



Capillary electrophoresis with contactless conductivity detection coupled to a sequential injection analysis manifold for extended automated monitoring applications

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ABSTRACT

A capillary electrophoresis (CE) instrument with capacitively coupled contactless conductivity detection (C⁴D) based on a sequential injection analysis (SIA) manifold was refined. Hydrodynamic injection was implemented to avoid a sampling bias by using a split-injection device based on a needle valve for precise adjustment. For safety and reliability, the integrity of the high voltage compartment at the detection end was fully maintained by implementing flushing of the high voltage interface through the capillary. With this set-up, extended fully automated monitoring applications are possible. The system was successfully tested in the field for the determination of the concentration levels of major inorganic cations and anions in a creek over a period of 5 days.

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1. Introduction

Instrumentation for capillary electrophoresis (CE) is much more simple than for column chromatography as the separation is achieved by the relatively straightforward application of voltages. High pressure pumps and eluents are not needed and the consumption of chemicals is very low. A significant further simplification was also brought about by the introduction of contactless conductivity detection (C⁴D), which, with the exception of a simple measuring cell based on a pair of short tubular electrodes, is fully electronic and thus less demanding in construction and power consumption than the common optical detection methods employing UV-radiation. For reviews see for example [1,2]. Field portable CE-instruments employing C⁴D have therefore been developed in our research group [3,4] and Hutchinson et al. [5] have demonstrated that a portable instrument may be employed for the identification of post-blast residues of IEDs (improvised explosive devices).

Capillary electrophoresis furthermore has potential for extended on-site measurement applications, such as in environmental monitoring or in process control. The coupling of conventional CE-instruments with flow-injection analysis (FIA) manifolds for sample handling ahead of the separation step has

indeed been reported for such applications. Arce et al. [6] have reported a system with analyte preconcentration for use in a water purification plant using a commercial CE-Instrument and indirect optical detection, and Sirén et al. [7] have reported an assembly for monitoring use in a paper mill.

Nevertheless, commercial CE-instruments designed for the laboratory are not well suited for on-site deployment and coupling to external sample handling manifolds. It is, on the other hand, relatively easy to construct a CE-separation unit as part of an extended FIA-manifold and such systems have been constructed by several researchers (see the recent review by Kubáň and Karlberg [8]). The use of C⁴D is also attractive for such a set-up and FIA-CE-C⁴D instruments have been reported [9–11]. Sprung et al. [10] detailed the construction of a system for on-line measurements, and Kubáň et al. [11] have demonstrated the on-line field monitoring of the drainage of a pasture for some inorganic anions and cations. The use of a sequential injection analysis (SIA) system, based on a syringe pump and a multi-position valve, instead of an FIA-manifold typically using a peristaltic pump, has several advantages, such as allowing sample pretreatment and automated flushing of the separation capillary. This combination was introduced by Růžicka and coworkers in 2002 [12,13] who used UV-detection. Kulka et al. [14] reported a similar system in 2006 and Horstkotte et al. [15,16] demonstrated the determination of nitrophenols. Zacharis et al. [17] designed an SIA-CE-instrument employing laser-induced fluorescence for detection. Wuersig et al. [18] used an SIA set-up to

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achieve fast injections into capillaries of only a few centimeters in length and could thus demonstrate the separation of inorganic cations and anions in approximately 10 s. C^4D was employed in the latter case for detection.

In this contribution we present an SI–CE– C^4D system designed for monitoring applications over extended unattended periods and demonstrate its functionality in several days of on-site monitoring of the concentrations of inorganic anions and cations in a creek. The new set-up incorporates a number of improvements compared to previous designs in order to achieve high reliability and specific adaptations to allow autonomous operation.

2. Experimental

2.1. Chemicals and materials

All chemicals were of reagent grade. Deionised water (Millipore, Bedford, MA, USA) was used throughout the experiments. Stock solutions (5 mmol L^{-1}) of chloride, nitrate, sulfate, nitrite, fluoride and phosphate were prepared from their potassium or sodium salts. Stock solutions (5 mmol L^{-1}) of ammonium, potassium, calcium, sodium, magnesium and lithium ions were prepared from their chloride salts. All chemicals were purchased from Fluka (Buchs, Switzerland) or Merck (Darmstadt, Germany). All multi-ion standards were prepared from these stock solutions. The separation buffer consisted of 12 mM L-histidine and 2 mM 18-crown-6 adjusted to pH 4 with acetic acid. The capillary was preconditioned with 1 M NaOH for 10 min and deionised water for 10 min prior to flushing with electrolyte solution (for 1 h). The capillary was then used continuously for successive analyses.

2.2. Instrumentation

The SIA manifold is based on a syringe pump (Cavro XLP 6000) and a 6-port channel selection valve (Cavro Smart Valve) (both purchased from Tecan, Crailsheim, Germany). The SIA–CE interface consists essentially of two consecutive T-junctions for connecting the capillary and electrophoretic ground electrode to the liquid channel. It was machined in a perspex block ($2\text{ cm} \times 2\text{ cm} \times 3\text{ cm}$); details have been given previously [19]. The micro-graduated splitting valve was obtained from Upchurch Scientific (P-470, Oak Harbor, WA, USA) and the isolation valves for pressurization from NResearch (HP225T021, Gümligen, Switzerland). All fluid connections to the selector valve were made with 0.02 in. inner diameter (id) and 1/16 in. outer diameter (od) Teflon PFA tubing (Upchurch Scientific) with the exception of the connection between the selector valve and the SIA–CE interface where 0.01 in. id and 1/16 in. od PEEK tubing (4 cm) was used in order to minimize dispersion.

The electrophoresis section is based on a dual polarity high voltage power supply (Spellman CZE2000, Pulborough, UK) with $\pm 30\text{ kV}$ maximum output. Polyimide coated fused silica capillaries of $50\text{ }\mu\text{m}$ id and $363\text{ }\mu\text{m}$ od from (Polymicro, Phoenix, AZ, USA) were used for separation. The detection end of the capillary was connected with a fitting to a perspex block, which contains a channel of 0.4 mm id and 2 cm length at the end of which the high voltage electrode is placed. This assembly was isolated in a safety cage made from perspex, which was equipped with a microswitch to interrupt the high voltage on opening. Detection was carried out with a C^4D -cell built in-house, and is based on two tubular electrodes of 4 mm length, which are separated by a gap of 1 mm and a Faradaic shield. Details on this detector can be found elsewhere [20]. The resulting signal was recorded with an e-corder 201 data acquisition system (eDAQ, Denistone East, NSW, Australia) connected to the USB-port of a personal computer.

For the field test the instrument was set up in a pumping station located next to the creek Kleine Aa, a tributary to Lake Sempach, Switzerland. A submersible pump conveyed a constant stream of water from the creek ($\sim 2\text{ L s}^{-1}$) into an overflowing bucket, from where a small part was diverted with a peristaltic pump to a beaker of 20 mL which was also overflowing (the excess was collected with a funnel underneath and led to a drain). Samples were aspirated into the SI-manifold from this beaker through an inlet filter ($10\text{ }\mu\text{m}$ pore size, Supelco, Buchs, Switzerland) in order to remove suspended matter. Occasional water samples were collected, filtered with $0.45\text{ }\mu\text{m}$ membrane filters, and inorganic anions and cations analyzed later in the laboratory by ion-chromatography (IC, Metrohm, Switzerland) within 2 days.

2.3. System control

The system was controlled with the personal computer using an RS232-serial connection to the syringe pump. The multi-position valve is daisy-chained to the syringe pump. Auxiliary TTL-output ports on the two units allow switching of the stop-valves, of the high voltage, the polarity of the high voltage and triggering of the recording of electropherograms with the help of a purpose built electronic interface. The two solenoid operated isolation valves were controlled via a special driver board obtained from the supplier of the valves (CoolDriver, 225D5X12, NResearch). The programming package LabVIEW (version 8.0 for Windows XP, from National Instruments, Austin, TX, USA) was used to write the control code for the SIA–CE system. Different modules were written to independently carry out tasks such as injection, flushing, separation etc. All modules were then assembled together to produce the instruction protocol for the entire analytical method. The program can be modified easily during the optimization steps or during setting up of the system.

3. Results and discussion

3.1. System design

A schematic drawing of the system is depicted in Fig. 1. The SI-manifold consists of the standard arrangement based on a two-way syringe pump and a multiport valve with a holding coil between the two units. This is used for the initial conditioning of the capillary by flushing with sodium hydroxide solution, rinsing the system with the separation buffer, and aspiration of a plug of the sample solution and passing this volume to the capillary inlet. Injection proper is carried out hydrodynamically. The volumes injected in capillary electrophoresis are in the nanoliter range and too small for direct handling with the SI-manifold. Thus only part of the dispensed sample plug is injected into the separation tubing by pressurization of the interface while pushing the sample plug past the capillary inlet. This is more difficult to implement than electrokinetic injection, but a sampling bias, which would arise with the latter mode, is avoided. Separation is carried out by applying the high voltage from the detection end, the second electrode in the SI–CE interface is grounded.

Two modifications have been made to the set-up compared to earlier designs [15,16,18]. The first of these concerns the method used for pressurization of the SI–CE interface for injection and flushing of the capillary. Previously, a length of flexible tubing was connected to the outlet of the interface, the end of which was closed with a valve for injection. Solution would thus be pumped into the expanding piece of tubing leading to a gradually increasing pressure. The performance of this set-up would depend on the length and the condition of the tubing. However, predictability and reproducibility are poor, and only one setting is possible which has to be

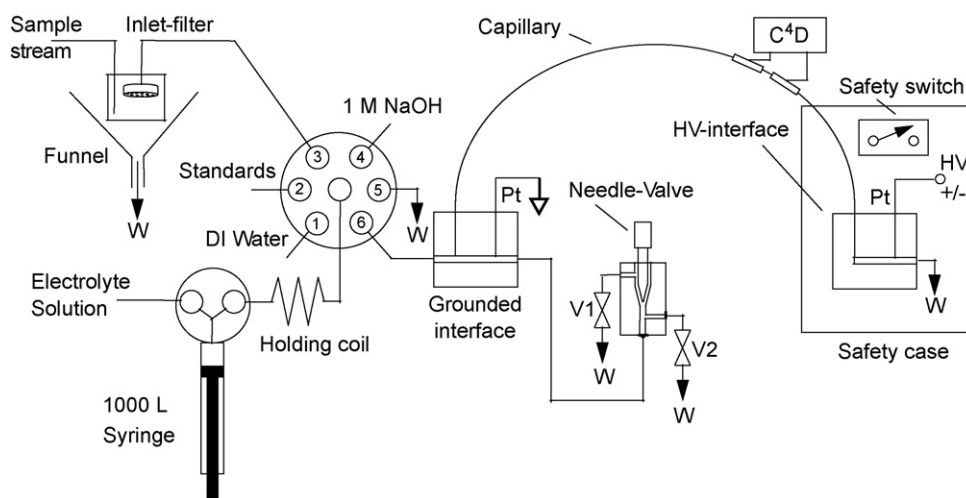


Fig. 1. Schematic drawing of the SI-CE-C⁴D system (not to scale). C⁴D: capacitively coupled contactless conductivity detector; HV: high voltage power supply; W: waste; Pt: platinum electrode; E: electrolyte solution. The high voltage interface is flushed through the capillary.

used for the two different tasks of injection and capillary flushing. The arrangement was thus replaced with an adjustable needle valve designed for the splitting of small flows into two streams (see Fig. 1). A graduated micrometer screw allows precise and reproducible setting of the splitting ratio and thus the backpressure created for injection on closing the solenoid operated isolation valve 1 (designated as V1 in the figure). Simultaneous closure of both valves (V1 and V2) allows fast capillary flushing.

The second modification concerns the detection end of the separation capillary where the high voltage is applied. In CE in general, when the separation voltage is applied, electrolysis occurs at the electrodes at both ends of the capillary, thus changing the ionic composition of the adjacent solutions. As this electrolyzed buffer can move through the capillary by electrokinetic and electroosmotic flow, it is frequently necessary not only to rinse the capillary but also to change the solutions in the containers at both ends. When carrying out long-term unattended operation, these steps need to be automated. At the grounded injection end, buffer replacement is trivial to implement with the SIA set-up, but this is not so easy at the high voltage end. In the previous system reported by our research group [18], which was not intended for long-term unattended operation, the buffer solution was simply changed manually. Horstkotte et al. [15,16] implemented automated flushing at the high voltage end by leading a separate tube from the multi-selection valve of the SI-manifold to the high voltage side and, in order to achieve electrical isolation, buffer solution was passed to the interface by letting it fall dropwise into it from above. In preliminary experiments, a similar system was set up in our laboratory. However, at least in our hands, such an arrangement was found not to be entirely satisfactory. While the configuration would work fine for some time, unpredictable electrical arcing was found to occur at times in dependence on air humidity, conditions of sur-

faces and the voltage level employed. As the electrolyte filled tubing to the selection valve constitutes a low conductivity electrical path, such arcing was then found to lead to the destruction of part of the electronic instrumentation. It was thus deemed essential to completely isolate the interface at the high voltage end of the capillary by enclosing it on all sides and maintaining complete integrity of this cage in order to be able to use high separation voltages. A special interface with minimal internal volume was thus designed in order to allow efficient flushing of the liquid volume at the high voltage electrode directly through the capillary. The arrangement essentially consists of an 'ion-delay' channel with a round cross-section of 0.4 mm diameter and 2 cm length between the end of the capillary and the high voltage electrode. The greatly enlarged cross-section compared to the internal channel of the capillary caused minimal field strength in this section of the separation manifold, and migration of any constituents from the solution surrounding the electrode back to the detector was not achieved within the time scale of a single separation. For flushing of the capillary and the high voltage interface, both outlets of the splitting valve were blocked by actuating both isolations valves (V1 and V2) in order to push all of the dispensed fluid through the separation tubing. In order to be able to carry this out relatively rapidly, isolation valves which can hold pressures up to 100 psi (~6 bar) were employed. Excess liquid was collected within the safety cage.

3.2. Operation

An overview of a typical sequence of the operations is given in Table 1. The protocol starts with an uptake of electrolyte solution from the reservoir. Rinsing steps follow for the flushing of the capillary and the high voltage interface. Note, that the flushing through the capillary has to be carried out at a relatively low flow rate in

Table 1
Typical operation sequence.

Step	Operation	Position of selection valve	Volume dispensed (μL)	Flow rate (μL s ⁻¹)	V1	V2
1	Buffer aspiration	–	900	20	Closed	Closed
2	Flushing of the SI-CE interface	6	100	20	Open	Open
3	Flushing of capillary and HV-interface	6	25	0.2	Closed	Closed
4	Backflush of the inlet filter	3	400	117	Open	Open
5	Pick up of sample	3	15	20	Closed	Closed
6	Sample injection	6	15	4	Open	Closed
7	Flushing of the SI-CE interface	6	100	20	Open	Open
8	Electrophoretic separation	6	Variable	67	Open	Open
9	Flushing of the SI-CE interface	6	50	20	Open	Open

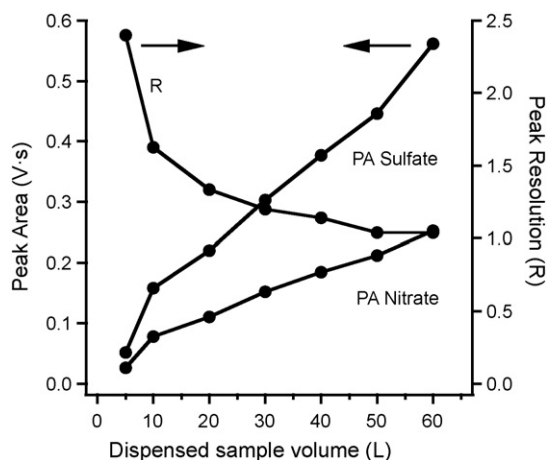


Fig. 2. Effect of dispensed sample volumes on peak area and resolution. Analytes: NO_3^- , SO_4^{2-} 50 μM in deionised water. Background electrolyte: His 12 mM, 18-crown-6 2 mM adjusted to pH 4 with acetic acid. Pumping rate: 4 $\mu\text{L s}^{-1}$. CE conditions: capillary 50 μm id, $l/l = 35 \text{ cm}/60 \text{ cm}$, $U = 20 \text{ kV}$.

order not to exceed the holding pressure of the valves, but can be carried out in just over 2 min. Subsequently, a backflush of the inlet tube and filter is performed removing previous sample from the tube and particles left on the outer surface of the inlet filter, thus preventing blockage due to accumulation of solids. Backflush of the filter is not needed for aspiration of standards, which were passed to the system via an alternate port of the selection valve. For sequential analysis of anions and cations, all steps in the table are repeated, with the polarity of the applied high voltage automatically switched prior to step 1 of each sequence.

The most critical step is the controlled and reproducible injection of sample into the capillary. The volume injected has to be optimized and a suitable compromise has to be found between sensitivity (peak area) and selectivity (peak resolution). Large volumes lead to high peak areas, but may also cause an overlap of peaks. The amount injected is determined by the pressure, length of the sample plug passing through the SI–CE interface and the flow velocity in the interface. These parameters in turn are controlled by the pumping rate of the syringe, the backpressure as adjusted by the splitting valve, and the dispensed sample volume. Thus an optimization has to be carried out by variation of these partially interdependent parameters. For this task, a standard of two inorganic anions (NO_3^- , SO_4^{2-}) at 50 μM and a separation buffer consisting of 12 mM histidine adjusted to a pH-value of 4 with acetic acid were used. First, the setting of the splitting valve and the flow rate was established by variation of these parameters for a fixed dispensed plug of 15 μL of the standard mixture. It was found that a flow rate of 4 $\mu\text{L s}^{-1}$ and a setting of the valve which gave a nominal splitting ratio of 1.5:100 (this is the splitting ratio measured without the backpressure from the capillary and corresponds to a numerical setting on the adjustment scale of the valve of 0.10) gave peaks which were neither of inadequate sensitivity nor overly broadened, and did not lead to excess backpressure (as otherwise indicated by a leakage of the valve). In a second step, a fine adjustment was carried out by variation of the length of the dispensed sample plug. The results in terms of peak area and peak resolution are shown in Fig. 2. As expected, the resolution between NO_3^- and SO_4^{2-} decreases with an increase in peak areas as the volume of the sample plug is increased. The actual setting to be chosen depends on the application at hand. As the resolution is dependent on the concentration, for relatively high concentrations smaller dispensed volumes will be necessary to avoid peak overlaps, while for low concentrations, larger volumes may be injected in order to achieve low limits of detection.

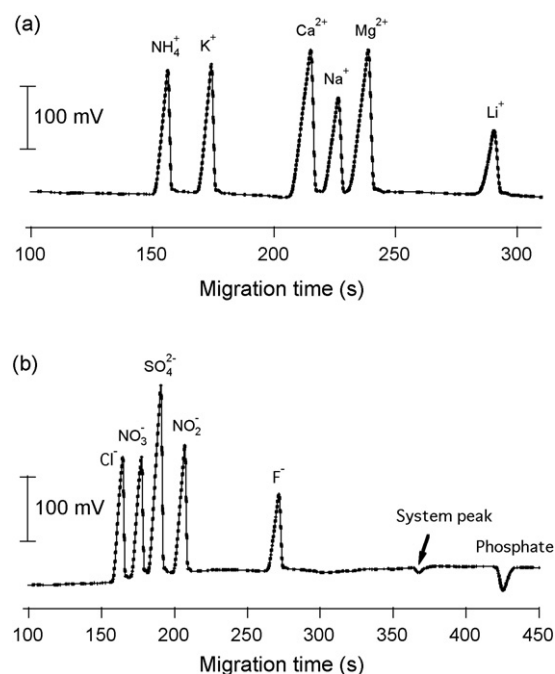


Fig. 3. Analysis of standard solutions containing either inorganic cations or inorganic anions prepared in deionised water. (a) Cations (50 μM), dispensed volume: 40 μL . (b) Anions (50 μM), dispensed volume: 60 μL . Other conditions as for Fig. 2.

3.3. Performance

A separation buffer system based on histidine and acetic acid previously reported to be suitable for the determination of inorganic cations as well as of anions by CE- C^4D [11,21], was adapted for the separation of the cations K^+ , NH_4^+ , Na^+ , Ca^{2+} , Mg^{2+} , Li^+ and the anions Cl^- , NO_3^- , SO_4^{2-} , NO_2^- , F^- and phosphate by subsequent electrophoresis with switched polarity and without using electroosmotic flow reversal. Optimization of the buffer composition was carried out by varying the concentration of histidine and of the pH-value by changing the amount of acetic acid added. Low histidine concentrations were found to give poor resolution of the anions Cl^- , NO_3^- , SO_4^{2-} and NO_2^- ; whereas high concentrations of histidine could not be used with low pH (high concentration of acetic acid), as the electrophoretic baseline was then not stable due to Joule heating. The best compromise electrolyte composition for both anion and cation separations was found to be 12 mM histidine and 2 mM 18-crown-6, adjusted to pH 4 with acetic acid. The crown ether improves the separation of some of the cations, but does not have an effect on the anion separation.

An example of the subsequent analysis of a standard mixture of cations and anions at 50 μM is shown in Fig. 3 using dispensed volumes of 40 and 60 μL respectively. As can be seen, baseline resolution is possible under these conditions. The calibration data obtained using the optimized conditions is given in Table 2. The detection limits achieved for the conditions are in the order of 0.5–1 μM and calibration curves were acquired from about 2 to 100 μM . For higher concentrations peak overlap would occur. The reproducibility of the measurement of peak areas was found to be between about 2 and 4%.

The system was then set up for a supervised test run over a period of 24 h, in which repeated measurements of the standard mixture of the cations and anions of 50 μM at intervals of 30 min were carried out. The results for the peak areas are shown in Fig. 4. The maximum deviations are less than $\pm 4\%$, which demonstrates the suitability of the system for automated operation.

Table 2

Calibration ranges, detection limits (LODs) and reproducibility for the determination of inorganic cations and anions with large dispensed volume injections.

Ion	Dispensed volume (μL)	Range (μM) ^a	Correlation coefficient r	LOD ^b (μM)	RSD% MT ^c ($n=6$)	RSD% PA ^d ($n=6$)
NH_4^+	40	2.5–100	0.9995	1.0	0.6	3.3
K^+	40	2.5–100	0.9994	1.0	0.6	3.6
Ca^{2+}	40	2.0–100	0.9997	0.7	0.8	3.9
Na^+	40	5.0–100	0.9995	1.0	0.6	4.0
Mg^{2+}	40	2.0–100	0.9998	0.7	0.9	3.7
Li^+	40	5.0–100	0.9995	2.0	0.9	3.0
Cl^-	60	2.5–100	0.9997	0.5	0.4	1.8
NO_3^-	60	2.5–100	0.9996	0.5	0.5	2.4
SO_4^{2-}	60	2.0–100	1.0000	0.5	0.5	3.3
NO_2^-	60	2.5–100	0.9996	1.0	0.7	3.2
F^-	60	5.0–100	0.9978	2.0	1.0	4.1
Phosphate	60	15.0–100	0.9979	5.0	1.8	5.8

^a 5 concentrations.^b Based on peak heights corresponding to 3 times the baseline noise.^c Migration time.^d Peak area.

3.4. Field test

In order to further evaluate the potential for unattended monitoring the system was set up at a pumping station next to the creek Kleine Aa, a tributary to Lake Sempach. It was found that the concentrations of some of the ions were higher than the conditions reported above allowed, and thus the dispensed sample volumes had to be reduced to 5 and 20 μL for the cations and anions respectively in order to prevent peak overlap due to overload. On the

other hand, some of the ions which had been included in the standard mixture could not be found in the natural water system at detectable levels, even for large volume injections. Automatic analysis of the water from the creek was then carried out at intervals of around 35 min for 5 days during a period of frequent rain (end of April, 2009). Cations and anions were determined sequentially by changing the polarity of the separation voltage as described above. As there was a large amount of suspended matter in the sample stream, filtering with automated backflushing was essential

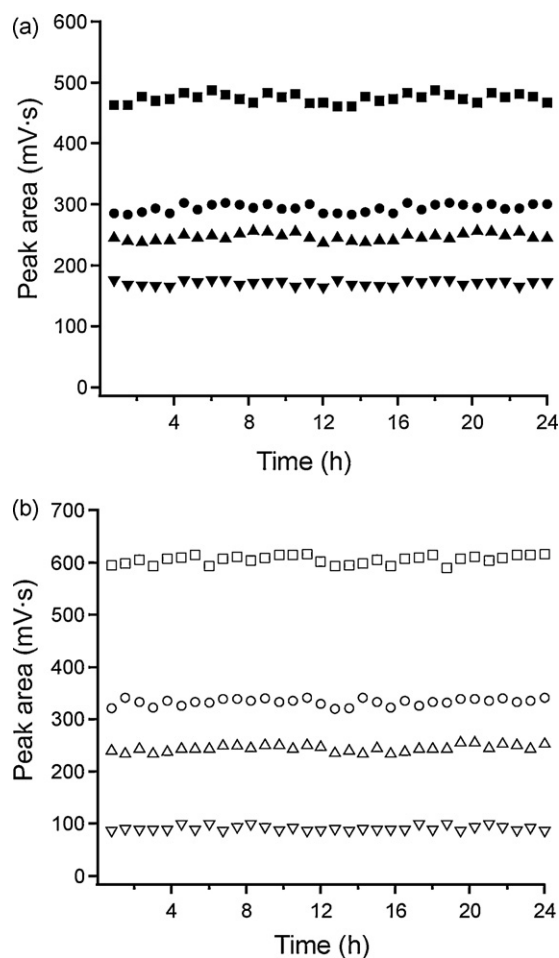


Fig. 4. Reproducibility of peak areas for some inorganic ions over a continuous 24 h run. (a) Cations 50 μM : Ca^{2+} (■), K^+ (●), Na^+ (▲) (○-○) Li^+ (▼). (b) Anions: 50 μM : SO_4^{2-} (□), NO_3^- (○), F^- (△), and phosphate (▽). Other conditions as for Fig. 3.

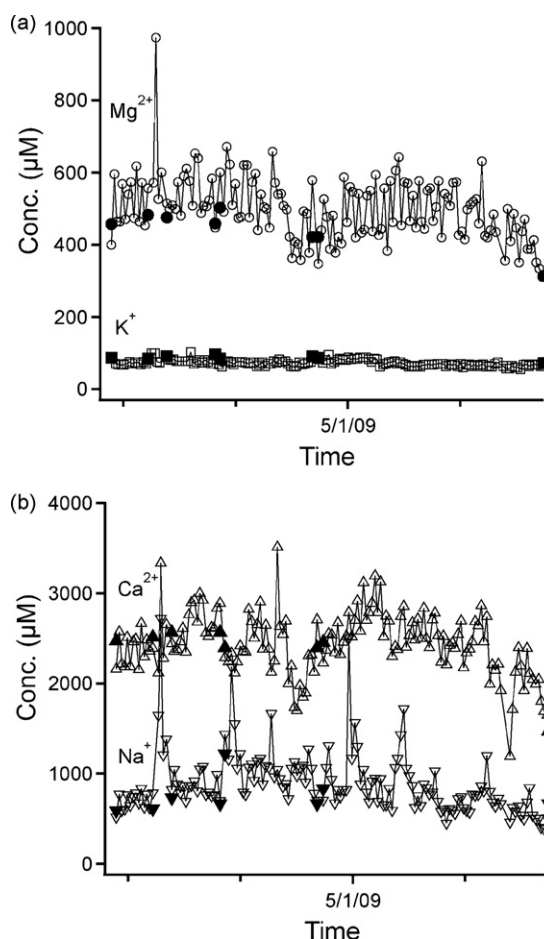


Fig. 5. Variations of some cation concentrations in the Kleine Aa during a rainy period. The solid symbols represent reference measurements for discrete samples carried out later in the laboratory by ion-chromatography.

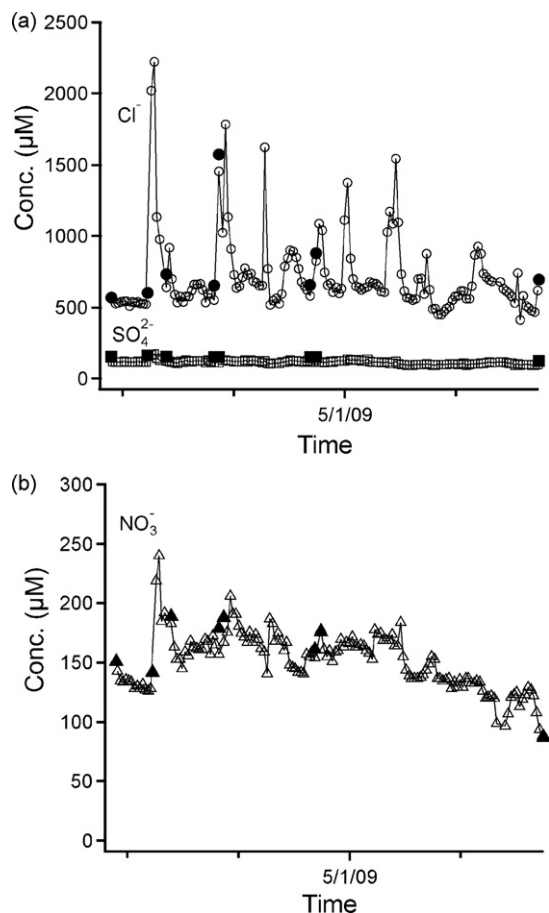


Fig. 6. Variations of some anion concentrations in the Kleine Aa during a rainy period. The solid symbols represent reference measurements for discrete samples carried out later in the laboratory by ion-chromatography.

in order to maintain the integrity of the system. The results for the monitoring test are shown in Figs. 5 and 6 for the cations and anions respectively, and convincingly show that the system is suitable for unattended long-term measuring tasks. Also included are the results for discrete samples, which were analyzed later in the laboratory using ion-chromatography, demonstrating the accuracy of the data obtained. The correlation coefficients (r) between the concentrations obtained with the SI-CE system at the time of sampling of the discrete batches and the results obtained for these by ion-chromatography are 0.989, 0.921, 0.894 for Cl^- , NO_3^- , SO_4^{2-} and 0.845, 0.891, 0.927, 0.826 for K^+ , Ca^{2+} , Na^+ , Mg^{2+} respectively. The correlation coefficients between the results from SI-CE-C⁴D and from IC are deemed acceptable considering that some deviations can be expected due to possible sampling bias.

4. Conclusions

The SI-CE-C⁴D system built in-house was found to be suitable for extended and unattended monitoring application. The use of both large and small dispensed sample volumes allows to quantify samples with very wide concentration ranges. Its flexibility and broad applicability to ion analysis allows easy adaptation to different tasks. The data in our trial was evaluated after completion of the monitoring run, but by developing appropriate software routines, real time concentration reporting should also be possible. Furthermore, connection of the instrument to the Internet for remote querying of data can be envisaged.

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