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TOPICAL REVIEW

Review on the development of truly portable and *in-situ* capillary electrophoresis systems

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Abstract
Capillary electrophoresis (CE) is a technique which uses an electric field to separate a mixed sample into its constituents. Portable CE systems enable this powerful analysis technique to be used in the field. Many of the challenges for portable systems are similar to those of autonomous *in-situ* analysis and therefore portable systems may be considered a stepping stone towards autonomous *in-situ* analysis. CE is widely used for biological and chemical analysis and example applications include: water quality analysis; drug development and quality control; proteomics and DNA analysis; counter-terrorism (explosive material identification) and corrosion monitoring. The technique is often limited to laboratory use, since it requires large electric fields, sensitive detection systems and fluidic control systems. All of these place restrictions in terms of: size, weight, cost, choice of operating solutions, choice of fabrication materials, electrical power and lifetime. In this review we bring together and critique the work by researchers addressing these issues. We emphasize the importance of a holistic approach for portable and *in-situ* CE systems and discuss all the aspects of the design. We identify gaps in the literature which require attention for the realization of both truly portable and *in-situ* CE systems.

Keywords: capillary electrophoresis, portable, *in-situ*, microfluidics, lab-on-a-chip, point-of-care, environmental monitoring/analysis, micro-total analysis systems, portable high voltage power supplies, sample injection schemes

(Some figures may appear in colour only in the online journal)

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1. Introduction

The aim of this paper is to critically review work from a worldwide range of research groups in the field of miniaturized capillary electrophoresis (CE) systems. This review discusses research with a view towards truly portable and *in-situ* CE systems. Here, we define truly portable as applying to all components of the system which therefore encompasses portable power supplies, miniaturized CE device, portable detection system and microfluidic control. The full aspects of truly portable systems are in line with many of the descriptions for the micro-total-analysis-system specified in 1990 by Manz and Harrison [1–3]. There are four main aspects which are discussed: the fabrication of microfluidic devices, including material choices and manufacturing methods; the detection system; ancillary hardware such as high voltage power supplies (HVPS) and pumps; and control software. These are each addressed individually and used as a basis for critiquing advances in truly portable/*in-situ* CE systems. Although there have been review papers on chip and non-chip CE systems [4, 5], the focus of this review paper is on the routes to truly portable devices rather than just miniaturized systems. Given the range of the design aspects listed above, it is clear that a holistic approach is critical to ensure a successful outcome. Often in the literature the individual aspects have been explored in-depth. In this review, we take the salient points of that research and describe how they can be applied to aid the development of truly portable and *in-situ* CE systems.

Electrophoresis describes the separation of charged species in a fluid when subjected to an electric field. This separation arises due to differences in the mobilities of individual species which in turn results in differences in the species velocity and therefore the distance travelled within a fixed time frame. A brief description of the theoretical operation of CE separations is given later. The surface properties of the capillary or mechanically formed channel that host the fluid are very important in CE due to their effect on a secondary fluid flow phenomenon, termed electroosmotic flow (EOF). CE is a widely used technique, applications of which include analysis of DNA [6, 7], environmental and water quality [8], metal ion detection [9], food and drink [10–12] and corrosion [13, 14].

In the literature two main reasons for miniaturization of CE become apparent: firstly for improving the portability of CE analysis; and secondly for point-of-care, and lab-on-a-chip devices. The aims of both are to increase the availability and usability of CE analysis. The focus here will remain on miniaturized CE devices where a holistic approach was implemented at achieving true portability and *in-situ* analysis. Where appropriate, the challenges pertaining to the portability of CE which have been overcome in the literature, even where the primary focus is not portability, will of course be included. With an increasing demand to perform detailed analysis out in the field, it is no surprise that there have been a large number of attempts at incorporating separation technologies into portable instruments. There have been two primary routes towards the development of portable CE systems: utilizing a shortened capillary or through the use of chip-based micro-manufacturing solutions [5, 6, 11, 15–21]. The majority of the reported work relates to field-portable or point-of-care devices. Research into the development of autonomous *in-situ* CE systems has received less attention.

There is a distinction between miniaturizing CE systems and the development of portable CE systems. Whilst there is overlap, the unique requirements of portability necessitate stringent and careful system design. This paper is focussed on portable CE systems but routes to general miniaturization are discussed where appropriate. Further to this we discuss approaches for *in-situ* CE systems which place even tighter requirements on the design.

Numerous authors have reported on the large number of advantages which can be gained from the miniaturization of fluidic systems [22]. The use of microfluidic systems for sensing and analysis in various environments is becoming increasingly popular. Commonly quoted advantages for these miniaturized systems are as follows:

- portability/towards *in-situ* monitoring,
- reduced cost,
- disposability,
- reduction in required sample volume,
- faster analysis times,
- ability to generate large electric fields more simply.

2. Background to CE

2.1. Development of CE

In order to monitor and understand various environments it is often necessary to take a sample from the environment for analysis. This sample is commonly a mixture of numerous components and this makes it difficult to perform in-depth analysis of the sample as a whole. Depending on how well controlled the environment under test is, one method for analysis is using an array of sensors where the sensors are tailored to detect the individual components (such as an array of different ion selective electrodes). Whilst this approach has many advantages, the bespoke nature of these systems tends to limit their use to specific applications. A second approach, which is the subject of this review paper, is to use CE to separate the sample into its individual components which can then be analysed individually in isolation. Depending on the methodology and mode of operation used, it may be possible for the sample to be analysed in a single run using a detector to identify both positively and negatively charged species in the sample. An example of this analysis is capillary zone electrophoresis, whereby both anionic and cationic species in the sample are separated due to differences in their electrophoretic mobility.

In 1937 Arne Wilhelm Kaurin Tiselius developed moving boundary electrophoresis and was awarded the Nobel Prize for Chemistry in 1948 for his efforts in advancing useful scientific methods in biochemistry [25]. Under the supervision of Tiselius, Stellan Hjertén of Uppsala University (Sweden) received his PhD in 1967, with the development of the first fully autonomous CE instrument. In 1981 James Jorgenson of the University of North Carolina developed the first modern

Figure 1. Left: Stellan Hjertén next to the first fully automatic CE instrument, 1967 (reproduced from [23], with permission of The Royal Society of Chemistry). Middle: Typical modern commercial CE system: PrinCE-C 700 series instrument developed by Prince Technologies. Right: Commercial portable CE system (CE-P2) developed by CE Resources Pte Ltd (reproduced with permission from [24]).

CE instruments utilizing 75 μm inner diameter capillaries [26]. Over the last few decades the focus of CE research has spread over numerous areas, such as buffer solution optimization, capillary fabrication/material development and various modifications to the methods/modes of operation. Since the first fully automated CE instrument there have been significant advances in making the system smaller, as highlighted in figure 1.

2.2. Overview of theoretical operation of CE

When an electric field is established along a channel, an ionic species will migrate through the channel at a velocity dependent on its electrophoretic mobility and the electric-field strength. Typical electric-field strengths range from 50 to 250 V cm^{-1}, though values as large as 53 kV cm^{-1} have been reported; in this case the authors reported sub-millisecond separation [27]. As the injected sample travels along the channel, the different ionic components migrate at different velocities by virtue of their different mobilities and in doing so will pass a detector positioned near the channel end at different times. Identification of the ionic species is commonly achieved by measuring the migration times. Quantification of the individual sample components depends on the detection method. Common methods are laser-induced fluorescence (LIF), UV detection and more recently electrochemical detection, which includes potentiometry, conductometry and amperometry.

The simplest form of CE is also known as capillary zone electrophoresis or free-solution capillary electrophoresis. It can be made to separate both anions and cations in the same run, but it cannot separate out uncharged species, though there are variations of CE discussed later which are able to do so.

2.3. Electroosmotic flow

Electroosmotic flow (also termed electroendosmotic flow) describes the movement of the support fluid (commonly referred to as the buffer solution) when subjected to an electric field. It occurs due to the presence of surface charge along the channel walls and their interaction with the buffer solution.

For a fused-silica capillary (common with laboratory-based CE instruments), the surface silanol (Si–OH) groups become ionized to negatively charged silanoate (Si–O$^-$) groups which in turn are catalyzed by the OH$^-$ ions in the solution [28]. A method of enhancing this ionization process in fused-silica capillaries is to flush a basic/alkali solution such as KOH or NaOH through the channel [29]. Cations present in the buffer solution are then attracted to the negatively charged surface and form an inner layer (the fixed or Stern layer). The density of cations at the inner layer will not be large enough to neutralize all the negative charges on the capillary surface and so an outer layer of cations is formed (the mobile layer) that extends into the bulk solution and away from the capillary walls. The result is a double diffuse layer formed by the two layers of cations. The potential between these two layers is referred to as the zeta potential.

The EOF velocity depends on the electric-field strength and the zeta potential which is related to the charge density of the channel wall [30]. Changing the pH alters the charge density and therefore affects the EOF rate, the limit being when the ionic groups along the wall of the channel become fully ionized.

Compared with Poiseuille (pressure-driven) flow, EOF has a flat flow profile which causes less variation in velocity across the channel cross-section. The flat flow profile exhibited by EOF is beneficial for separation systems, since a variable velocity across the channel cross-section contributes to band-broadening (sample dispersion). Band-broadening occurs when the sample travels at different speeds depending on its position from the channel wall. To minimize band-broadening, pressure differences during separation should be minimized.

2.4. Variations on modes of operation for CE

There are a variety of methods for applying CE. Each method has its advantages and disadvantages specific to the range of applicable uses. The majority of the literature focuses on miniaturization of standard CE rather than its variants.

2.4.1. Capillary gel electrophoresis. Developed before CE, capillary gel electrophoresis (CGE) is widely used in biology and biochemistry laboratories. Instead of using a liquid buffer

solution, a gel is used which unlike CE, does not necessarily require a capillary; a slab of gel being sufficient. When a capillary is used it is referred to as CGE. Commonly polyacrylamide or agarose gels are used. The gel contains pores which allow analytes to pass at a rate dependent on their size. Smaller molecules pass through more easily than larger molecules, and therefore arrive at the capillary end first. The gel used in CGE systems suppresses the heating induced by the electric field and strongly retards the movement of analytes. To prevent or reduce the gel from eluting the capillary, the capillary walls are usually treated to eliminate EOF. CGE separates out samples based on the molecule size and therefore is not suitable for use where there is no variation in the size-to-charge ratio of the analytes [29].

A miniaturized gel electrophoresis system was demonstrated by Demianova *et al* [31]. Fabricated from poly (methyl methacrylate) (PMMA), the chip measured ~30 mm × 25 mm × 10.4 mm. It is beyond the scope of this review to investigate all the variations of gel electrophoresis but a common feature they share are long analysis times. For example, in the case of pulsed field gel electrophoresis, Li *et al* [32] stated that typical analysis times could take 10–15 h. In their work, Li *et al* managed to reduce the analysis time for one run by using a miniaturized gel slab apparatus to 60–90 min.

2.4.2. Capillary isoelectric focussing. This method separates amphoteric solutes based on differences in their isoelectric points (pI). The capillary is filled with a solution containing ampholytes and the sample (usually proteins). An amphoteric solution behaves differently depending on the pH and the pI of an ampholyte is defined as that pH at which the ampholyte charge is neutral. A pH gradient is set up along the channel and the solutes migrate to a zone where their net charge is zero. There are a variety of methods to set up a pH gradient, one of which is to use a tapered channel, which will have an electric field which changes magnitude along the length of the channel. The variable electric-field strength along the channel length will cause a progressive amount of Joule heating and therefore a temperature gradient. This temperature gradient can have a direct effect on the pH of some electrolytes. For example, the acid dissociation constant (pK_a) and therefore the pH of a tris-based buffer is temperature sensitive. Different proteins have different pIs and so move into different zones. Once all the solutes have moved to their zones, the zones are moved en masse past a detector.

Raisi *et al* [33] discuss their system which consisted of a 60 mm long channel; analysis of peptides was achieved in 5 min. Capillary isoelectric focussing (CIEF) is useful for the study of protein–protein interactions. Tan *et al* [34] describe their work on a miniaturized CIEF system for this purpose. A more in-depth review of work on miniaturized CIEF systems has been presented by Dolnik *et al* [35].

2.4.3. Micellar electrokinetic capillary chromatography. Micellar electrokinetic capillary chromatography (MEKC) combines electrophoretic separation and EOF with a chromatographic separation mechanism for separating solutes within a sample. MEKC is able to separate electrically neutral molecules. In MEKC the buffer solution is modified by adding surfactants which form micelles. Separation occurs due to differences in the hydrophobicity of the sample-micelles. The components of the buffer solutions and sample have different hydrophobicities and therefore present different solubilities to the miscelles; very hydrophobic molecules are highly soluble to the micelles and therefore spend most of their time travelling along the capillary within the micelles. Less soluble molecules spend less time in the micelle and so their progress along the capillary is less hindered. Since the non-soluble molecules do not enter the micelle they emerge from the capillary first at the rate of EOF as illustrated in figure 2.

Pumera [36] compared microchip MEKC against conventional CE for the analysis of a wide variety of explosive compounds. For example, microchip MEKC was used for the successful separation of neutral nitroaromatic explosives in a portable analysis system for counter terrorism measures. Wakida *et al* [37] discussed their work towards a portable analyser for performing MEKC analysis of phenolic chemicals which are of interest in many environmental monitoring applications.

2.4.4. Capillary (electro)-chromatography. This is a combination of high-performance liquid chromatography and CE where EOF is used instead of a hydraulic pump to move the mobile phase through the capillary [38, 39]. Strictly, capillary (electro)-chromatography (CEC) is not a variation on CE but a variation on chromatography since the separation of analytes is not based on differences in the electrophoretic mobility. It is discussed here because it bears significant similarities and challenges. Unlike CE systems, CEC is able to separate out neutral solutes. Szekely *et al* [40] discussed the difficulty of maintaining a stable EOF, in their miniaturized CEC system due to pH changes; a consequence of electrolysis in the small buffer reservoirs inherent in many microfluidic systems. They measured moderate changes in the pH of buffered solutions following the application of a high voltage to the reservoirs. Further to this the authors noted that as system dimensions decrease the application of high pressures becomes more difficult thus making the EOF a more attractive option. Ladner *et al* discuss the production of monoliths in cyclic olefin copolymer (COC) microchips for portable CEC analysis [41].

2.4.5. Isotachophoresis. In isotachophoresis (ITP), instead of having just a single buffer solution to support the separation, there is a leading electrolyte and a terminating electrolyte enclosing the sample solution, where the leading electrolyte has the highest mobility and the terminating electrolyte has the lowest. The constituents of the sample are restricted to those that have values of mobility that lie within the range defined by the leading and terminating electrolytes. By introducing the sample between the two electrolytes and applying a potential across the channel, an electric field is established with a lower strength over those components with the higher mobilities. Equation (1) shows the separation velocity, u_{sep}, which is the velocity at which the sample plug travels:

$$u_{sep} = \mu_L E_L = \mu_S E_S = \mu_T E_T, \quad (1)$$

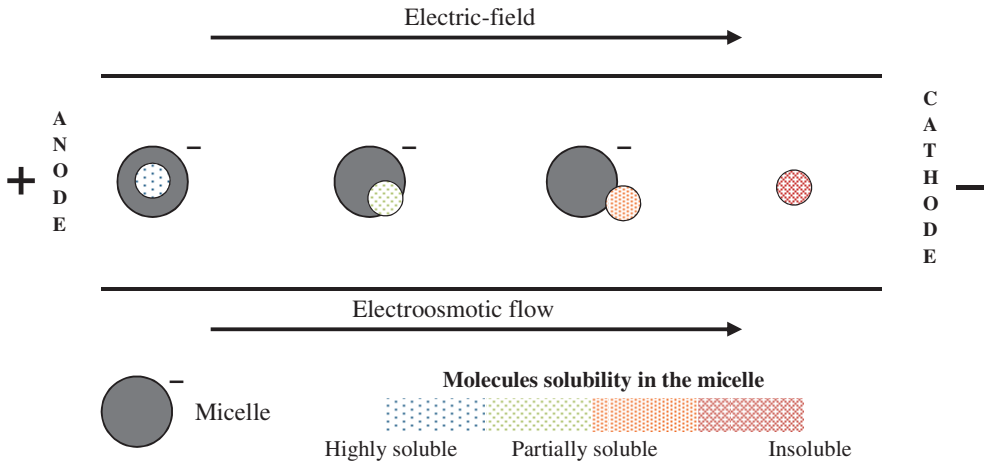

Figure 2. Representation of MEKC. Non-soluble molecules do not enter the micelle and so move through the capillary at the rate of EOF. The highly soluble molecules spend more time in the micelles and thus they move towards the capillary at a rate less than the EOF, the reduction owing to the pull from the anode on the negatively charged micelle.

where μ denotes mobility and E denotes the electric field; the subscripts L, S and T represent the leading electrolyte, sample analyte and terminating electrolyte, respectively. This shows how the electric field is distributed across the electrolyte zones. The sample electrolyte itself will be composed of numerous analytes which each have their own individual values of mobility and therefore could be represented as follows:

$$\mu_S E_S = \mu_{S1} E_{S1} + \mu_{S2} E_{S2} + \cdots + \mu_{Sn} E_{Sn}, \qquad (2)$$

where n is the number of analytes in the sample to be separated. From this it can be seen that the magnitude of the electric field over the different sections will be inversely proportional to the mobility of that section. Separation of the analytes in the sample occurs as the sample moves along the channel. The separation is further assisted by the self-sharpening effect. Consider the instance where a sample has three components (analytes 1 to 3). At all boundaries, even between the leading and terminating electrolytes, there is likely to be some diffusion. Since each component of the fluid moving along the channel is now arranged in order of electrophoretic mobility from equation (2) it is clear that the strength of the electric field will be different across each section. If, for example, an individual analyte from the analyte 3 region were to diffuse into the analyte 2 region, it would experience a higher electric field than it did in the analyte 3 region, and since it has a higher mobility than the other analytes in the analyte 2 region, it would move faster and return to the analyte 3 region. The opposite is true for analytes diffusing into regions of higher mobility.

ITP cannot separate a sample containing both anions and cations in a single run. Prest *et al* [42] and Hirokawa *et al* [43] have conducted work on bi-directional ITP. Here, the researchers moved the ions in two directions along the channel using different methods; Prest's group injected the mixture into the middle of a channel along which an electric field was applied. The anions migrated towards the cathode and the cations to the anode. As explained earlier, ITP requires the sample to be loaded between two electrolytes, which is difficult to achieve in bidirectional ITP. Due to the low Reynolds number two streams could flow parallel to each other with almost no mixing. This means that with a hydrodynamic injection scheme it is possible to setup the sample as required for bidirectional ITP. Details of the separation conditions for bidirectional ITP are given in their paper [42]. More recently the groups' work on miniaturized ITP systems has focussed on analysis of explosive residues [19]. Hirokawa and co-workers used ethylenediaminetetraacetic acid as a chelating agent to modify a variety of different metal cations and then began separation. The advantage of using bidirectional ITP is that it can save on analysis time and enables the simultaneous separation of anions and cations. There is however, the requirement for two detectors at each end of the channel.

More recently, Professor Santiago of Stanford University has spearheaded research into microchip ITP; his group has published 22 papers on the topic since 2006, for example [44–46]. The reader is directed to their work for further information on recent developments in microchip ITP. Some of their work on on-chip ITP has progressed towards a portable devices [47].

3. Design considerations and challenges for miniaturized CE systems

CE requires a fluidic channel or capillary and a high voltage source along with a form of detection system. CE analysis uses low currents to avoid Joule heating of the separation medium. This is important for portable systems where lower currents result in lower power consumption and hence longer operational lifetime. To keep the current low, narrow channels/capillaries are used with low conductivity buffer solutions. High current flow leads to Joule heating which is detrimental on the performance of CE [48]. As well as causing temperature increase, it can also create a temperature gradient. Both of these effects have an impact on the EOF and separation, which can cause sample dispersion and reduce the analysis resolution [49]. Joule heating can also cause the formation of gas bubbles. Though CE operates with a low current, the high electric field means that the power usage

is not negligible. Depending on the power requirements and battery system employed, reports on the operational time show values which vary from 2 h up to 15 h [8, 50].

Material choice is an important consideration for the design of portability or *in-situ* CE systems. For *in-situ* monitoring in particular, the material will need to be robust to ensure a good device lifetime. Portable instruments are not so constrained; though robustness is desirable it may be traded against cost/convenience. For example, the difficulty of developing a robust fluidic chip with an anti-fouling surface and reliable cleaning system may be avoided by developing a system where the fluidic-chip is replaceable.

In the application of drug development and analysis for example, moving to the micro- and nano-scale has the advantages in that it can significantly reduce the cost and analysis time. There are two primary benefits; firstly a smaller device requires less of the drug to test. Secondly, a smaller sample volume reduces the material cost and analysis time, which in turn means that more tests can be conducted and more samples can be evaluated in a shorter period of time. Increasingly microfluidic systems are using electrokinetic methods for moving samples and buffers around microfluidic chips. The smaller channel lengths mean that smaller voltages can be used to generate the high electric fields required for EOF. This method of fluid control/flow is also an obvious advantage for miniaturized CE systems where the operating principle relies on electric fields.

As research progresses the fabrication of narrow/shallow channels becomes easier and more reliable. With this scaling down of the device size, there are negative impacts on other parts of the system. For example, if an optical detection system is used, then its sensitivity can become compromised. On the other hand, amperometric detection techniques benefit from the use of smaller microelectrodes due to enhanced analyte flux towards the electrode surface [51].

The numerous advantages of miniaturization highlighted above have been exploited by researchers to enable a large number of analytical techniques and methods to be applied in a wide variety of fields. This not only enables laboratory level analysis to be done in the field, but enables sensors and detection systems to respond to a much wider range of stimuli, producing useful informative data. There is still however, a significant amount of research required to further improve the integration of CE into intelligent sensor systems.

3.1. Metrics for comparing state-of-the-art for portable/in-situ CE systems

To define 'state-of-the-art' we must consider a large number of criteria to compare against, such as:

- overall device size,
- quality of material choice—robustness of material, chemical inertness,
- fabrication method—complexity, cost, speed, resolution, reliability,
- separation efficiency,
- analysis time,
- operation lifetime,
- level of required user interaction.

There is significant overlap in many of the above criteria. For example, portability requires the device to be small and lightweight, but it also requires a self-contained power source and batteries can be large and heavy. With battery power analysis time may be limited, but since analysis times tend to be short, the real issue becomes the number of analyses which can be performed within the battery lifetime. This becomes an important consideration when evaluating the devices applicability to *in-situ* monitoring; it would be undesirable to have to regularly change the batteries. Significant costs could be incurred in terms of both the batteries and the human labour to change them. The flexibility of the device, with regards to its placement also becomes compromised; if the power source requires changing every few hours or weekly, then it needs to be placed somewhere which is easily accessible to change the batteries. There would be a high likelihood that a place easily accessible would also have access to mains power, and thus the issue of whether to make the device mains powered or battery powered needs to be addressed. The end-user application also strongly dominates the design of the microfluidic CE system, making a general purpose miniaturized separation device difficult.

3.2. Considerations for portable CE systems

To give a metric by which to quantify the success of a truly portable CE system we describe the ideal miniaturized CE system as follows:

- Size: to fit comfortably in palm of hand.
- Weight: less than a few kg.
- Power supply lifetime:
  - For field measurements, changing/charging batteries daily is acceptable.
  - For *in-situ* monitoring, lifetimes in the order of weeks are required.
- Device lifetime: should be made of a material which can be reliably cleaned and which resists contamination.
- Autonomous: sample loading, microfluidic priming and pumping, cleaning, operation and analysis.
- Universal buffering system with minimal/no sample preparation.
- Fast analysis performed on microchip and displayed on device.

The ideal device here is defined as being a portable system capable of performing CE analysis for any appropriate application; this is clearly unfeasible but it is a useful concept to help map and guide research/design. It is also useful to refer to the ideal device when developing a practical design idea for miniaturized and portable CE systems. An understanding of how all the components fit together and their importance enables the designer to evaluate all of the advantages and disadvantages of the design choices. With the specification of the end users' requirements in mind, a comparison with the concept of the ideal device gives a useful insight into

the extent of the compromises and their effect on the end device. We should also highlight the areas where the design constraints of *in situ* differ from those for portable CE systems. Being *in-situ* requires an autonomous control system; it must be capable of functioning without a user present. Regarding the power supply lifetime, stating this as a time may be confusing given that the lifetime depends strongly on the system usage. Authors are keen to report long lifetimes usually where they have conducted continuous analysis. This is useful for portable systems where the researcher in field wishes to perform multiple CE runs in a single field trip.

3.3. Considerations for in-situ CE systems

Since many of the major challenges that face portable CE also face *in-situ* CE, often *in-situ* CE is considered as an extension of portable CE. For example, if you take a portable CE system and modify the control system such that it automatically initiates an analysis when required, then provided the fluid control system is capable of acquiring a sample, the system could be considered *in situ*. It should be noted that an *in-situ* system does not necessarily need to be portable and therefore a number of the constraints pertaining to portability do not apply.

In situ implies complete autonomy; therefore the system must acquire samples from the environment without a user. It must prepare and clean the microfluidic channels automatically and operate without maintenance for significantly long periods of time. If powered by a limited power source, such as batteries, the lifetime should be sufficient to enable an adequate number of analyses. Authors are keen to report long lifetimes usually where they have conducted continuous analysis. This is useful for portable systems, where the researcher in field wishes to perform multiple CE runs in a single field trip. Many *in-situ* applications however, would not require continuous monitoring, but periodic measuring. By considering the lifetime in terms of the number of CE runs it becomes clear that the battery systems for portable CE systems would often also be suitable for *in-situ* CE systems. Whilst their power supply lifetime is typically a few hours, the analysis time is only a few minutes, and so an *in-situ* device could function for many weeks depending on the number of CE runs performed per day.

3.4. CE system fabrication

Generally there are two commonly exploited routes for fabricating miniaturized CE systems. In one method a miniaturized system is built around a shortened capillary (such as a fused-silica capillary). The second method is to fabricate a microfluidic channel using microfabrication techniques. We shall refer to the first method as non-chip-based CE systems and the second as chip-based CE systems. As well as fabrication of the channel and supporting structures, the design of portable HVPS and detection systems need to be considered. There are a large number of problems which must be addressed and overcome when building a miniaturized portable CE analysis system. The following six areas have been identified as key factors which must be considered:

- Channel dimensions,
- Device material,
- Shape of the channel path,
- Sample injection,
- Detector method and placement,
- Generation of the electric field.

The channel dimensions, device material and shape of channel are considerations for both chip- and non-chip-based CE devices. For non-chip-based CE, however, a cylindrical fused-silica capillary is commonly used and therefore the capillary length is the primary consideration. Filling the channels with fluids as they become smaller can become an issue especially in the case of long narrow channels due to increased surface tension. Often capillary forces alone can pull a fluid along a channel a certain amount but may not be capable of filling the channel. There are a variety of methods to fill the channel such as using pressure to force the fluid down, or submerging the device in the fluid and lowering the surrounding pressure [52].

3.4.1. Typical fabrication methods for microfluidic chips. A common device layout for miniaturized CE devices is to have two channels that intersect each other as shown in figure 3. The channels in the substrate are often sealed by covering the device with a block of the same material. It is not uncommon however, for a device to have a channel created in one material, a polymer for example, and then sealed to a glass substrate. Where there are electrodes deposited on a substrate they may need to be insulated, such as when using contactless conductivity detection (CCD), and the insulation material is often different to that which hosts the channels. This can have undesirable effects on the EOF and consequently the separation resolution achievable.

There are a number of techniques routinely used to fabricate microfluidic devices. Examples include, moulding [53–58], injection moulding [59–61], hot embossing [11, 62], micromachining [63], milling [42, 64, 65] and screen printing [53, 66].

In recent years there has been a significant shift in the material of choice for microfluidic devices. The first microfluidic devices were built using standard microfabrication techniques many of which were originally developed for the electronics industry. These processes were well established and suited for production of microfluidic devices. Further to this they were developed to such a stage that much of the production which would have otherwise been a complex fabrication development task became greatly simplified. Using current state-of-the-art technology, transistors are routinely fabricated on silicon wafers with micro-fabrication technology capable of creating line widths of the order of 10s to 100s of nm. The technology has received a substantial amount of interest and funding over many decades and still continues to advance to smaller feature sizes. The dimensions used with microfluidic devices are much larger than those used at the forefront of microfabrication technology and as a result the processes are well understood. Whilst there is a requirement for specialist tools, machinery

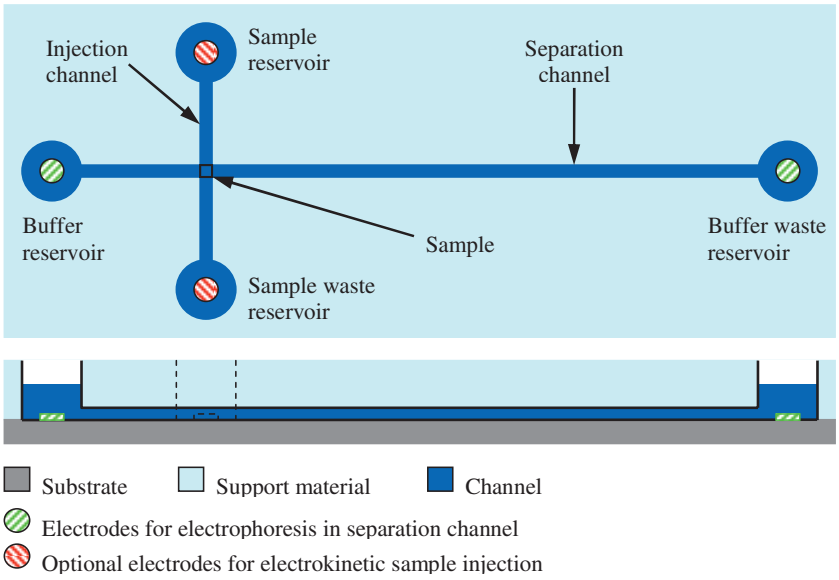

Figure 3. Typical layout for miniaturized CE device.

and equipment it is reasonable to say that it is now relatively simple to create a microfluidic device in a range of materials using these well understood methods. These methods may include a number of processing steps such as: lithography; chemical etching; high-temperature annealing and so on.

More recently the rapid production of microfluidic channels to a high standard has become an increasingly popular research theme, with many papers focussed solely on the fabrication method rather than the application for the resulting device. For chip-based CE systems, particularly in recent years, the popularity of polymer materials compared to glass-based systems has grown significantly. This trend is attributed to the lower cost of the polymers and their ease of fabrication [67]. Further to this, polymers can be more robust than glass which is often too fragile for field use. Their greater mechanical robustness is even more important for *in-situ* monitoring; especially in the case of harsh environments. *In-situ* devices however require a material which can be reliably and repeatedly cleaned; there are a number of well-established cleaning methods for glass, which has good chemical resistance for a range of contaminants. Many polymers are not compatible with organic solvents and do not offer the same chemical inertness as glass or silicon, and as such are prone to surface contamination. This detrimentally affects their performance and lifetime; for portable CE systems, many of the approaches, design the system such that the fluidic component which contains the channel is replaceable. This yields some flexibility in the design though for *in-situ* CE, channel replacement is not an option and so a cleaning regime for the selected material needs consideration. It should be noted that generally the polymers used in microfluidics are stable in both acid and alkaline environments. COC (also referred to as cyclic olefin copolymers (COP)) and polyimide are often quoted as having high acid, alkali and solvent resistance [59]. An in-depth discussion on polymers for microfabrication is presented in a review paper by Becker *et al* [67].

3.5. Detection systems

The detection system needs to be capable of detecting the species being analysed. There is a large variety of detection systems commonly used in standard laboratory CE systems. For miniaturized CE systems the focus has typically been on electrochemical and some optical detection methods, the pros and cons of which are discussed here.

3.5.1. Optical detection. The simplicity of targeting a laser or light beam onto a channel and measuring the response has kept optical detection methods popular, with LIF being one of the most widely used methods [4]. In 2004, Guijt *et al* [68] stated that high pressure (or performance) liquid chromatography (HPLC) used optical detection methods much more so than any other method and that electrochemical techniques such as amperometry were only employed about 5% of the time. Whilst optical methods have proven popular with HPLC, ion chromatography has tended to favour conductometric detection methods [68].

One obvious disadvantage is that for analytes which do not naturally fluoresce, is the requirement to use fluorophores. These tend to be 'bulky', and consequently can cause the analytes to exhibit similar mobilities. This increases the difficulty of separating the analytes and consequently schemes such as longer separation channels may need to be employed. Recently Behnam *et al* [69] developed an integrated circuit (IC) to help enable portable and *in-situ* CE. It was capable of providing a high voltage and included LIF detection. This was interesting since miniaturized CE systems, especially those designed for portability have moved away from LIF, which was once the most widely used detection method in CE. One of the reasons for the shift from LIF to other detection systems, such as electrochemical detection methods, was because the electrochemical methods are suited to miniaturization. One of the main drawbacks of LIF is that detection requires

analytes which do not naturally fluoresce to be marked with fluorophores. For portable and *in-situ* systems it is desirable to minimize or remove the requirement for any sample pre-treatment. Unlike electrochemical detection systems, optical methods are inherently electrically isolated from the large voltages.

3.5.2. Electrochemical detectors. There are three types of electrochemical detector (ECD) schemes commonly employed within miniaturized CE systems. These are potentiometry (the measurement of potential at given current conditions), conductometry (the measurement of conductance) and amperometry (the measurement of current at a given potential). Each of these detector schemes has various methods for implementation depending both on the application and the CE device.

A very simple method of incorporating an amperometric detection scheme was presented by Schwarz *et al* [70] in which only two electrodes are required. In conventional amperometry a potential is held, with respect to a reference electrode, and a current is measured between two electrodes—the counter and working electrode. To achieve results with only two electrodes, Schwarz *et al* [70] used a working and an electrophoretic ground electrode; the latter serving as both the counter and the reference electrode. The amperometric detection technique strongly relies on the redox characteristics of the analyte molecules and consequently it may not be suitable for all separation applications [68].

An improvement in the signal to noise ratio, which enables a lower limit of detection, can be gained by decreasing the electrode size; as the electrode size is reduced the electroactive species diffusion changes from planar to hemispherical diffusion and flux rates at the surface increase. The result of this is an improvement in the collection efficiency at the surface of the electrode [53]. A disadvantage is that the magnitude of the current signal decreases and for accurate measurements electronic shielding may be required.

3.5.3. Detector placement. Another consideration for the design of a detection system is the placement of the detector electrodes. There are three schemes regarding the placement of ECD electrodes which are commonly discussed [71]. The detector can be placed in-channel, off-channel, or at the end of the channel. Each position carries its own advantages and disadvantages.

As the name implies, with in-channel detection the detector electrodes are placed inside the channel and as a result are subjected to the electric field across the channel. This can be problematic since to make a measurement in the channel a decoupler or isolator may be required, though some researchers have found ways to get around this. For example Martin *et al* [20] developed a miniaturized and highly portable electrically isolated potentiostat to make the measurements. An advantage of in-channel detection however is that by virtue of its location the detector is not subjected to errors caused by post-capillary broadening: a phenomenon experienced by ions as they pass out of the end of the channel, irrespective of the separation technique [51]. Commonly, amperometric methods are used with in-channel detection which requires careful selection of the electrode material; often noble metals such as platinum or gold are used.

With continual use the surface of the working electrode will become fouled, affecting the detector performance. However, the lifetime of these electrodes, and subsequently the CE device, has been significantly increased by the incorporation of pulsed amperometry detection (PAD) [51]. The process of PAD combines amperometric detection with anodic cleaning and cathodic reactivation of the noble metal electrode surface. This ensures an electrode surface which is continuously self-cleaned and remains active [51]. Another method to overcome the problem of surface fouling, is described by Lin *et al* [72]. They developed an in-channel ECD scheme where the electrode can be drawn out once the electrode becomes fouled. Moving the electrode a small amount ensures that a fresh electrode surface is available to be used by the detector. Once this surface becomes fouled, the electrode is drawn out a little more and the process is repeated until the electrode is fully removed. One drawback of this process compared with the PAD method is that it requires human interaction to move the electrode, unless a system for autonomously moving the electrode was employed.

An in-channel CCD detection scheme was described by Coltro *et al* [73], which has the electrodes placed in the channel, separated by a layer of insulation. Whilst CCD is less sensitive than other methods, it has the advantage that there is no risk of electrode fouling. A further advantage is that there is inherent electrical isolation from the large separation electric field.

With end-channel placement, the electrodes are placed outside the channel, close to the ground electrode, and therefore do not require decoupling from the high separation field. Wu *et al* [71] claimed that from their review of the literature, a majority elected to use end-channel amperometry as the detection mode for their CE devices. As well as providing insolation from the separation voltage, it is easier to fabricate end-channel devices since there is no requirement to get an electrode into the very narrow channels. Since the metal electrode is placed at the end of the channel, care must be taken to ensure that it does not block the channel or upset the fluid flow. For accurate measurements, good electrode alignment is required which can often cause complexities with regards to positioning the electrodes. The technique of electrode refreshment reported by Lin *et al* in their in-channel system has been adopted for end channel use to enable easy cleaning/replacement of the electrode surface [74]. Here a channel was created across the end of the separation channel, through which a metal wire electrode was inserted. Drawing this electrode out of the channel in small increments presented a fresh electrode surface for successive measurements.

The placement of electrodes for an off-channel EC detection scheme is similar to that for in-channel; however the high separation voltage is shunted to ground using a decoupler before the detection electrodes [75]. A common method to achieve this is to introduce a fracture into the separation channel [4], though one problem which can occur from this is

the generation of backpressure. Wallingford *et al* [76] showed that provided the EOF is strong enough and that the length from the fracture to the detector is kept minimal, then there is only a small loss of efficiency.

4. Portable CE systems

4.1. Non-chip-based

Here, by non-chip-based CE we refer to miniaturized CE systems whereby the fluidic channel is not embedded in a substrate but is a capillary. One of the major advantages of using a capillary is that it has been well characterized due to many years of investigations by numerous researchers. This enables reasonably accurate predictions of the device performance to be made. Further to this, cleaning and preparation protocols have been established and the channel wall material is a single material. Fused-silica capillaries are known to be rugged and well characterized. Further to this the cylindrical nature of the capillary presents maximum volume-to-surface ratio [5]. The other obvious advantage for non-chip CE is that both the financial and labour costs of fabrication are reduced or avoided. One of the major challenges for miniaturized non-chip-based CE systems is attaining reliable, accurate and repeatable sample injections.

One of the first reports of a non-chip-based portable CE was presented in 1998 by Kappes and Hauser [78]. The capillary used by the instrument had a length of 72 cm or 90 cm depending on the sample being analysed. This instrument consisted of a fused-silica capillary, a high voltage module, detection electronics and a data acquisition board which integrated with a palmtop PC. Excluding the PC, all the equipment was housed together in a PVC case of dimensions 340 mm $\times$ 175 mm $\times$ 175 mm, along with compartments and supports to align and secure the components in place. An illustration of the instrument can be seen in figure 4, which highlights many similarities that it bears to commercial CE instruments. The total weight of the instrument was 7.5 kg; the main contributor being the two 12 V dc lead acid batteries, though this size and weight can be considered portable. The use of narrow capillaries (25 μm inner diameter) restricted the electrophoretic current flow and so the lead acid batteries could last for 5 h on a single charge. Their first field portable CE instrument incorporated only potentiometric detection. This instrument formed the basis for much research on different detection schemes which were incorporated into the instrument. In 1999 the authors reported on a similar device where they integrate both potentiometric and amperometric detection methods [79]. Further details on the specifics of their amperometric detection method can be found in [80]. In 2001 they added conductometric detection capabilities to the instrument [77]. The use of three different but complementary electrochemical detection methods made the instrument very versatile in the range of analytes that it could separate [77]. The authors showed results demonstrating the ability of the device to separate a range of inorganic anions and cations, as well as numerous organic species. Unlike bench top-based CE instruments, which use integrated pumps for flushing the capillaries, here the capillary is flushed manually using a syringe. The use of a syringe negates the need for pumps which would have reduced the portability by increasing the weight and power consumption. Injection of the sample was achieved electrokinetically.

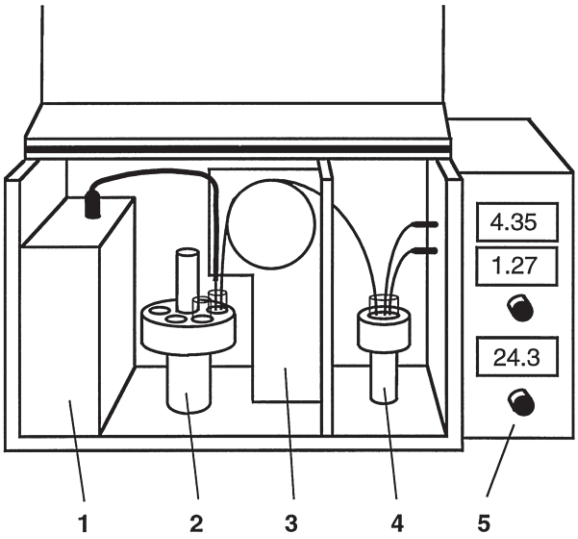

Figure 4. Illustration of the instrument developed by Kappes *et al* (reprinted from [77], copyright (2001), with permission from Elsevier). (1) HVPS; (2) carousel for sample vials; (3) capillary holder; (4) detector compartment; (5) detection electronics.

Gerhardt created an elegant miniaturized non-chip-based CE system (see figure 5); however his interest was focussed on the development of a robust detection method [81]. This system incorporated a 30 cm long capillary, over which a high voltage up to 10 kV could be applied. Further to this the system was made completely autonomous; each sample vial could be moved by a stepper-motor and lifted for analysis as well as for capillary cleaning and preparation. Whilst it was not mentioned in the report [82] the high voltage module, from Spellman (model: MM10PN) was one of the larger features; the datasheet for the HV module states a case size of 42 mm $\times$ 76 mm $\times$ 101 mm [83]. Further to this, it was not made clear where the HV module or the motors, pumps and control system got their power.

Kubáň and Hauser further extended the work by Kappes and Hauser [77] to incorporate dual opposite end injection [84]. This enabled the separation of anions and cations in a single run by injecting the sample at opposite ends of the separation capillary; the analytes moved towards the centre of the capillary where a CCD was placed [84, 85]. An interesting aspect of their work was their approach to sample injection where they used a flow injection-capillary electrophoresis (FI-CE) system. Here a sample capillary is connected to the separation capillary via a valve composed of ceramic and polymeric parts [84]. There is generally no problem with high voltages damaging the FI equipment at the end of the capillary where the injection is commonly situated, since the potential here tends to be close to electrical ground. For the dual opposite end injection scheme however, there will always be one injection point at a high voltage and so the

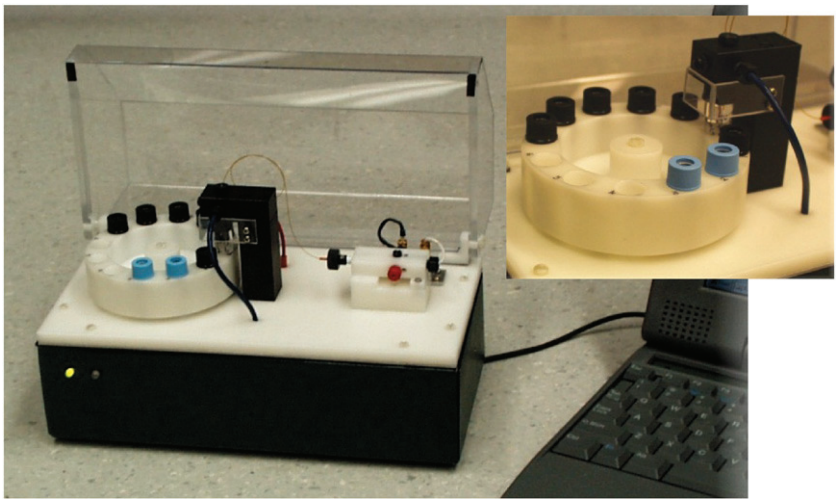

Figure 5. Miniaturized CE system developed by Gerhardt; it featured an automated sample carousel, which would lift to inject a sample. Photograph reprinted with kind permission from Dr Geoff Gerhardt.

insulating properties of the valve components were important in protecting the FI equipment.

From the schematic given by Kubáň *et al* [86], the layout of the portable CE device was similar to that by Kappes *et al* [77], though the dimensions were slightly different: 310 mm × 220 mm × 260 mm. This meant that the volume was 1.7 times greater than that of the work by Kappes *et al*. Further to this the control electronics to operate the portable CE system were housed in a separate aluminium box of dimensions 70 mm × 205 mm × 160 mm. The device developed by Kubáň *et al* did not require the high voltage modules to be swapped depending on the polarity desired, unlike that of Kappes *et al*. This is probably one of the contributing factors to the size increase. The high voltage modules were powered by 12 V lead acid batteries. In the device by Kubáň *et al* a further two 12 V lead acid batteries were used to give a ±12 V supply for the electronics. With this large power supply, the detector and data acquisition system, which used separate batteries, the system could operate continuously for 9 h. This length of time could be considered just adequate for a day's worth of in-field or on-site testing.

In more recent work by Kubáň and Seiman *et al* [87, 88] the authors used milled PMMA and polyimide blocks to facilitate the sample injection. This system is a kind of hybrid of chip and non-chip CE. This method benefits from simple manufacturing techniques, as well as well-defined and characterized separation capillary surface. Unlike in chip-based CE where the channel surface is very important, the milling of the polymer cross samplers is not critical because the separation 'channel' is a fused-silica capillary. An image of the PMMA cross sampler is shown in figure 6. The system designed by Seiman *et al* fitted into a box of dimensions 330 mm × 180 mm × 130 mm, weighed less than 4 kg and was powered by 10 AA batteries. In 2011, a collaboration between Kubáň and Seiman *et al* [88] published details on their portable CE system with dimensions of 300 mm × 300 mm × 150 mm and weighing approximately 5 kg.

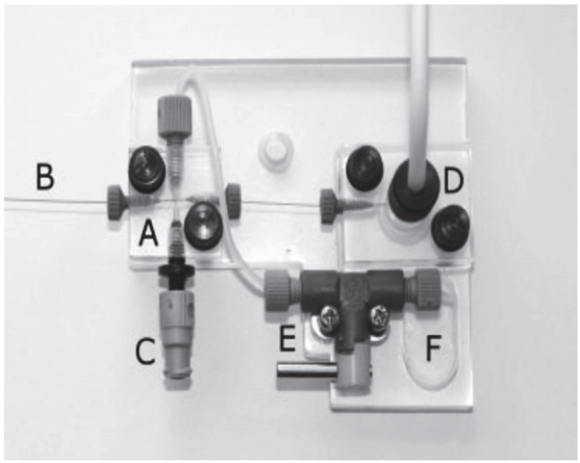

Figure 6. Image of a PMMA cross-sampler used to enable easy injection into the capillary. A: cross-sampler, B: separation capillary, C: syringe socket, D: buffer vessel with electrode lead, E: shut-off valve and F: waste reservoir (reprinted with permission from [87] copyright (2009) John Wiley and Sons).

A portable non-chip-based CE system designed by Xu *et al* had dimensions 320 mm × 230 mm × 150 mm and weighed less than 2 kg [8]. They developed a CCD cell through which they threaded a capillary. The CCD cell operated with an input signal of 240 V_{pp} at 125 kHz. The whole system was powered by an internal battery and could operate for 2 h. The system was heavily based on the CE-P2 system; a commercial available portable CE system (figure 1). By using a pre-built portable CE system, they had little control over design compromises which limited the degree to which they could further miniaturize their system. It should be noted that the aim of their work, however, was focussed on the detection of a specific sample for their application, rather than the portability of a CE system.

Wang *et al* fabricated a hybrid chip-non-chip CE device with a capillary length of 55 mm and held in polydimethylsiloxane (PDMS) [89]. Whilst the height of the microfluidic device size was not given, the system fitted on top

Table 1. Summary of portable non-chip-based CE systems.

Ref.	Size (mm × mm × mm)	Weight (kg)	HV range (kV)	Capillary length (cm)	Injection method	Power supply lifetime (h)	Power source	Detection method
[77, 79, 80]	340 × 175 × 175	7.5	±30	40, 72, 90, 104	EK	5	12V lead acid (× 2)	PMD, AMD, CCD
[81, 82]	254 × 127 × 203	–	10	30	HY	–	NiCd	PMD
[89]	–	–	1.5	5.5	FI	–	–	CCD
[86]	310 × 220 × 260 +70 × 205 × 160	Several	±15	62, 75	EK/HY	9	12V lead acid (× 3)	CCD
[8]	320 × 230 × 150	<2	−25	60	EK	2	–	CCD
[87]	330 × 180 × 130	<4	25	48	HYCS	>4	AA (× 10)	CCD

EK: electrokinetic; HY: hydrodynamic; HYCS; hydrodynamic cross-sampler; PMD: potentiometric; AMD: amperometric; and CCD: contactless conductivity detection.

of a glass slide of size 20 mm × 70 mm × 1 mm, excluding peripheral (or ancillary) hardware. This microfluidic device is essentially just a capillary with detection electrodes built in and bears many similarities to the chip-based approach to miniaturizing CE.

It is clear from a survey of the literature on non-chip-based CE that there are not many groups who have explored this technique with a view to portability. The review by Ryvolová *et al* [5] discussed work by various research groups but overlooked the collaboration between many of them, a consequence of which is that it makes the area of non-chip CE look larger than it actually is. A summary of the portable and *in-situ* non-chip-based CE systems is given in table 1. With regard to detection strategies, due to its convenience, the preferred method of detection is CCD, usually using two or four electrodes.

4.2. Chip-based

Unlike non-chip-based CE systems, chip-based devices are often fabricated in new and emerging materials. The channel surface is important and it needs to resist contamination and as discussed earlier plays an important role in the generation of the EOF. The use of these new and emerging materials introduces the problem of unpredictability which is exacerbated by the fact that different fabrication methods affect the channel surface in a variety of ways [90, 91]. Further to this, whereas a capillary has just one material for the channel wall, many of the fabrication methods for chip-based systems use two or more materials which results in a channel with unknown EOF characteristics.

Jackson *et al* first reported on an instrument they had developed, focussing primarily on the compact battery HVPS and its use in microchip CE [92, 93]. This instrument was combined with a microchip CE device, which highlighted its applicability as a step towards a portable CE system [93, 94]. Later amperometric detection circuitry was integrated into the instrument. The dimensions for this instrument were approximately 102 mm × 152 mm × 25 mm with a weight of 0.35 kg. This accompanied a microchip CE device to render the main parts of a portable CE system [50]. This system weighs over 20 times less and is significantly smaller than the system by Kappes and Hauser described earlier making it more portable. The primary reduction in weight was enabled

Figure 7. Photograph of the μChemLab hand-held CE system. Reprinted with permission from [95]. Copyright (2005) American Chemical Society.

by the use of AA batteries to power the HV module and a 9 V battery for the electrochemical detection system as opposed to the bulky lead acid batteries. The HV system by Jackson *et al* was capable of producing a dual output of ±1 kV. The use of microchip CE rather than capillary-based CE resulted in short channel lengths and this meant that separation was possible with lower voltages. Jackson *et al* [50] achieved 15 h of continuous operation with 4 AA rechargeable 1300 mA h NiMH batteries, where continuous operation was defined as time the separation voltage could be kept active.

A hand-held CE system named μChemLab was discussed by Renzi *et al* [95], though the concept of μChemLab was first discussed by Lindner in 2001 [96]. It is an example of where a holistic approach has resulted in a truly portable CE system. This system contained a HVPS capable of providing ±5000 V for currents up to 100 μA. Unlike most other portable CE systems which tend to use electrochemical-based detection methods, the μChemLab system uses LIF. Figure 7 shows the μChemLab housed in an ergonomic case (115 mm × 115 mm × 190 mm) which weighs less than 2 kg and is clearly a convenient size and weight. The device consumes 4.5 W and is able to run for several hours on batteries. The microfluidic chips were designed for repeated use and the authors stated that the chips had well-characterized

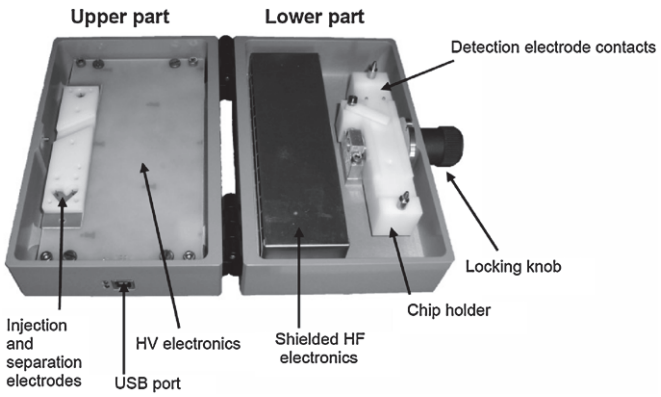

Figure 8. Portable CE instrument developed by Becker *et al*. Reprinted with permission from [10] and SPIE.

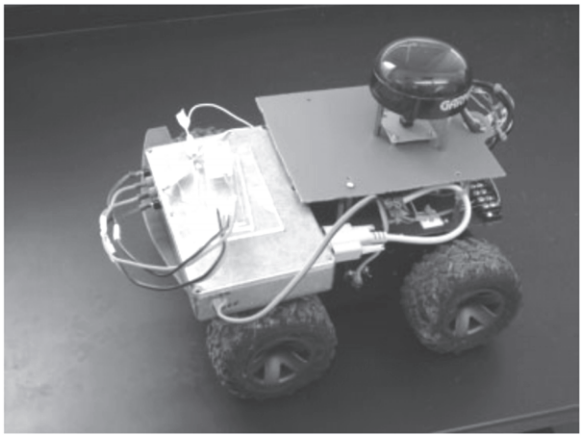

Figure 9. Photograph of the lab-on-a-robot system. Reprinted with permission from [98]. Copyright (2008) John Wiley and Sons.

electrokinetic surfaces, which could be cleaned and were suited to surface property modification. The sample passes an in-line filter before entering the microfluidic channels to help protect the channels.

In a publication by Zhang *et al* [97], the main components required for a portable CE system are discussed. Their fluidic system was fabricated in glass with a channel of width, depth and length of 100 μm, 28 μm and 60 mm, respectively. Their detection scheme was composed of integrated platinum electrodes serving part of a simplified conductivity detector. To generate the high voltage required for CE, Zhang *et al* used piezoelectric transformers because they offer a high transformation ratio whilst being smaller and cheaper than magnetic transformers. In their paper they stated that their HVPS was capable of producing an output of 14 kV with a ripple of less than 0.2% [97]. The paper showed promising simulation results but no experimental data or any performance data, such as operational time, power consumption, etc, was given.

In 2008 there was a publication by Mühlberger *et al* who collaborated with Becker *et al* to produce a report on their work. The technical report by Becker *et al* [10] discusses the performance and applications of the finalized device whereas the publication by Mühlberger *et al* [11] focuses on device fabrication and development, investigating various materials and discussing their properties. Figure 8 shows the device developed by Becker *et al;* the design is similar though slightly larger to that presented by Mühlberger *et al* [11]. The overall size of Becker's instrument was 190 mm × 120 mm × 80 mm whereas MinCE (Mühlberger's instrument) was 170 mm × 100 mm × 70 mm. The polymer substrates investigated were PMMA, polycarbonate, polypropylene, COC and polyether ether ketone. The microchannels were fabricated using a hot embossing method where processing parameters such as temperature and pressure profiles were varied for the different polymer substrates. The channels were thermally sealed to a thin foil of thickness from 15 to 80 μm; further fabrication details are described in the paper [11]. The channels had square cross-section with a height and width of 50 μm. Becker *et al* state that for their system the HVPS system was composed of two commercial miniature unipolar power supply modules (each capable of 4 kV) coupled together to provide a bipolar driving power supply; this was required to enable the separation of anions and cations [10].

The chip-based CE systems, with the incorporation of small HVPS and on-chip detection systems, have led to the development of numerous truly portable CE devices. A summary of literature on *in-situ* CE systems is given in table 2.

5. *In-situ* CE systems

The concept of lab-on-a-robot was discussed by Berg *et al* [98]. Their system is a wireless mobile unit fitted with a global positioning system, capable of navigating to a location, acquiring a gaseous sample, performing CE and sending the data to a remote station. The gaseous sample is pumped into the sample reservoir which initially contains buffer solution using a micropump; after a few minutes of pumping a CE analysis is run. This system contains components which are important for portable systems which bridge the gap towards *in-situ* devices. The HVPS on the system, capable of providing a voltage up to 1200 V, was based on the commonly used HV-dc-to-dc converters manufactured by EMCO High Voltage Corporation. An image of the system can be seen in figure 9.

Fernández-la-Villa *et al* [99] developed a portable CE system which incorporates amperometric detection. They used a mini-HVPS-PT001 purchased from MicruX Fluidic, which used 1 W and a maximum output current of 0.34 mA. The system is controlled by a laptop or PC, which adds to the cost and reduces its feasibility as an *in-situ* device. As the author notes however, it helps pave the way towards *in-situ* analysis. Whilst a lifetime in terms of hours was not specified, they stated that on one charge the device would last for a day of experiments. The power was supplied by a Li-ion polymer battery rated at 3300 mA h. They also purchased the Pyrex chip from MicruX Fluidic; a downside of ordering standard components has been that it limited their ability to miniaturize the system. Here the size of the system is strongly limited by the size of the HVPS which was 150 mm × 165 mm × 70 mm.

An *in-situ* CE system which used a four-layer chip and contained eight CE systems has been designed by Benhabib *et al* [100]. The system included a completely autonomous

Table 2. Summary of portable chip-based CE systems.

Ref.	Size (mm × mm × mm)	Weight (kg)	HV range (kV)	Channel material	Channel length (mm)	Power source	Detection method
[50, 92]	HVPS and detection circuitry[a] 102 × 152 × 25	0.35	±1	Glass	20	AA (× 4) 9 V (× 1)	PMD, AMD
[97]	–	–	14	Glass	60	–	CD
[11]	170 × 100 × 70	–	–	Various polymers	∼75–85	–	CCD
[10]	190 × 120 × 80	–	4	PMMA	75	–	CCD

CD: conductivity detection.
[a] excluding microchip.

fluidic control system and it was demonstrated by analysing a variety of organic compounds. The aim of their project is the development of an instrument to perform analysis in places inhospitable to humans, hence the requirement for complete user independence. It contains three HVPS and is capable of producing voltages to –15 kV though no details were provided on the battery system used. The cleaning step consisted of filling the reservoirs with buffer solution and using the EOF to flow the buffer solution through the channels.

Mai *et al* [101] developed a sequential injection CE system to monitor levels of inorganic anions and cations in a creek *in situ*. A constant stream was pumped into a bucket from which another pump fed the sample into the injection manifold through a filter. The analysis took 35 min and was operated for five days. The paper lacks details on the whole system size, weight and the power source used. Unlike the other work on *in-situ* systems discussed here, the system by Mai *et al* used a non-chip-based approach. This system incorporated earlier work, by Hauser's group, on CCD on capillaries. Prior to this work, a similar set-up was described by Wuersig *et al* [102], who discussed a number of shortened capillary lengths depending on the sample being analysed.

A summary of the *in-situ* CE systems discussed here can be found in table 3. There have been a number of publications on *in-situ* CE systems [103], comparable with that discussed by Hauser's group. These often consist of portable CE instruments which are modified (or adapted) such that they automatically obtain samples. Often the method is referred to as flow-injection or sequential-injection CE. A table summarizing the work by a range of groups in this area has been published by Wu *et al* [104].

6. Sample injection schemes and fluid control

This is one clear area where the chip-based CE systems hold an advantage over the non-chip-based approaches. Non-chip CE systems require sample injection into a capillary, which introduces design complexities. This problem has been addressed however, and there are various simple solutions. Sample injection methods for chip-based CE systems tend to consist of a sample channel crossing the separation channel; in terms of fabrication this usually adds no further complexity. To inject a sample into the channel the user simply needs to pass a sample from the sample reservoir to the sample waste reservoir. The cross-section is a defined area which will then be filled with sample and so this gives a simple and repeatable method for sample injection. If the sample is pulled through the sample injection channel by use of pressure, for example using a pump or syringe then this is referred to as hydrodynamic injection. One of the downsides of manual injection is that it is difficult to attain highly reproducible injections [105]. Whilst the importance of reproducibility in portable/*in-situ* devices may not be as critical as in laboratory-based analytical chemistry, it is clearly desirable to ensure that the sample injection varies as little as possible.

Often researchers will use electrokinetic injection where a voltage is applied between the sample and sample waste reservoirs to drive the sample across the separation channel. The advantage is that there is no requirement for hardware such as pumps to create a pressure difference which saves space and reduces power consumption. One downside of electrokinetic injection is that it can lead to sample biasing during injection, due to the differences in mobility of the sample constituents. Furthermore the presence of a voltage on the sample reservoir could induce a pH change due to electrolysis, which in turn could alter analyte behaviour due to processes such as complexation [106].

Another method discussed in the literature is FI; in this a sample is injected into the separation channel whilst the fluid is flowing along the channel. Using this method it is possible to attain numerous separations sequentially by repeated injections. Where electrokinetic injection is used, there is the additional option of using a pinched injection scheme. This is where the electric field is controlled to cause the fluid to flow towards the sample waste reservoir in a manner which pinches the flow where the separation channel crosses the sample injection channel. Usually a potential is applied to all four reservoirs (buffer, buffer waste, sample and sample waste) to control flow for the pinched injection. The use of a pinched injection scheme enables accurate and well-defined sample volumes which in turn lead to repeatable, high separation efficiencies [106].

FI requires very precise fluidic control which is quite difficult to attain in a portable device for field measurements. For priming the channels, flushing buffer solutions and setting up the device, a pump is required. Due to the small capillary/channel cross-sectional areas in CE systems there tends to be large hydraulic resistances which need to be overcome by the pump. This usually means that the pump cannot be too small and that it will consume a non-negligible level of power. Since the volumes of fluid concerned tend to be relatively small there is the possibility for the use of

Table 3. Summary of *in-situ* CE systems.

Ref.	Size (mm × mm × mm)	Weight (kg)	HV range (kV)	Channel/capillary material	Channel/channel length (mm)	Power source	Detection method
[98]	Lab-on-a-robot	–	1.2	PDMS	–	9 V (× 1) 12 V (× 1)	PAD
[99]	HVPS: 150 × 165 × 70	2	±2.5	Pyrex	40–50	Li-ion polymer	AMD
[100]	324 × 127 × 310	–	−15		215	–	RTFS
[101]	–	–	±30	Fused-silica capillary	–	–	CCD
[102]	–	–	±30	Fused-silica capillary	80–250	–	CCD

PAD: pulsed amperometric detection and RTFS: real-time fluorescence spectroscopic analysis.

micropumps, designed specifically for moving small amounts of fluid. Due to the typically high values of hydraulic resistance, most micropumps will struggle to achieve high flow rates but this becomes a compromise for size, weight, power consumption and simplicity.

For flushing capillaries or channels, a simple, cheap and low power method, discussed by Kappes *et al* [79] is the use of a syringe. They used a syringe for capillary flushing but performed sample injection by electrokinetic means. Making the user push/pull a syringe to create a positive/negative pressure at a reservoir is a technique that can be used to flush the channels at a reasonable flow rate, and through appropriate choice of valves it is also able to provide sample injection. Alternatively, given that high voltages are required for the separation and so in principle are already available, electrokinetic injection is a useful sample injection technique since it does not require any additional pumps. On the downside there does however, need to be either a physical switch or circuitry to control the high voltage.

There is a clear trade-off which needs to be considered regarding electrokinetic versus hydrodynamic injection, and this will depend strongly on the application. For example, if the device is portable it implies that there is a user present and so the option of using a syringe, or similar manual pump is a viable option though care needs to be taken when considering the control of fluid flow. *In-situ* devices however are inherently autonomous (excluding in principle some maintenance) and therefore fluid control is required for both capillary/channel preparation and sample injection. A pump will also be required to take a sample from the monitored environment. With a view to minimize the number of components, a system of valves would enable the same pump to be used for sample injection. A HVPS would then be used to drive the separation. Alternatively the HVPS for the separation could be switched with a system of relays and therefore could also be used to electrokinetically inject the sample. For the design of *in-situ* CE systems, the notion of multi-functionality of components is of great importance since it minimizes size, cost, complexity and power usage.

7. High voltage power supplies

In many of the earliest attempts at designing portable CE systems the commercial HVPS tended to be one of the larger components limiting size, weight and lifetime. Later, solutions where the researchers designed and built their own power supplies yielded more portable systems. Whilst high performance power supplies are desirable, there needs to be a compromise between size, power consumption and performance, and this will depend strongly on the application. The requirement for a high voltage does of course raise safety considerations and the safety of the user is of the utmost importance and so any device needs to be designed such that it is impossible for the user to accidentally access any connection to the high voltage. A common safety precaution used by many researchers is to incorporate trip switches into the instrument case to cut off the high voltage the moment a case is opened.

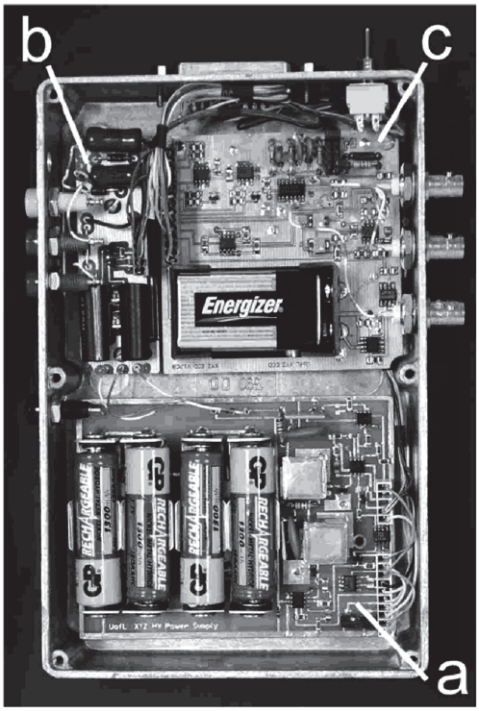

Figure 10. Photograph of instrument developed by Jackson *et al*. a: portable HVPS; b: interface circuitry; and c: amperometric detection circuitry. Reprinted with permission from [50]. Copyright (2003) American Chemical Society.

As discussed earlier, Jackson *et al* [50] developed a small HVPS combined with the detector circuitry in a single box (figure 10). The high voltage module was powered by 4 AA batteries and could operate for 15 h. The dual-source HVPS was enabled using a commercial dc-to-dc converter module which operated at 0.5 W. The dc-to-dc converter chips used by Jackson *et al* are developed by EMCO High Voltage Corporation. These PCB mountable HV supply modules are not particularly low power (∼0.5–1.25 W) when considering battery use, but they have reasonably small dimensions of

only 12.7 mm × 12.7 mm × 12.7 mm and weight just over 4 g. With separation times in the range of a few minutes, this enables a reasonable number of separations to be performed before battery replacement is required. There are a large range of HV dc-to-dc converter chip devices available, capable of providing up to 10 kV for a 5 V input [107]. Since portable and *in-situ* CE systems tend to have relatively short channel lengths, a power supply providing up to 10 kV will yield a suitably high electric field for separation.

Using two types of HV dc-to-dcC converters from UltraVolt Inc. one positive polarity and the other negative, García *et al* [108] were able to generate potentials up to ± 4000 V. The power consumption of their HVPS was up to 30 W, implying that it could support an electrophoretic current up to 7.5 mA. During their separations they used their HVPS up to 1200 V, enabling generation of electric fields with a magnitude of over 20 kV m^{-1}, highlighting an advantage of shorter channels for portable/*in-situ* CE systems.

A HV system designed to be used with PDMS-based microfluidic systems by Erickson *et al* [109, 110] also used the EMCO dc-to-dc converter. Their complete integrated system made mainly of PMMA on which PDMS devices were placed measured 2.1 cm × 2.5 cm × 10 cm, and voltages up to 700 V could be generated by the system. Interestingly the authors detailed the power usage of the systems components which used the most energy; the HVPS used 55% and the control circuitry used a further 37%. Their system was powered by a coin cell to aid miniaturization, and although coin cells tend to have lower energy storage than many other types of battery, they were still able to perform 40 runs. The power use varied from 145 to 71 mW, depending on the number of cycles and hence the charge state of the power source.

In 2007 Jiang *et al* [111] described their USB-powered mini-HVPS, which had dimensions of 47 mm × 56 mm × 25 mm. They used the commercial dc-to-dc converter from EMCO and performed separations with a HV in the range of 400 to 1500 V. One focus of their work which has not been widely considered elsewhere was on reducing the power wasted by the HVPS. One way in which they achieved this was by decreasing the number of components wherever possible. They highlighted that in many systems which use electrokinetic injection, the power consumption could be decreased by using a single HVPS and a system of relays instead of two HVPS and switching between the two; this is not an option if pinched sample injection is desired. They measured power consumption for three periods, during injection (1.9 W), separation (0.6 W) and idling (0.2 W) [111].

Earlier the LIF detection systems incorporated into the IC designed by Behnam *et al* [69] was discussed. The IC was also able to provide a voltage up to 300 V; further details solely on the HV part of the IC are described in an earlier paper [112]. The IC is less than 5 mm × 5 mm and has a power consumption of 28 mW. The HV CMOS chip was mounted on a 70 mm × 70 mm PCB to test, though this could be shrunk further with careful consideration of component placement.

Given the high voltage nature of CE, there will always need to be a reasonable amount of power usage and so the lifetime is limited by the capacity of batteries. The advantage of chip-based CE systems is that the channels tend to be quite short, and therefore an electric field can be established in the channel with the application of a lower voltage. Furthermore separations can be attained quicker and so more runs can be performed in a short amount of time. The smallest, lowest power and most flexible solutions discussed here were for the case where the HVPS was designed by using a HV dc-to-dc converter. Recent developments and reports on the use of dc-to-dc converters has meant that HVPS are no longer an issue for portable or *in-situ* CE systems.

8. Conclusions and outlook

Whilst at first glance it would seem relatively straight-forward to miniaturize CE into a portable format, there are clearly a number of compromises that must be made; the full effects of which need to be understood from the start of development to reduce further avoidable compromises. In the introduction, we listed six areas which need consideration. These six areas can be broken down into three sub-sections one of which is the fabrication of the device, be it chip or non-chip, with regards to: material choice channel/capillary shape, and all other device dimensions. The second section addressed the detection method of which there are a wide range of options, each with their individual merits and weaknesses. Finally the design and implementation of HVPS were considered. These need to be of low power, small in size and weight, and intrinsically safe.

We discussed the requirements of the ideal solution. Whilst the ideal device is an unrealistic concept, when designing portable or *in-situ* CE systems it is useful to identify which aspects of the ideal device are of most importance to the application at hand. For example, if the application suits a miniaturized CE system which will have access to a mains power supply then all the low power constraints are no longer as important. The ideal device is a useful concept to guide design and help understand the cost of compromises. Some of the requirements of *in-situ* systems overlap with portable systems, though there are clear differences between the two. Notably *in-situ* CE systems require complete autonomous control, whereas portable systems will have an operator. Further to this, a portable system requires its own power source; this would not be true of all *in-situ* systems.

Optical detection methods for miniaturized systems have been declining in favour of electrochemical methods, in particular CCD. A recent review on CCD for microseparation systems was given by Kubáň and Hauser [113] discussing recent developments over the last two years. There is a clear trend towards the use of CCD because it is simple to implement and suited to miniaturization.

The insulation layer between the detection electrodes and the channel should be made very thin. This results in a large capacitance and as a result the detection circuitry can be greatly simplified, either by operating at lower voltages and/or frequencies. This makes it possible to further miniaturize the detection circuitry, which saves both space and power. Another advantage is the ease of implementing a CCD system. In the case of chip-based CE systems, the additional processing steps that would be required are only in the making of the mask to

define the electrode and the insulation layer areas. For non-chip-based CE systems, fused-silica capillaries are readily available with a large range of inner and outer diameters. Internal diameters range from 2 to 700 μm, and outer diameters from 90 to 900 μm [114].

The small cross-sectional areas of capillaries and channels result in low power consumption which in turn leads to longer operational lifetime. With microfluidic channels, the fabrication of narrow channels is more easily achieved, leading to a reduction in the power consumption. Based on our review of the literature, the outlook for portable CE and *in-situ* systems is heading towards a lab-on-a-chip approach rather than a non-chip-based approach. Chip-based CE offers greater flexibility in terms of dimensions, fabrication method and materials. Further to this the implementation of various detection methods, particularly electrochemical detection methods, are more easily achieved. Small channel dimensions are important to ensure low current flow, which results in low Joule heating and lower power consumption. Whilst shorter channels decrease the electrical resistance and therefore increase electrical current, they offer the possibility of faster analysis times; reducing the channel length will increase the current flow but decrease the analysis time. It should also be noted however that a short channel length makes attaining separation of samples, especially where the constituents have similar values of electrophoretic mobility, more difficult. It is important when designing the miniaturized CE system that careful consideration is given to the types of sample that will be analysed.

Over the last 5–10 years there has been a strong push towards portable CE systems which has led to a variety of successful devices. Research has shown that battery powered small HVPS are possible; combining the lower power HVPS with the improvements in battery capacity over recent years enables long power supply lifetimes for the devices, without needing to compromise on size. It has also shown that numerous detection methods can be incorporated for both chip and non-chip-based CE systems; with certain methods favouring miniaturization better than others. Whilst the restraints of *in-situ* CE systems have been discussed in this review, a challenge for the CE research community now is the further development of *in-situ* CE analysis systems.

The work in this paper has focussed on portable and *in-situ* CE systems; the coupling of CE to other separation and detection methods was deemed out of the scope of this paper, e.g. the coupling of CE with mass spectrometry [115]. A quick search in the literature reveals a number of successful applications and can provide an interesting route forward to future portable instrumentation.

Many of the techniques used in the development of portable CE systems can be applied with a holistic approach to aid the development of *in-situ* CE systems. The main difference will be the requirement for autonomous sample procurement, from the monitored environment and device self-cleaning. The work on flow-injection analysis and sequence injection analysis has already addressed many of these issues.

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