Grass samples	NaOH	HPAEC	-	-	PAD	-	[116]
411	2017	Fructose	Spirulina platensis	NaOH, Na Ac, water	HPAEC	-	Au, PH-Ag/AgCl, -	PAD	0.02	[116]
412	2017	Fucose	Spirulina platensis	NaOH, Na Ac, water	HPAEC	-	Au, PH-Ag/AgCl, -	PAD	0.02	[116]
413	2017	Galactose	Spirulina platensis	NaOH, Na Ac, water	HPAEC	-	Au, PH-Ag/AgCl, -	PAD	0.02	[116]
414	2017	Galactose	Astragalus residue	-	HPAEC	TL-FC	Au, Ag, -	IPAD	82	[117]
415	2017	Galacturonic acid	Spirulina platensis	NaOH, Na Ac, water	HPAEC	-	Au, PH-Ag/AgCl, -	PAD	0.01	[116]
416	2017	Glucose	Spirulina platensis	NaOH, Na Ac, water	HPAEC	-	Au, PH-Ag/AgCl, -	PAD	0.02	[116]
417	2017	Glucose	Astragalus residue	-	HPAEC	TL-FC	Au, Ag, -	IPAD	74	[117]

2017	Glucuronic acid	Spirulina platensis	NaOH, Na Ac, water	HPAEC	-	Au, PH-Ag/AgCl, -	PAD	0.01	[116]
2017	Mannitol	Spirulina platensis	NaOH, Na Ac, water	HPAEC	-	Au, PH-Ag/AgCl, -	PAD	0.02	[116]
2017	Mannose	Spirulina platensis	NaOH, Na Ac, water	HPAEC	-	Au, PH-Ag/AgCl, -	PAD	0.021	[116]
2017	Rhamnose	Spirulina platensis	NaOH, Na Ac, water	HPAEC	-	Au, PH-Ag/AgCl, -	PAD	0.02	[116]
2017	Ribose	Spirulina platensis	NaOH, Na Ac, water	HPAEC	-	Au, PH-Ag/AgCl, -	PAD	0.02	[116]
2017	Sucrose	Spirulina platensis	NaOH, Na Ac, water	HPAEC	-	Au, PH-Ag/AgCl, -	PAD	0.02	[116]
2017	Xylose	Spirulina platensis	NaOH, Na Ac, water	HPAEC	-	Au, PH-Ag/AgCl, -	PAD	0.01	[116]
2017	Xylose	Astragalus residue	-	HPAEC	TL-FC	Au, Ag, -	IPAD	91	[117]
2017	Cellobiose	Astragalus residue	-	HPAEC	TL-FC	Au, Ag, -	IPAD	91	[117]
2018	Galactose	Galactooligosaccharides	PBS	HPAEC	-	Au, pH-Ag/AgCl, -	PAD	300	[118]
2018	Glucose	Galactooligosaccharides	PBS	HPAEC	-	Au, pH-Ag/AgCl, -	PAD	300	[118]
2018	Lactose	Galactooligosaccharides	PBS	HPAEC	-	Au, pH-Ag/AgCl, -	PAD	300	[118]
Sulfur containing compounds									
1998	Ampicillin	Milk	ACN, Na Ac	RP-LC	TL-FC	Au, Ag/AgCl, Pt	IPAD	10	[119]
1998	Cephapirin	Milk	ACN, Na Ac	RP-LC	TL-FC	Au, Ag/AgCl, Pt	IPAD	20	[119]
1999	Sulfur contains antibiotics	Pharmaceutical capsule	NaAc, CH_3CN, MeOH; 3.7	HPLC	TL-FC	Au, PH-Ag/AgCl, Ti	IPAD	8	[120]
2001	Cephalosporin	Pharmaceutical tablets	KOH	RP-HPLC	TL-FC	Au, pH, Ti	IPAD	-	[21]

2001	Lincomycin	Pharmaceutical tablets	KOH	RP-HPLC	TL-FC	Au, pH, Ti	IPAD	-	[21]
2005	Thio-based additives	Pharmaceutical	NaOAc buffer, CH_3CN; 4.5	HPLC	TL-FC	Au, Ag/AgCl, Pt	PAD	0.2-1	[121]
Monitoring bioprocess									
1997	Monosaccharide	Wheat starch	NaOH	HPAEC	-	-, Ag/AgCl, -	IPAD	-	[122]
1998	Maltosaccharides	Maize starch	NaOH, Na Ac	HPAEC	TL-FC	Au, -, -	PAD	-	[123]
1998	Monosaccharide	PP in human serum	PBS	HPLC	-	-	PAD	-	[124]
2005	N-linked oligosaccharide	Immunoglobulin G	NaOH, Na Ac, water	HPAEC	-	Au, Ag/AgCl, -	PAD	-	[125]
2005	Oligosaccharide	MA in sea water	NaOH, Na Ac	HPAEC	TL-FC	Au, pH-Ag/AgCl	PAD	-	[125]
2008	Monosaccharide	Natural cyclodextrins	ACN, water	HPLC	-	Au, -, -	PAD	-	[126]
2008	Monosaccharide	Yeast	NaOH	HPAEC	-	-	PAD	-	[127]
2011	Asiaticoside	CA leaf, ointment	-	RP-HPAEC	-	Au, Ag/AgCl, -	PAD	0.05	[128]
2011	Madecassoside	CA leaf, ointment	Ethanol, ACN	RP-HPAEC	-	Au, Ag/AgCl, -	PAD	0.05	[128]
2012	Monosaccharide	Carbohydrates	NaOAc, NaOH	HPAEC	-	Au, -, -	PAD	-	[129]
2015	Hyaluronan oligosaccharide	Commercial	water, NaOH	HPAEC	-	Au, Ag/AgCl, -	PAD	-	[130]
2016	Arabinan oligosaccharide	Commercial	NaOH, Na Ac, water	HPAEC	-	-	PAD	7-25	[131]
2016	Galactan oligosaccharide	Commercial	NaOH, Na Ac, water	HPAEC	-	-	PAD	10-25	[131]
2016	Oligosaccharide	Human milk	NaOH, NaOAc	HPAEC	-	-	PAD	-	[132]

Acid-soluble biomass-derived compounds									
2015	2,6-dimethoxyphenol	Commercial	NaOH, NaOAc	HPAEC	-	Au, AgCl, -	PAD	140	[133]
2015	3,5-dim-4-hyd	Commercial	NaOH, NaOAc	HPAEC	-	Au, AgCl, -	PAD	140	[133]
2015	4-met-oxyben-alc	Commercial	NaOH, NaOAc	HPAEC	TL-FC	Au, AgCl, -	PAD	140	[133]
Antioxidants									
2010	Ascorbic acid	Pharmaceutical tablets	AA, PAB, H_2SO_4; 1.6/4.7	FIA	-	Au/GC, Ag/AgCl, Pt	PAD	19.80	[46]
2014	Ascorbic acid	Commercial	KCl	-	-	rGO-GC, Ag/AgCl, Pt	PAD	123	[84]
2014	Ascorbic acid	Commercial	PPB; 7	-	-	Au/rGO/GC, SCE, Pt	PAD	8.9×10^7	[84]
2018	Sinapic acid, tyrosol	-	Methanol, B-RB	FIA	-	GC, Ag/AgCl, Pt	MPAD	-	[134]
Phenolic antioxidants									
2015	4-Hydroxycumarin	Commercial	SPP, Me, β-CD; 2	HPLC	TL-FC	Au, H, SS	PAD	25	[135]
2015	Caffeic acid	Commercial	SPP, Me, β-CD; 2	HPLC	TL-FC	Au, H, SS	PAD	75	[135]
2015	Catequin	Commercial	SPP, Me, β-CD; 2	HPLC	TL-FC	Au, H, SS	PAD	16	[135]
2015	Chlorogenic acid	Commercial	SPP, Me, β-CD; 2	HPLC	TL-FC	Au, H, SS	PAD	378	[135]
2015	Ferulic acid	Commercial	SPP, Me, β-CD; 2	HPLC	TL-FC	Au, H, SS	PAD	170	[135]
2015	Gallic acid	Commercial	SPP, Me, β-CD; 2	HPLC	TL-FC	Au, H, SS	PAD	29	[135]

2015	Myricetin	Commercial	SPP, Me, β-CD; 2	HPLC	TL-FC	Au, H, SS	PAD	43	[135]
2015	q-coumaric acid	Commercial	SPP, Me, β-CD; 2	HPLC	TL-FC	Au, H, SS	PAD	34	[135]
2015	Quercetin	Commercial	SPP, Me, β-CD; 2	HPLC	TL-FC	Au, H, SS	PAD	35	[135]
2015	Quercitrin	Commercial	SPP, Me, β-CD; 2	HPLC	TL-FC	Au, H, SS	PAD	23	[135]
2015	Resveratrol	Commercial	SPP, Me, β-CD; 2	HPLC	TL-FC	Au, H, SS	PAD	23	[135]
2015	Rutin	Commercial	SPP, Me, β-CD; 2	HPLC	TL-FC	Au, H, SS	PAD	79	[135]
Environmental Protection Agency (EPA) priority pollutants									
2005	Pentachlorophenol	Water	PPB; 12.4	CE	-	Au, Ag, Pt	PAD	225	[136]
2005	Phenol	Water	PPB; 12.4	CE	-	Au, Ag, Pt	PAD	82	[136]
2015	1,5-Di-O-caf-lqu acid	Commercial	AA, ACN; 6	LC	TL-FC	GC, Ag/AgCl, SS	PAD	0.2	[137]
2015	3,4-Di-O-caf-lqu acid	Commercial	AA, ACN; 6	LC	TL-FC	GC, Ag/AgCl, SS	PAD	0.4	[137]
2015	3,5-Di-O-caf-qu acid	Commercial	AA, ACN; 6	LC	TL-FC	GC, Ag/AgCl, SS	PAD	0.2	[137]
2015	3-Hydroxytyrosol	Commercial	AA, ACN; 6	LC	TL-FC	GC, Ag/AgCl, SS	PAD	0.008	[137]
2015	4,5-Di-O-caf-lqu acid	Commercial	AA, ACN; 6	LC	TL-FC	GC, Ag/AgCl, SS	PAD	0.3	[137]
2015	4,6-dinitro-o-cresol	Water	PPB; 12.4	CE	-	Au, Ag, Pt	PAD	130	[136]
2015	Apigetrin	Commercial	AA, ACN; 6	LC	TL-FC	GC, Ag/AgCl, SS	PAD	0.01	[137]
2015	Caffeic acid	Commercial	AA, ACN; 6	LC	TL-FC	GC, Ag/AgCl, SS	PAD	0.014	[137]

2015	Catechol	Commercial	AA, ACN; 6	LC	TL-FC	GC, Ag/AgCl, SS	PAD	0.006	[137]
2015	Chlorogenic acid	Commercial	AA, ACN; 6	LC	TL-FC	GC, Ag/AgCl, SS	PAD	0.03	[137]
2015	Cinaroside	Commercial	AA, ACN; 6	LC	TL-FC	GC, Ag/AgCl, SS	PAD	0.4	[137]
2015	Criptochlorogenic acid	Commercial	AA, ACN; 6	LC	TL-FC	GC, Ag/AgCl, SS	PAD	0.07	[137]
2015	Cynarin	Commercial	AA, ACN; 6	LC	TL-FC	GC, Ag/AgCl, SS	PAD	0.05	[137]
2015	Ferulic acid	Commercial	AA, ACN; 6	LC	TL-FC	GC, Ag/AgCl, SS	PAD	0.013	[137]
2015	Neochlorogenic acid	Commercial	AA, ACN; 6	LC	TL-FC	GC, Ag/AgCl, SS	PAD	0.02	[137]
2015	Oleuropein	Commercial	AA, ACN; 6	LC	TL-FC	GC, Ag/AgCl, SS	PAD	0.016	[137]
2015	p-Coumaric acid	Commercial	AA, ACN; 6	LC	TL-FC	GC, Ag/AgCl, SS	PAD	0.003	[137]
2015	Syringic acid	Commercial	AA, ACN; 6	LC	TL-FC	GC, Ag/AgCl, SS	PAD	0.005	[137]
2015	Tyrosol	Commercial	AA, ACN; 6	LC	TL-FC	GC, Ag/AgCl, SS	PAD	0.004	[137]
2015	Verbascoside	Commercial	AA, ACN; 6	LC	TL-FC	GC, Ag/AgCl, SS	PAD	0.016	[137]
Nonsteroidal anti-inflammatory drugs									
2006	Acetaminophen	Blood	Borate buffer; 11.5	CE	-	Au, Ag, Pt	PAD	0.19	[138]
2006	DCF	Blood	Borate buffer; 11.5	CE	-	Au, Ag, Pt	PAD	0.23	[138]
2006	DFS	Blood	Borate buffer; 11.5	CE	-	Au, Ag, Pt	PAD	0.26	[138]
2006	Salicylic acid	Blood	Borate buffer; 11.5	CE	-	Au, Ag, Pt	PAD	0.23	[138]

Aliphatic carboxylate								
2015	Biotin	Commercial	NaOH	HPAEC	TL-FC	Au, pH-Ag/AgCl, Ti	In. PAD	2-6	[139]
2015	Gabapentin	Commercial	NaOH	HPAEC	TL-FC	Au, pH-Ag/AgCl, Ti	In. PAD	3-8	[139]
2015	Lysin	Commercial	NaOH	HPAEC	TL-FC	Au, pH-Ag/AgCl, Ti	In. PAD	1-2	[139]
2015	Methionine	Commercial	NaOH	HPAEC	TL-FC	Au, pH-Ag/AgCl, Ti	In. PAD	2-4	[139]
2015	Vegabatin	Commercial	NaOH	HPAEC	TL-FC	Au, pH-Ag/AgCl, Ti	In. PAD	1-3	[139]
Renal function markers									
2003	Creatine	Urine	Borate buffer; 9.4	CE	-	Au, Ag/AgCl, Pt	PAD	250	[140]
2003	Creatinine	Urine	Borate buffer; 9.4	CE	-	Au, Ag/AgCl, Pt	PAD	80	[140]
2003	Uric acid	Urine	Borate buffer; 9.4	CE	-	Au, Ag/AgCl, Pt	PAD	270	[140]
Synthetic colorant in food									
2003	Brilliant blue	Food	H_2SO_4	FIA	-	BDD, Ag/AgCl, SS	MPAD	-	[140]
2003	Sunset yellow	Food	H_2SO_4	FIA	-	BDD, Ag/AgCl, SS	MPAD	-	[140]
2003	Tartrazine	Food	H_2SO_4	FIA	-	BDD, Ag/AgCl, SS	MPAD	-	[140]

β-agonists drug									
2006	Clenbuterol	Commercial	-	FIA	-	BBD/Ag/AgCl/Pt	PAD	0.3	[141]
2006	Salbutamol	Commercial	-	FIA	-	BBD/Ag/AgCl/Pt	PAD	0.1	[141]
2006	Terbutaline	Commercial	-	FIA	-	BBD/Ag/AgCl/Pt	PAD	0.5	[141]
Miscellaneous									
2002	Aliphatic organic acid	Food, beverages	$HClO_4$	HPLC	TL-FC	Pt, Ag/AgCl, SS	PAD	0.5-7	[142]
2003	Furosemide	Commercial	ACN, NaH_2PO_4	FIA/HPLC	TL-FC	SCF, Ag/AgCl, Pt	PAD	0.17	[143]
2004	Acrolein	Vegetable oils	$HClO_4$	LC	TL-FC	Pt, Ag/AgCl, SS	PAD	8.41	[144]
2004	Chlortetracycline	Pharmaceutical tablets	PDHP, NaOH; 5-10	FIA	TL-FC	Au, Ag/AgCl, Pt	PAD	1-100	[145]
2004	Doxycycline	Pharmaceutical tablets	PDHP, NaOH; 5-10	FIA	TL-FC	Au, Ag/AgCl, Pt	PAD	1-100	[145]
2004	Formalin	Food	ACN, water	FIA	-	Au, Ag/AgCl, Pt	PAD	0.013	[146]
2004	Thiols	Commercial	Borate, NaOH; 9.4	CE	-	C, Pt , -	PAD	7.5	[104]
2005	Bromide	Infant formula	NaOH	AEC	TL-FC	Ag, Ag/AgCl, Ti	PAD	5	[147]
2005	Cyanide	Infant formula	NaOH	AEC	TL-FC	Ag, Ag/AgCl, Ti	PAD	2	[147]
2005	Iodide	Infant formula	NaOH	AEC	TL-FC	Ag, Ag/AgCl, Ti	PAD	5	[147]
2005	Sulfide	Infant formula	NaOH	AEC	TL-FC	Ag, Ag/AgCl, Ti	PAD	1	[147]
2005	Tetracycline antibiotics	Food	ACN, PPB; 2.50	HPLC	TL-FC	BBD/Ag/AgCl/Pt	PAD	50-100	[148]

2005	Thiocyanate	Infant formula	NaOH	AEC	TL-FC	Ag, Ag/AgCl, Ti	PAD	10	[147]
2006	Acrylamide	Food	H_2SO_4	HPLC	TL-FC	Pt, Ag/AgCl, SS	PAD	1.44	[149]
2006	Acrylic acid	Food	H_2SO_4	HPLC	TL-FC	Pt, Ag/AgCl, SS	PAD	3.24	[149]
2006	Ethyl glucuronide	Urine	AA, ACN	RP-HPLC	-	Au, Ag/AgCl, SS	PAD	30	[150]
2006	Orotic acid	Milk	NaOH, $NaNO_3$	AEC	TL-FC	Au, pH-Ag/AgCl, Ti	APAD	8.0	[151]
2007	Cyanide	Drinking water	NaOH, water	AEC	-	Ag, pH-Ag/AgCl, -	PAD	1.0	[152]
2007	Imipramine	Pharmaceutical tablets	LiCl, IHCl	FIA	-	-, Ag/AgCl, Pt	PAD	280	[153]
2007	Tacrine	Pharmaceutical tablets	LiCl, IHCl	FIA	-	-, Ag/AgCl, Pt	PAD	19.80	[154]
2008	Paracetamol	Pharmaceutical tablets	AA, PAB, H_2SO_4; 1.6/4.7	FIA	-	Au/GC, Ag/AgCl, Pt	MPAD	19.80	[44]
2010	Butalyted hydroxyanisole	Food	Ethanol, KNO_3; 1.50	FIA	-	BDD, Ag/AgCl, -	MPAD	0.03	[155]
2010	Butalyted hydroxytoluene	Food	Ethanol, KNO_3; 1.50	FIA	-	BDD, Ag/AgCl, -	MPAD	0.40	[155]
2011	Caffeine	Pharmaceutical tablets	AA, Acetate buffer; 4.7	FIA	-	BDD, Ag/AgCl, Pt	MPAD	0.87	[31]
2011	Paracetamol	Pharmaceutical tablets	AA, Acetate buffer; 4.7	FIA	-	BDD, Ag/AgCl, Pt	MPAD	0.66	[31]
2012	Astragalin	Plant	ACN, water	RP-HPLC	-	Au, Ag/AgCl, -	PAD	360	[156]
2012	Astragolaside	Plant	ACN, water	RP-HPLC	-	Au, Ag/AgCl, -	PAD	20	[156]
2012	Lisinopril	Human plasma	NaOH	AEC	TL-FC	Au, pH-Ag/AgCl, -	IPAD	0.12	[157]
2014	Iodine	Serum and urine	-	AEC	-	-	PAD	82-145	[158]
2015	2-methylimidazole	Beverages	PPB; 12.4	RP-HPLC	TL-FC	Au, pH, -	IPAD	20	[159]

562	2015	4-methylimidazole	Beverages	PPB; 12.4	RP-HPLC	TL-FC	Au, pH, -	IPAD	15	[159]
563	2015	5-hyd-met-fur	Beverages	PPB; 12.4	RP-HPLC	TL-FC	Au, pH, -	IPAD	100	[159]
564	2015	5-hyd-met-fur	Sugarcane bagasse	AA, acetate buffer; 4.7	HPLC	WJ-FC	Ni-GC, Palladium, Pt	PAD	-	[160]
565	2015	Caffeic acid	Commercial	AA, ACN; 6	-	TL-FC	GC, Ag/AgCl, Pt	PAD	14	[161]
566	2015	Caffeine	Commercial	ACN, PPB; 7	FIA	-	BDD, -, -	MPAD	0.15	[45]
567	2015	Clenbuterol	Commercial	AA, ACN; 6	-	TL-FC	GC, Ag/AgCl, Pt	PAD	0.1	[161]
568	2015	Cyanide	Liquor sample	KOH	IC	-	Ag, pH-Ag/AgCl, Ti	PAD	1	[162]
569	2015	Furanic aldehydes	Sugarcane bagasse	AA, Acetate buffer; 4.7	HPLC	WJ-FC	Ni-GC, Pd, Pt	PAD	3.8 x 10^7	[160]
570	2015	Gluconate	Nuclear waste	ACN, water	HPAEC	-	Au, -, -	PAD	-	[163]
571	2015	Ibuprofen	Commercial	ACN, PPB; 7	FIA	-	BDD, -, -	MPAD	0.16	[45]
572	2015	Myoinositol	Infant formula	NaOH, Na Ac, water	AEC	-	Au, Ag/AgCl, Ti	PAD, QPAD	-	[164]
573	2015	Paracetamol	Commercial	ACN, PPB; 7	FIA	-	BDD, -, -	MPAD	0.163	[45]
574	2016	8-Chlorotheophylline	Commercial	H_2SO_4	BIA	-	BDD, Ag/AgCl, Pt	MPAD	40.7	[165]
575	2016	Diphenhydramine	Commercial	H_2SO_4	BIA	-	BDD, Ag/AgCl, Pt	MPAD	45.96	[165]
576	2016	Etimicin sulfate	Commercial	ACN, TFA, NaOH; 3.5	LC	-	Au, pH-Ag/AgCl, Ti	PAD	81	[166]
577	2016	Prazosin	Pharmaceutical	PPB; 4	FIA	-	BDD, Ag/AgCl, Pt	MPAD	31.77	[167]
578	2016	Pyridoxine	Commercial	H_2SO_4	BIA	-	BDD, Ag/AgCl, Pt	MPAD	91.35	[165]
579	2017	Ami-met-pho acid	Drinking Water	ACN, water, TFA	HPAEC	WJ-FC	Au, Pt, -	IPAD	< 1	[168]

580	2017	Cyanide	Urine / Saliva	NaOH, NaCN	IC	-	-	PAD	0.1-0.5	[169]
581	2017	Glyphosate, AMPA	Drinking Water	ACN, water, TFA	HPAEC	WJ-FC	Au, Pt, -	IPAD	1	[168]
582	2017	Keratan sulfate	SCS	NaOH	HPAEC	-	-	PAD	-	[170]
583	2017	Lactic acid	Sugarcane Vinasse	NaOH, CH_3COONa, water	HPAEC	-	Ni-BDD	PAD	1 x 10^8	[171]
584	2017	Malic acid	Sugarcane Vinasse	NaOH, CH_3COONa, water	HPAEC	-	Ni-BDD	PAD	8.1 x 10^4	[171]
585	2017	N-linked glycans	Glycoproteins	-	HPAEC	-	Au, pH-Ag/AgCl, -	PAD	-	[168]
586	2017	Tartaric acid	Sugarcane Vinasse	NaOH, CH_3COONa, water	HPAEC	-	Ni-BDD	PAD	4.2 x 10^4	[171]
587	2017	Warfarin	Pharmaceutical	PPB; 7	FIA	-	BBD/Ag/AgCl/-	MPAD	154	[172]
588	2015	Tramadol	Pharmaceutical	H_2SO_4	FIA	-	BDD, Ag/AgCl, SS	MPAD	10.5	[173]
589	2015	8-chlorotheophylline	Pharmaceutical	ACN, H_3PO_4	BIA	-	BDD, Ag/AgCl, Pt	MPAD	40	[165]
590	2015	Acetaminophen	Pharmaceutical	H_2SO_4	FIA	-	BDD, Ag/AgCl, SS	MPAD	4.5	[173]
591	2015	Captopril	Pharmaceutical	Acetic acid/acetate buffer	BIA	-	BDD, Ag/AgCl, Pt	MPAD	189	[174]
592	2015	Diphenhydramine	Pharmaceutical	ACN, H_3PO_4	BIA	-	BDD, Ag/AgCl, Pt	MPAD	45	[165]
593	2015	Enalapril	Pharmaceutical	H_2SO_4	FIA	WJ-FC	BDD, Ag/AgCl, SS	MPAD	3.76	[175]
594	2015	Hydrochlorothiazide	Pharmaceutical	H_2SO_4	FIA	WJ-FC	BDD, Ag/AgCl, SS	MPAD	59.5	[175]
595	2015	Hydrochlorothiazide	Pharmaceutical	Acetic acid/acetate buffer	BIA	-	BDD, Ag/AgCl, Pt	MPAD	113	[174]
596	2015	Myo-Inositol	Food	NaOH	HPLC	TL-FC	Au, -, -	PAD	-	[176]
597	2015	Pyridoxine	Pharmaceutical	ACN, H_3PO_4	BIA	-	BDD, Ag/AgCl, Pt	MPAD	91	[165]

598	2016	Sucrose acetates	6-O-acetyl sucrose	ACN, water	HPLC	-	Au, Ag/AgCl, SS	PAD	8.4	[177]
599	2017	Fructooligosaccharides	Onion	Water, NaOH, NaOAc	HPAEC	-	Au, -, -	PAD	-	[178]
600	2017	Isoflavonoids	Astragali Radix	ACN, water	RP-HPLC	-	-	IPAD	-	[179]
601	2017	Triterpene saponins	Astragali Radix	ACN, water	RP-HPLC	-	-	IPAD	-	[179]
602	2018	Chlorine ions	Milk	Na_2SO_4	FIA	-	Au, Ag/AgCl, Pt	PAD	5000	[180]
603	2018	5-HIAA	Commercial	$HClO_4$, CH_3COONa	RP- HPLC	TL-FC	-	IPAD	6 x 10^{-5}	[86]
604	2018	Allura red	Candy	H_2SO4	FIA	TL-, WJ-FC	BDD, Ag/AgCl, SS	MPAD	122	[181]
605	2018	Amfepramone	Dietary supplements	Ammonium acetate	RP-HPLC	-	-	PAD	2720	[182]
606	2018	Andhomovanillic acid	Commercial	$HClO_4$, CH_3COONa	RP-HPLC	TL-FC	-	IPAD	0.0024	[86]
607	2018	Bisacodyl	Dietary supplements	Ammonium acetate	RP-HPLC	-	-	PAD	740	[182]
608	2018	Caffeine	Dietary supplements	Ammonium acetate	RP-HPLC	-	-	PAD	320	[182]
609	2018	Clonazepam	Dietary supplements	Ammonium acetate	RP-HPLC	-	-	PAD	260	[182]
610	2018	Colchicine	Pharmaceutical, urine	-	FIA	-	BDD, Ag/AgCl, Pt	MPAD	8.3, 25	[183]
611	2018	Diazepam	Dietary supplements	Ammonium acetate	RP-HPLC	-	-	PAD	430	[182]
612	2018	DOPAC	Commercial	$HClO_4$, CH_3COONa	RP-HPLC	TL-FC	-	IPAD	2 x 10^{-5}	[86]
613	2018	Fenproporex	Dietary supplements	Ammonium acetate	RP-HPLC	-	-	PAD	40	[182]
614	2018	Fluoxetine	Dietary supplements	Ammonium acetate	RP-HPLC	-	-	PAD	310	[182]
615	2018	Furosemide	Dietary supplements	Ammonium acetate	RP-HPLC	-	-	PAD	120	[182]

2018	Indigo carmine	Candy	H_2SO_4	FIA	TL-, WJ-FC	BDD, Ag/AgCl, SS	MPAD	700	[181]
2018	Lorazepam	Dietary supplements	Ammonium acetate	RP-HPLC	-	-	PAD	120	[182]
2018	Midazolam	Dietary supplements	Ammonium acetate	RP-HPLC	-	-	PAD	150	[182]
2018	Oxcarbazepine	Pharmaceutical	Acetate buffer	FIA	WJ-FC	BDD, Ag/AgCl, Pt	MPAD	4.2-10.3	[184]
2018	Serotonin (5-HT)	Commercial	$HClO_4$, CH_3COONa	RP-HPLC	TL-FC	-	IPAD	5×10^{-5}	[86]
2018	Sertraline	Dietary supplements	Ammonium acetate	RP-HPLC	-	-	PAD	920	[182]
2018	Sildenafil	Dietary supplements	Ammonium acetate	RP-HPLC	-	-	PAD	1600	[182]
2018	Tadalafil	Dietary supplements	Ammonium acetate	RP-HPLC	-	-	PAD	230	[182]
2018	Verapamil	Pharmaceutics, urine	H_2SO_4	FIA	-	BDD, Ag/AgCl, Pt	MPAD	7.2	[185]
2018	Yohimbine	Dietary supplements	Ammonium acetate	RP-HPLC	-	-	PAD	70	[182]

Application: Di-O-caf-lqu acid: Di-O-caffeoylquinic acid; 3,5-dim-4-hyd: 3,5-dimethoxy-4-hydroxybenzaldehyde; 4-met-oxyben-alc: 4-methoxybenzylalcohol; 5-hyd-met-fur: 5-hydroxymethylfurfural; Ami-met-pho acid: Aminomethylphosphonic acid; C filled PTFE: carbon filled polytetrafluoroethylene; CA: Centella asiatica; DCF: Diclofenac (sodium o-2,6-dichloroanilino-phenyl acetate); DFS: Diflunisal (5-(2,4 difluorophenyl) salicylic acid); FA: Furanic aldehydes; MA: Mannuronan alginate.

Sample matrix: SCS: Sodium Chondroitin sulfate

Solvent: AA: Acetic acid; ACN: Acetonitrile; BaAc: Barium acetate, CH_3COONa: Sodium acetate trihydrate; EtOH: Ethanol; $HClO_4$: Perchloric acid HFBA: Heptafluorobutyric acid; IHCl: Imipramine hydrochloride; MeOH: Methanol; MSA: Methanesulfonic acid; Na Ac: Sodium Acetate; Na phosphate: Sodium phosphate; OA: Oxalic acid; B-RB: Britton-Robinson buffer; PAB: Potassium acetate buffer; PBS: Phosphate-buffered saline; PDHP: Potassium dihydrogen phosphate; PDHP: Potassium dihydrogen phosphate; PFPA: Pentafluoropropionic acid; PPA: Phosphoric acid; PPB: Phosphate buffer.

SOSP: Sodium-1-octanesulphonate; SPP: Sodium phosphate; SS: Sodium sulphate; TFA: Trifluoroacetic acid; THF: Tetrahydrofuran; β-CD: β-cyclodextrin.

Instrument: BIA: Batch injection analysis; HPAEC: High performance anion exchange chromatography; HPCEC: High performance cation exchange chromatography; RP-LC: Reversed phase liquid chromatography.

Electrode: WE: Working electrode; RE: Reference electrode; AE: Auxiliary electrode; BBD: Boron-doped diamond; GC: Glassy carbon; rGO: reduced graphene oxide; H: Hydrogen; PP: Pichia pastoris; PP: Polyphenol; SCE: Standard calomel electrode; SCF: Single carbon fibre; SS: Stainless steel.

EC mode: In. PAD: Indirect PAD; IPAD: Integrated PAD; MPAD: Multiple PAD; QPAD: Quadrupole PAD; SPAD: Six-potential PAD.

7. Future directions

3D printed flow cells with integrated versatile and exchangeable electrodes can be made commercially available for EC detection [186]. The strength of 3D printing designs is the ease of creation and the flexibility of the design. These devices consist of removable and reusable polymer-based body parts and fittings and allow the various electrode materials (such as carbon, gold, platinum, and silver) to be easily added to a threaded receiving port printed on the device. The technology spans a wide range of applications such as NO detection, neurotransmitter detection, and measuring oxygen tension in a stream of red blood cells [186]. Erkal *et al.* [186] utilised 3D printed microfluidic EC detectors for an AD of dopamine and nitrite in FIA platform. However, we haven't yet observed the applications of 3D printing in PAD techniques. Additionally, use of NMs such as zirconium dioxide nanoparticles was reported to facilitate simple modification of electrodes, increased electroactive surface areas, good electrical conductivity, and better EC response for the determination of propranolol [187]. Therefore, we envisage that in near future the rapid evolution of 3D printed EC detectors and the incorporation of NMs in EC detection will speed the development of enhanced EC detection including PAD in flow-based systems. We also envisage that in near future multi-modal EC detection (including a combination of PAD with PPD [188], PAD with AD [18] as well as a combination of various PAD cycles discussed in section 3) can gain attention to address detection of analytes that cannot be detected in one particular EC detection mode.

8. Conclusions

Over the last three decades, PAD has served as an electroanalytical detection technique for the determination of various organic aliphatic compounds using CE, FIA, and LC separation methods. Some unique advances of PAD techniques such as pulsed potential cleaning, low-cost instrumentation, minimal reagent usage, high sensitivity and high selectivity have expanded the range of applications of PAD in the field of analytical chemistry. Disposable microelectrodes have opened new horizons for the field of PAD, providing equal or better detection limits, and higher reproducibility and calibration linearity than with non-disposable electrodes. Additionally, the application of NMs-based EC detection has been reported to exhibit greater conductivity, improved catalytic effects during EC reactions, enhancement of faster electron transfer between electrode surfaces, and the ability to perform as reactants in EC analysis. The growing interest in utilising metal nanomaterial properties, 3D printing, and multi-modal detection in EC technology over the last two decades is gradually leading towards establishing advanced pulsed EC detection of wide range of analytes in biological, and complex sample matrices especially electro-inactive aliphatic organic compounds such as formic acid, acetic acid, maleic acid and β-cyclodextrin complexes.

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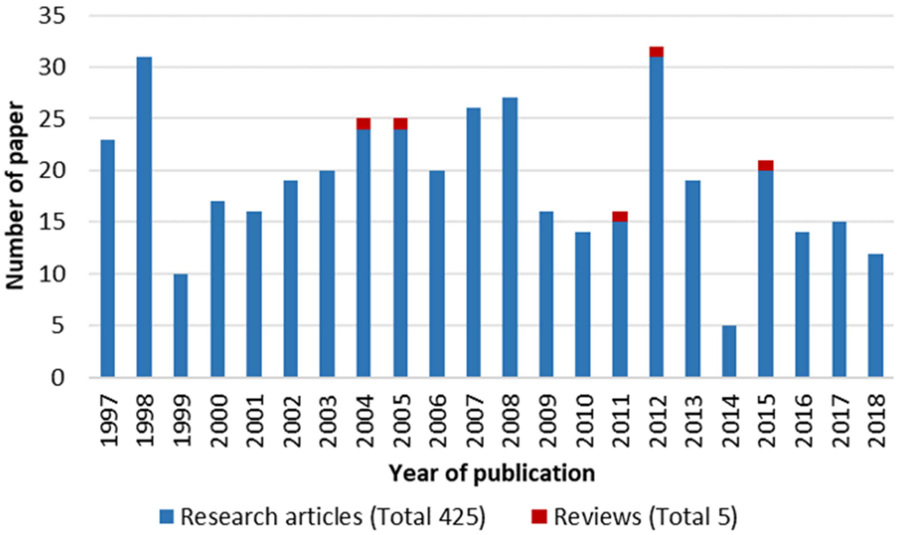
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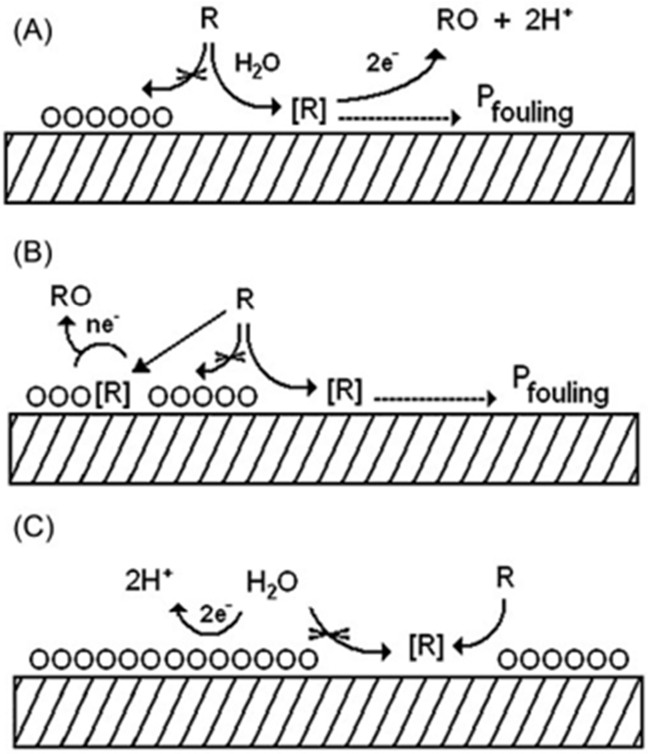
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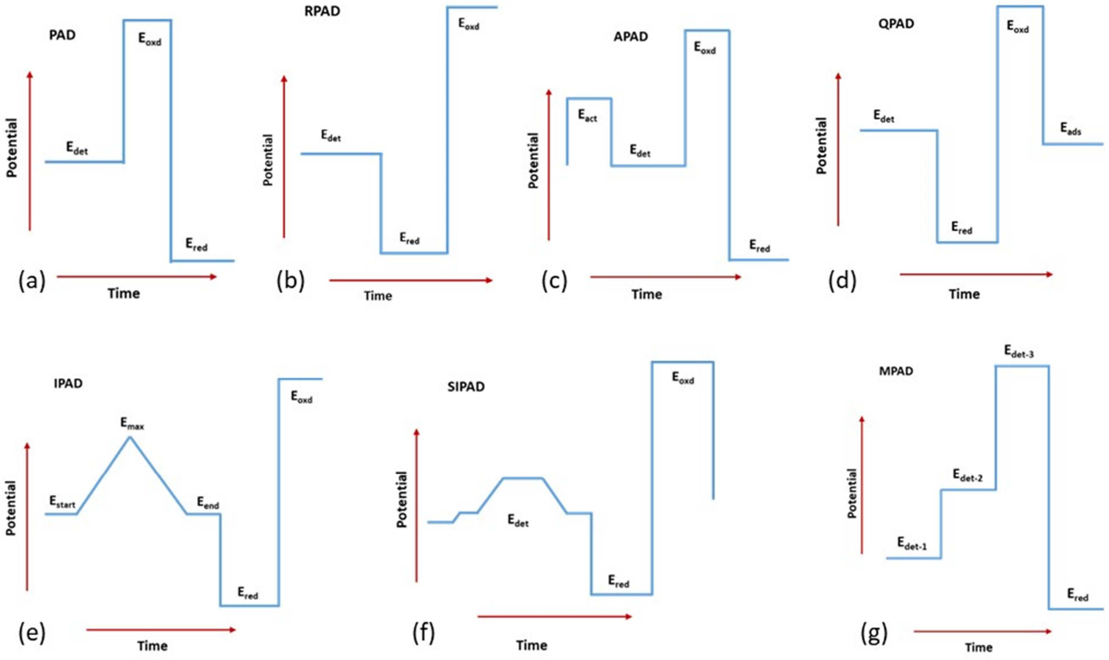
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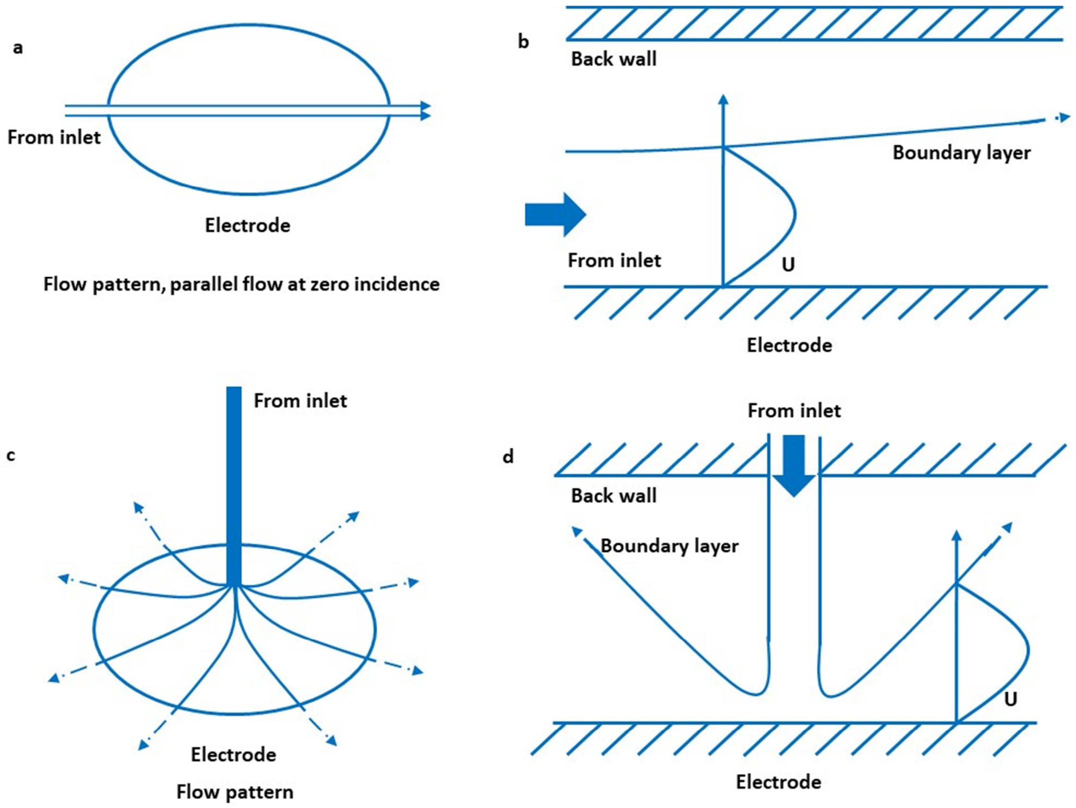
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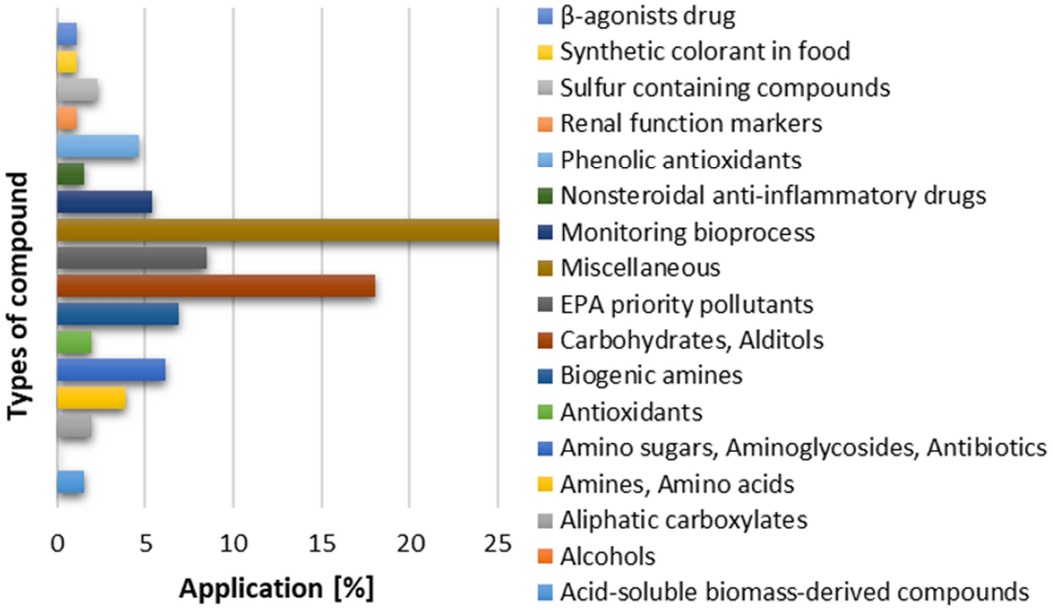
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Biogenic amines
Antioxidants
Amino sugars, Aminoglycosides, Antibiotics
Amines, Amino acids
Aliphatic carboxylates
Alcohols
Acid-soluble biomass-derived compounds

Prospects of pulsed amperometric detection in flow-based analytical systems - A Review

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Highlights

- The fundamentals and waveform designs of pulsed amperometric detection (PAD).
- Electrochemical (EC) detector designs are commonly used for PAD.
- The technological advancement of PAD and its selected applications since 1997-2018.
- Future directions of PAD such as 3D printed EC detector, nanomaterials, multi-modal EC detection.

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