Research Article

Advancements in capacitance-to-digital converter-based C⁴D technology for detection in capillary electrophoresis using amplified excitation voltages and comparison to classical and open-source C⁴Ds

This work introduces new hardware configurations for a capacitively coupled contactless conductivity detector (C⁴D) based on capacitance-to-digital conversion (CDC) technology for CE. The aim was to improve sensitivity, handling, price, and portability of CDC-based C⁴D detectors (CDCD) to reach LODs similar to classic C⁴Ds with more sophisticated electric circuits. To achieve this, a systematic study on the CDCDs was carried out including a direct comparison to already established C⁴D setups. Instrumental setups differing in electrode lengths, measurement modes, and amplification of excitation voltages were investigated to achieve LODs for alkalimetalions of 4 to 12 μM, similar to LODs obtained by classic C⁴D setups. Lowest LODs were achieved for a setup with two 10 mm electrodes at a distance of 0.2 mm and an excitation voltage of 24 V. The detection head was exceptionally lightweight with only 2.6 g and covered only 20 mm of the capillary on total. This allowed the use of multiple detectors along the separation path to enable spatial tracking of analytes during separation. The entirely battery-powered detector assembly weighs less than 200 g, and the data are transmitted wirelessly for possible portable applications. The freely accessible hardware and software were optimized for fully automated measurements with real time data plotting and allowed handling multidetector setups. The new developments were applied to quantify the potassium salt of glyphosate in its herbicide formulation.

Keywords:
Automated measurements / Capacitance-to-digital conversion / Capacitively coupled contactless conductivity detection / Glyphosate formulation analysis / Multidetector setup
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Additional supporting information may be found online in the Supporting Information section at the end of the article.

1 Introduction

The miniaturization of the analytical separation techniques increases separation efficiency and speed of the separation. It helps to decrease running costs, to enhance portability as well as to reduce sample, solvent, and reagent consumption and finally the amount of waste generated during the separation process [1]. On the one hand, this led to the development of microchip separation systems [2–4] and Lab-on-a-Chip technologies [5] and on the other hand to portable separation systems [6]. The latter not only requires miniaturization of the separation path, but also of the entire setup including liquid handling, driving force (pressure, voltage) and detection head. One promising separation technique for miniaturization is CE, since the instrumentation is simple and its applicability for portable systems has already been shown [7–9]. Common detection systems for CE are UV absorbance [10], MS [11], laser or LED-induced fluorescence [12,13], electrochemical detection [14], or capacitively coupled...
contactless conductivity detection (C^4D) [15]. In principle, the most universal detection system for CE is C^4D due to the separation of charged analytes. C^4D technology is used to measure the change of the complex conductivity ( admittance) between electrodes in the presence of an external excitation signal [16,17]. Different detectors were presented: an axial geometry of C^4D electrodes for CE was reported independently by da Silva and do Lago [18] as well as by Zemann et al. [19]. The electrodes were either made of silver paint or consisted of parts of hypodermic needles, the latter enabling to freely position the detection head along the capillary. In both cases, the removal of the protective outer coating of the capillary was not necessary. In addition to home-built C^4Ds, both commercial C^4D and an open-source project, called OpenC^4D, were introduced [15,20]. Descriptions of the working principle, development, and the universal applicability of C^4Ds can be found in [15] and references therein.

Capacitance-to-digital conversion (CDC) technology is similar to C^4D, because both technologies use a similar working principle [16,17,21]. This leads to the fact, that the output value of the CDC is not only affected by changes in capacitance, but it is also influenced by the capacitance and resistance to ground as well as by parallel and serial resistances to the capacitor to be measured [21]. The impact to the output value by the serial resistance can be exploited by using the CDC-technology for a C^4D. It can be seen from alternating current theory that CDC-technology does not distinguish between a change in output value resulting from a change in capacitance or a change in conductivity when the phase shift between the excitation and the pick-up voltage is not considered.

CDC-technology as a detection unit has been used in various applications. Takeuchi et al. used a CDC with an integrated circuit (IC) on an evaluation board, together with two 2 mm long electrodes on a 1.45 mm polyimide coated glass tube as replacement for a conventional galvanic bipolar pulse conductance detector for suppressed ion chromatography [22]. Kiplagat et al. used the same evaluation board in a portable ion chromatographic system [23]. The detection head used, was equipped with 10 mm electrodes made from hypodermic needles. For metal cations separated by ion chromatography in a 75 μm id fused silica capillary, the LOD was in the range of 1–2 μM. Drevinskas et al. used a similar setup for conductivity detection in CE. They utilized a CDC-IC together with an Arduino-based microcontroller. The influence of electrode length, measurement mode (single-ended versus differential), as well as different power supplies were investigated for best LOQ, ranging from 250 to 500 nM for alkali metal ions, and baseline stability [24,25]. This detector was also applied in a portable CE system [26], a CE system integrated into a drone [27] and in a setup for multichannel separations [28]. A microcontroller with a similar CDC-IC was equipped with planar electrodes with an interdigital finger design for the detection of the size and speed of microdroplets [29]. Another application for microdroplets is described by Isgor et al., they analyzed the content of microdroplets using coplanar electrodes [30].

In this work, we introduce for the first time a CDC-based C^4D detector (CDC-IC, AD7745) in combination with an operational amplifier (LT1360) for enhanced excitation voltages up to 24 V and therefore lower LODs. We also provide a more systematic and extensive study of instrumental configurations compared to previous studies of the CDC-based C^4D detectors (CDCD). The parameters considered are electrode length and the use of a differential versus single-ended measurement mode. To assess the performance, a direct comparison between the new CDCD configurations presented here, the OpenC^4D and a commercial C^4D is provided. Further important advancements of the developed CDCD setup here were ease of handling, the possibility of battery supply and wireless data transmission, as well as compact design, maximum flexibility with regard to positioning the detector head along the capillary, and a high degree of automation with real time data plotting. As model application, the analysis of glyphosate and potassium in a herbicide formulation is presented.

2 Materials and methods

2.1 Chemicals

l-Histidine (His) (USP grade) and glyphosate (>99.7%) were purchased from Fluka (Buchs, Switzerland). 2-(N-morpholino)ethane sulfonic acid monohydrate (MES) (>99.5%), potassium dihydrogen phosphate (KH2PO4) (>98.0%), and sodium hydroxide (>98.0%) were purchased from Sigma-Aldrich (Steinheim, Germany), lithium chloride monohydrate (LiCl) (>99%) and tris(hydroxymethyl)aminomethane (Tris) (99.8–100.1%) were delivered by Merck (Darmstadt, Germany). Hydrochloric acid and (3-glycidoxypropyl)trimethoxysilane (GPTMS) (97%) were purchased from Thermo Fisher Scientific (Schwerte, Germany), and methanol for LC-MS (99.95%) was bought from Th. Geyer (Renningen, Germany). Roundup Powerflex was purchased from Bayer (Leverkusen, Germany). Further, doubly distilled water (ddH2O) from a purification system from ELGA LabWater (Celle, Germany) was used.

2.2 Instrumentation

CE-analyses were performed using a Prince 560 capillary electrophoresis system from Prince Technologies (Emmen, The Netherlands) with WPrince 7.1.02.10.01 software. For conductivity detection, different self-developed CDCDs were used as well as an OpenC^4D (OC^4D), see [20]. Further, a commercial C^4D (eDAQ), an ET120 C^4D Headstage for CE and an ER225 Contactless Conductivity C^4D System, all from eDAQ (Denistone East, Australia), were used for comparison and as a secondary detector. The eDAQ was used with the included PowerChrom 2.8.3 software with C^4D-Profiler for the determination of optimal settings. The CDC-IC AD7745 was from Analog Devices (Norwood, MA). A replica of an
Arduino Nano, a NRF24L01+ radio module and battery charger TP4056 were purchased from Makershop (Armsheim, Germany). The operational amplifier LT1360 and the voltage regulator LT1761-5 were ordered from Linear Technologies (Milpitas, CA). The voltage regulator LP2992IM5-5.0 was from Texas Instruments (Dallas, TX). The lithium polymer batteries, two EREMIT 3.7 V 4.000 mAh High Cap., equipped with an integrated protective circuitry and alligator claps, were purchased from Eremit (Eschborn, Germany). The printed circuit boards (PCB) were developed with the software Eagle from Autodesk (Mill Valley, CA) or KiCad and manufactured by Multi Circuit Boards (Brunnthal, Germany). Small electronic parts were purchased from Mouser (Mansfield, TX) or Reichelt (Sande, Germany). During the development for automated measurements, a 7100 Agilent CE System (Waldbronn, Germany) was used. Origin 2020 from OriginLab (Northampton, MA) was used for peak evaluation and data smoothing with a five-point window adjacent averaging function. Further calculations were performed with Excel 2019 from Microsoft (Redmond, WA).

### 2.3 Sample preparation and electrophoretic separation

#### 2.3.1 Detector evaluation

The BGE was an aqueous 20 mM MES/His buffer (pH 6.1). Model analyte stock solutions of 60 mM were made for KH₂PO₄, Tris, and LiCl (dried at 120°C overnight for dehydration). A mixture with a concentration of 3000 μM for each of the three substances was made and diluted prior to injection. All solutions were stored at −18°C. The separation was performed in a bare fused silica capillary from Polymicro Technologies (Phoenix, AZ) with 50 μm id and 50 cm length. Prior to the first use, the capillary was purged with MeOH, 1 M HCl, 1 M NaOH, and ddH₂O for 20 min each at 1.5 bar. Prior to each analysis, the capillary was sequentially flushed with BGE for 3 min. The sample was injected for 5 s at 50 mbar. All solutions were stored at −18°C. The separation voltage was set to 14.0 kV (slope 6 kV/s). The resulting current was 2.6 μA. The CDCD or the OC²D were mounted at an effective length (L_eff) of 31.5 mm. The eDAQ was mounted at L_eff = 33.5 mm and was configured for an excitation frequency of 200 kHz at an amplitude of 100% and an activated head stage gain. For differential measurements with the CDCD, a reference capillary (50 μm id) filled with BGE was used.

#### 2.3.2 Model application

The CE-separation of a sample of Roundup PowerFlex, a glyphosate potassium salt containing herbicide formulation, was carried out in the same 20 mM MES/His buffer. The sample was diluted 1:20 000 with ddH₂O and stored at −18°C. The separation was performed in a bare silica fused capillary with a length of 65 cm and an id of 50 μm. The position of the CDCD was at L_eff = 45.5 cm.

For the determination of K⁺, the capillary was purged at 1.5 bar prior to the first usage with MeOH, 1 M HCl, 1 M NaOH, and ddH₂O for 20 min each. Prior to each run, the capillary was flushed at 1 bar for 2.5 min with 0.1 M NaOH, for 1.5 min with ddH₂O, and for 5 min with BGE. The separation voltage was set to 20 kV.

For the determination of glyphosate, the capillary was preconditioned prior to the first run with 1 M NaOH for 20 min at 1.5 bar and filled with a 3 mM glyphosate solution and immersed for approximately 60 h at room temperature to achieve a surface coating with glyphosate as the binding to bare fused silica is very strong and more or less irreversible at pH 6.1. No leaching was observed, which is demonstrated by the high migration time precision of <1.5% RSD (n = 15) [31]. After immersion, the capillary was immediately used for CE separation. Between runs, flushing with BGE for 5 min at 0.75 bar was sufficient. The sample was injected at 50 mbar for 5 s, followed by injecting a plug of BGE for 5 s × 50 mbar. During separation –20 kV and 50 mbar were applied. The glass vials containing samples with glyphosate were coated with GPTMS to prevent its adsorption to the surface using a procedure adopted from Shao et al. [32]: 10 min ultrasonication in 1 M NaOH, 1 M HCl, ddH₂O. After each step, the vials were rinsed with ddH₂O. The cleaned vials were then immersed in a mixture of 2 mL GPTMS and 18 mL ddH₂O and ultrasonicated for 10 min. After another 30 min, the mixture was removed and the vials left empty. The whole procedure was repeated on the following day.

### 2.4 Capacitance detection system design

A scheme of the entire CDCD assembly is shown in Fig. 1A with its components. On the CE side, two detection devices were mounted. Each consisted of the detection head on the capillary and a modular supply unit. The data were transmitted wirelessly to the master device which was connected to a computer. The wireless connection was established automatically after an initial learning step. A home-written Python 3 program with graphical user interface was used for data acquisition allowing automated and manual measurements with up to five detectors simultaneously. The data were plotted in real time. For automated measurements, the trigger from the CE could be connected either to one of the detection devices or to the master device. The trigger was designed to work with different instruments (a 7100 Agilent CE System requiring an additional module [see Supporting information] and a Prince 560 capillary electrophoresis system).

The detection device consisted of two parts: the detection head and the supply unit. A schematic diagram of the main part of the circuit of the detection head is depicted in Fig. 1B and was adapted from the circuitry published by Drevinskas et al. [25]: only the main component, the CDC-IC AD7745, and its voltage supply, LT1761-5 (see Supporting information), were identical to the published circuitry. The excitation
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3 Results and discussion

3.1 Optimization of CDCDs

To investigate the capabilities of CDCDs, a CE-separation of equimolar mixtures of KH₂PO₄, LiCl, and Tris was defined as the reference system [25]. The concentrations ranged between 3 and 1500 μM. As BGE, a 20 mM MES/His electrolyte (pH 6.1) was chosen since it proved advantageous for the CE-C⁴D [15,35–38]. Over our entire investigation high migration time precision (≤1.6% RSD [n = 3], 0.8% on average) was achieved.

To characterize the CDCDs, the LODs and the sensitivity (based on the slope of the calibration curve using the peak area) were determined. A further parameter was the plate number to estimate the size of the detection window. All figures of merit are summarized in Table 1 and partially displayed in Fig. 2. To estimate LOD and LOQ via a S/N of 3 and 10, the S/N for every concentration was calculated based on the signal height of analyte peaks and the peak-to-peak noise. Linear regression between the two points nearest to the associated S/N was made and the concentration corresponding to the S/N was determined. The slope of the calibration curve of the peak area was determined for the range 250 μM (approx. LOQ of Li⁺ for most detectors) to 1500 μM. The plate number N was calculated from the full width at half maximum FWHM and the migration time tₘ (peak maximum) using

\[ N = 8 \times \ln(2) \times \left( \frac{t_m}{FWHM} \right)^2. \]

Drevinskas et al. showed that a shielding around the entire detector resulted in a low noise. They also demonstrated that the electrode length has a crucial impact on the S/N: longer electrodes reveal higher S/N [24,25]. For this reason and for the sake of simplicity, we started with two 20 mm long electrodes with shielding from the surroundings and used the
Table 1. Overview over all figures of merit for the CDCDs, the OC4D, and the eDAQ

| Detector Configuration | 2×05  | 2×10 | 2×15 | 2×20 | 4×10 | 4×20 | 2×10 | 2×15 | 2×20 | 4×10 | 4×20 | OC4D | eDAQ |
|------------------------|-------|------|------|------|------|------|------|------|------|------|------|------|------|
| E/P (mm)               | 5/5   | 10/10| 15/15| 20/20| 10/10| 15/15| 20/20| 10/10| 15/15| 20/20| 10/10| 20/20|       |
| LOD (μM)               |       |      |      |      |      |      |      |      |      |      |      |      |       |
| Li⁺                    | 1013  | 93.3 | 197.2| 291.5| 62.9 | 59.8 | 3.9  | 8.3  | 8.8  | 8.7  | 6.6  | 7.6  | 3.7  |
| TrisH⁺                 | -     | 156.4| 376.4| 655.8| 92.4 | 152.5| 12.2 | 16.4 | 22.3 | 20.7 | 15.4 | 12.3 | 8.3  |
| LOQ (μM)               |       |      |      |      |      |      |      |      |      |      |      |      |       |
| Li⁺                    | 206   | 597  | 1181 | 132  | 172  | 9.9  | 10.4 | 24.1 | 18.1 | 14.0 | 14.7 | 8.9  |       |
| TrisH⁺                 | -     | 406  | 1188 | -    | 300  | 359  | 17.8 | 23.1 | 42.4 | 32.9 | 27.3 | 27.0 | 14.5 |
| Li⁺ 125 μM Height (a.u.) | 0.267 | 0.270| 0.257| 0.263| 0.252| 1.288| 1.338| 1.160| 1.141| 1.141|      |      |       |
| S/N                    | 3.8   | 2.1  | 1.4  | 5.0  | 4.6  | 61.3 | 46.1 | 27.6 | 32.6 | 40.8 | 33.76| 66.4 |
| N(10^3)                | 20.7 ±1.1| 17.9 ±3.4| 30.5 ±10.8| 223 ±2.2| 23.8 ±6.8| 235 ±0.8| 21.8 ±0.9| 23.1 ±1.4| 22.7 ±0.5| 243 ±0.1| 56.4 ±5.2| 71.1 ±2.0|
| Li⁺ 500 μM Height (a.u.) | 0.583 | 0.811| 0.796| 0.712| 0.732| 0.730| 3.263| 3.558| 3.418| 3.325| 3.405|      |       |
| S/N                    | 2.0   | 11.6 | 6.1  | 3.8  | 13.8 | 13.3 | 155.4| 122.7| 81.4 | 95.0 | 121.6| 81.49| 168.0|
| N(10^3)                | 20.5 ±6.9| 12.6 ±0.8| 12.2 ±0.3| 14.7 ±1.1| 13.0 ±0.4| 13.2 ±0.4| 14.8 ±0.4| 13.5 ±0.7| 13.9 ±0.6| 14.4 ±0.3| 14.3 ±0.3| 19.5 ±0.3| 28.7 ±0.8|
| Noise (a.u.)           | 0.286 | 0.070| 0.131| 0.186| 0.053| 0.055| 0.021| 0.029| 0.042| 0.035| 0.028|      |       |
| Slope* (a.u. ± %)      | -     | 4.52 ±1.7| 4.06 ±3.6| 4.16 ±7.0| 4.79 ±5.4| 3.88 ±3.0| 17.59 ±2.7| 24.64 ±7.6| 21.54 ±2.8| 16.22 ±5.5| 19.33 ±3.2|       |

* Slope of peak area for Li⁺

The CDCD setups are compared regarding: shielding configuration; measurement modes of the CDC (single-ended (2 electrodes, 2×) and differential mode (4 electrodes, 4×); reference electrodes: connected to negative input of CDC; inserted capillary filled with BGE); length of excitation (E); and pick-up (P) electrodes. LOD and LOQ of K⁺, Li⁺, and TrisH⁺, if the upper calibration range limit is not exceeded (1500 μM); peak heights, S/N, and plate number (N) for a peak caused by a 125 and 500 μM Li⁺ sample; peak-to-peak noise; slope of the calibration curve of the peak area (250–1500 μM).
Figure 2. (A) LOD (S/N = 3, Li⁺) (B) peak-to-peak noise (plain bars) and peak height (n = 3) using shielded (-S, gray) and shielded plus amplified (-SA, light gray) CDCDs, OC³D and commercial C 4D (eDAQ) determined from a CE separation of K⁺, Li⁺, and TriH⁺. Common nomenclature in (A,B,C): For CDCD, 2 × (single-ended mode) and 4 × (differential mode) represent the number of electrodes and 05, 10, 15, 20 represents the electrode length in mm. Detector settings: CDCD: excitation voltage: 32 kHz, square wave, amplitude 5 V (-S) and 24 V (-SA); L_{eff} = 31.5 cm. OC³D: excitation voltage: 1.1 MHz, sinus wave, amplitude 5 V; L_{eff} = 31.5 cm. eDAQ: excitation voltage: 200 kHz, 100% amplitude, activated head stage gain; L_{eff} = 33.5 cm. Separation conditions: 20 mM MES/His-BGE, injection: 5 s × 50 mbar, fused silica capillary (50 cm × 50 μm id), separation voltage: 14 kV.

3.1.1 Electrode lengths, symmetry, and detection head shielding

The requirement for a more compact detector led to a reevaluation of the influence of the electrode length in smaller steps compared to the publication of Drevinskas et al. [24,25]. Setups with the same length (5, 10, 15, 20 mm) for both excitation and pick-up electrode were investigated first. Regarding the noise, the signal height of analyte peaks and the LOD for all detectors, a reduction of the overall electrode length was advantageous. Results from experiments with different length of excitation and pick-up electrode showed similar behavior. The positioning of the longer electrode proved to be irrelevant for LODs. An exception was observed for the CDCD 2 × 05-S detector: this setup showed the highest noise of all detectors and the lowest peak height of all setups, see, for example, hatched bars in Fig. 2B for a 500 μM Li⁺ sample. The slope of the calibration curve of the peak area was similar for all other detectors (3.9–4.5 a.u.), revealing a similar sensitivity corroborating findings of Drevinskas et al. (S/N for 2 × 05; 2 × 15) [24]. During the study, the effectiveness of the shielding of the detector’s head was confirmed. The CDCD 2 × 20-S showed a 3.7-times lower LOD compared to the same detection head without grounded shielding. With the fine tuning of electrode lengths in our study, we were able to lower the LOD and enhance the S/N: shorter electrodes were beneficial since they were easier to mount and the section of the capillary covered by the detector was shorter allowing a more freely positioning of the detector along the migration path. The lowest LOD with 93 μM was achieved for the CDCD 2 × 10-S.
Detectors with 5 mm electrodes were discarded because of their high noise, high LOD, and low sensitivity. No advantages of setups with different length of the excitation and pick-up electrode were observed, they were not further investigated.

### 3.1.2 Differential measurements

It was possible to conduct differential measurements with the CDC-IC. For this, the detection head was equipped with four identical electrodes. The pair of electrodes connected to the negative input channel of the IC was placed around a capillary filled with BGE. The differential setup proved to be particularly advantageous for the detector with higher noise (CDCD $2 \times 20$-S). Due to lower noise achieved in differential measurement mode, the LODs for CDCD $2 \times 10$-S and CDCD $2 \times 20$-S were reduced by a factor of 1.5 and 4.9 reaching an LOD of approximately $60 \mu M \text{Li}^+$. The sensitivity was 23% higher for the CDCD $4 \times 10$-S than for the CDCD $4 \times 20$-S, see Table 1, again demonstrating the positive effect of shorter electrodes. The lower LODs obtained in the differential measurement mode was also described by Drevinskas for CDCD with 20 mm and an excitation voltage of 3.3 V, however, shorter electrodes were not investigated [25].

### 3.1.3 Amplification

Finally, the influence of the amplification of the peak-to-peak excitation voltage of the CDC-IC from 5 to 24 V with an operational amplifier was investigated for the shielded detectors ($2 \times 10$-S, $2 \times 15$-S, $2 \times 20$-S) in single-ended as well as in differential ($4 \times 10$-S, $4 \times 20$-S) measurement mode, compare Table 1. An amplification of the signal of 4.8 would be expected if the excitation voltage and the signal height increase to the same extent. This was reached in our CE-experiments with the same extent as the excitation voltage and the noise for both single-ended and differential setups were reduced. The peak-to-peak noise for the shielded plus amplified detectors after applying a five-point moving average function was between 21 and 42 a.u. This matched well with the 5- to 10-fold specified resolution of 4 aF (equals a.u.) of the CDC-IC (AD7745) [21].

### 3.1.4 Summary of the optimization process

The LOD for Li$^+$ reached with all amplified CDCDs, displayed in Fig. 2A and summarized in Table 1, were between 3.9 and 8.8 µM. Overall, LODs reached in this study were in the same order of magnitude for the amplified setups. The CDCD $2 \times 10$-SA showed the lowest noise. It was also the most compact and simplest setup of the detectors with amplifier. It provided the lowest LOD of 3.9 µM for Li$^+$. A measurement with a concentration just above the LOD is depicted in Fig. 3A.

### 3.1.5 Detection window

A narrow detection window is desired to reach a higher spatial resolution and, thus, separation efficiency with the related precision in determining migration times. In Table 1, the plate number for all CDCDs are summarized for the Li$^+$ peak when injecting a 125 and 500 µM solution. Due to the better LOD, only detectors with amplifiers were discussed. The peak caused by a 500 µM Li$^+$ sample, was already that broad, that the limiting factor was the electrophoretic separation and not the detection. This resulted in plate numbers of 14 000 to 15 000 (500 µM) and 22 000 to 24 000 (125 µM) for peaks caused by Li$^+$. No significant effect of the electrode length on the plate number was observed.

### 3.2 Comparison of CDCDs to established C4D

#### 3.2.1 Comparison regarding the LOD

To judge the performance of the CDCDs, the LOD and the plate number were compared to those achieved by the OC4D and the C4D from eDAQ; all data are summarized in Table 1 and Fig. 2. With all shielded plus amplified CDCDs and both C4Ds, the LODs for Li$^+$ were between 3.7 and 8.8 µM. The LOD of the CDCD $2 \times 10$-SA (with lowest LOD of all CDCDs of 3.9 µM) was not significantly different from the commercial C4D from eDAQ (LOD 3.7 µM) for a Li$^+$ sample. The OC4D reached LODs of 7.6 µM. The eDAQ, which was always mounted as a secondary detector on the same capillary, showed a SD of 1.0 µM ($n = 4$) at the LOD. A direct comparison to literature values is difficult as different injection volumes, capillary dimensions, effective lengths, and BGE concentrations were used. LODs ($S/N = 3$) for C4Ds in literature (mostly LODs for K$^+$) were reported between 0.1 and 3.7 µM (LOQs of 0.3 to 12.3 µM) [20,39–50]. Reported LODs for Li$^+$ were between 0.8 and 4.0 µM [20,49]. Using
Figure 3. Electropherograms of the separations of K\(^+\) (1), Na\(^+\) (2) impurity, Li\(^+\) (3) and TrisH\(^+\) (4) in a 20 mM MES/His BGE, see Fig. 2 for experimental details. (A) Baseline-subtracted electropherogram at analyte concentrations of 6.25 \(\mu\)M recorded by the CDCD 2\(\times\)10-SA at \(L_{\text{eff}} = 31.5\) cm. (B) Electropherograms at analyte concentrations of 125 \(\mu\)M recorded by a multidetection setup (see Section 3.3) consisting of: (A) CDCD 2\(\times\)10-SA at \(L_{\text{eff}} = 24.5\) cm, (B) CDCD 2\(\times\)15-SA at \(L_{\text{eff}} = 31.5\) cm (–14 a.u. offset), and (C) an OC\(^4\)D (light gray, right scale, \(L_{\text{eff}} = 36\) cm). Excitation electrodes of the CDCDs pointed to each other.

A very similar detection setup and measuring conditions, Drevinskis et al. calculated LOQs for K\(^+\) (0.31 \(\mu\)M), Na\(^+\) (0.25 \(\mu\)M), and TrisH\(^+\) (0.55 \(\mu\)M). A direct comparison of the data presented for the shielded plus amplified CDCDs, determined via the S/N = 3 criterion for the peak height to data presented by Drevinskis et al. [25] is difficult, as the authors calculated their LOQs from the calibration curve of the corrected peak area, which disregards to some extend the noise of the detector. Additionally, the lowest measured concentration of the calibration curve to determine the LOD was about the 25-fold LOD. According to DIN 32 645:2008-11, the LOD can only be determined from a calibration curve in the range of zero to the ten times the LOD. Therefore, the lowest measured concentration by Drevinskis et al. is too high for a good estimate of the LOD. In literature, LODs (S/N = 3) of 0.6 and 0.8 \(\mu\)M for K\(^+\) and Li\(^+\) were published for the OC\(^4\)D using a 10 mM MES/His BGE [20]. The LODs are 7.5-9.5-fold lower than those obtained in this study for the OC\(^4\)D, presumably due to different measurement conditions but not detector performance.

### 3.2.2 Comparability of CDCDs and eDAQ for quantitative analysis

For the quantitative comparison of the CDCDs (CDCD 4\(\times\)20-SA) with the eDAQ, the RSD of the ratio of the peak areas for Li\(^+\) at a concentration of 125 to 1500 \(\mu\)M (called RSD(CDCD/eDAQ), \(n = 3\)) was calculated, see Table S1 in the Supporting information. This ratio proved robust if both detectors were installed to the same capillary and when they recorded the same run concurrently but at different effective lengths. With an RSD(CDCD/eDAQ) \(\leq\) 0.7\%, it is clear that both detectors performed comparably. The precision of the peak area was similar for the CDCD and the eDAQ reaching 2.2 to 8.9\% RSD (\(n = 3\)) for Li\(^+\). This corresponds well to literature values (2.7–7\%) [39–41,43,44]. The high values of the RSD of the peak areas compared to those of RSD(CDCD/eDAQ) showed, that the variation between repeated CE-runs is more pronounced than the variation between both detector types. The repeatability of the CE-separation depends on injection precision, the changes of EOF between runs and the electrophoretic mobility, caused by shifts in the BGE composition during a series of measurements. Analogous observations were made for all detectors under investigation.

### 3.2.3 Comparison regarding the plate number and peak shapes

A comparison of the plate numbers revealed 2.4 to 3.1 times lower plate numbers for the CDCD 2\(\times\)10-SA (23 000 at 125 \(\mu\)M Li\(^+\)) versus the OC\(^4\)D (56 000 at 125 \(\mu\)M Li\(^+\)) and the eDAQ (71 000 at 125 \(\mu\)M Li\(^+\)). This points to a narrower detection window of the OC\(^4\)D and the eDAQ compared to those of the CDCDs. This correlates with a higher precision in determining migration times and higher resolution. Another reason for the lower plate numbers of the CDCD compared to those of the C\(^4\)Ds can be the different excitation frequencies of the detectors. The frequencies were set to 32, 1100, and 200 kHz for the CDCDs, OC\(^4\)D, and the eDAQ, respectively. For C\(^4\)D, it is known that the plate number is reduced when using longer electrodes at low excitation frequencies [33].

The shape of analyte peaks when injecting samples with concentrations above 250 \(\mu\)M depended on the detector: the CDCDs showed symmetrical peaks whereas with the C\(^4\)Ds triangular peaks were recorded due to electrodispersion. We presume that the CDCDs have a broader detection window compared to the C\(^4\)Ds. The integration over a larger capillary segment results in a smoothing effect with respect to the shape of the peak.

### 3.2.4 Comparison of instrumental aspects

The CDCDs presented here had a noticeably light weight (1.7–2.6 g depending on the configuration) and a more
compact detection head compared to the OC4D and the eDAQ. This allowed the capillary to carry the detection head without the need for further support, so that it could be positioned freely along the capillary facilitating handling. The section of the capillary occupied by the detection head was shorter with the OC4D than with the CDCD. A shorter detection head is favorable for multidetector setups as detectors can in principle be positioned more closely to each other, then only limited by possible interferences between detectors (see Section 3.3). The setups developed here were power supplied by batteries, allowed wireless data transfer, and offered the further advantage to use up to five detectors in parallel (see Section 3.3), as well as to connect a trigger either to a detection device or to the master device wired via USB to the computer. The trigger was optimized to work for an Agilent 7100 CE System or a Prince 560 CE. The entire detection device, including the batteries weighed less than 200 g using two 4000 mAh batteries; a protective housing, if regarded as necessary, would weigh approximately 20 g. In contrast, both C4Ds used for comparison needed mains power and a wired data communication. The power consumption of the CDCDs with amplifier plus the belonging master device (680 + 170 mW) was only about 1.5-times higher compared to the OC4D (580 mW [detector] + 170 mW [microcontroller]) despite the integration of wireless data transmission. The nonamplified CDCDs (250 + 170 mW) were about twice as power efficient as the detectors with amplification. Further, the manufacturing of the CDCDs was simple. The cost of the CDCD assembly with one detection device and an OC4D (60–80 EUR) was similar but may differ for the power supply. A summary of instrumental parameters is given in Table 2 for all detectors.

### Table 2. Comparison of size, power consumption, and weights of shielded CDCDs with (CDCD-SA) or without (CDCD-S) amplification, OC4D and eDAQ

| Detector | Size of detection head (mm) | Covered capillary section (mm) | Power consumption of detection device + master device | Weight of detection head (g) | Weight w/o battery (g) |
|----------|-----------------------------|--------------------------------|------------------------------------------------------|-----------------------------|------------------------|
| CDCD-SA  | 10 × 25 × 21                | 21                             | 94 mA @ 7.2 V + 34 mA @ 5 V                          | 2.6                         | 24.1                   |
| CDCD-S   | 10 × 25 × 21                | 21                             | 34 mA @ 7.2 V + 34 mA @ 5 V                          | 1.7                         | 20.3                   |
| OC4D     | 21 × 30 × 13                | 13                             | 34 mA @ 12 V + 34 mA @ 5 V                           | 11.5                        | -                      |
| eDAQ     | 27 × 13 × 31                | 27                             | -                                                     | 19.0                        | -                      |

For CDCD: total battery weight: 172 g; dimensions supply unit: 97 × 22 × 22 mm³.

Several detectors can be placed along the capillary. Care must be taken to avoid interferences between them when the distance becomes too short. We determined the minimum distance required for interference-free multidetector setups. Using two CDCDs (CDCD 2 × 10-SA, CDCD 2 × 15-SA), it was crucial that the excitation or the pick-up electrodes pointed to each other. This allowed a minimal distance between the PCBs of 5 cm without affecting the LOD. A shorter distance decreased LODs due to interferences and, therefore, higher noise. No such restrictions were observed for setups combining a CDCD with an OC4D/eDAQ or combining two OC4Ds.

A multidetector setup consisting of the two single-ended CDCDs with the lowest LODs (CDCD 2 × 10-SA, CDCD 2 × 15-SA) and an OC4D were used to allow spatial tracking of the migrating analytes in the reference system (electropherograms see Fig. 3B). The distances between the detectors were 7.0 and 4.5 cm. The excitation electrodes of the CDCDs pointed to each other. This setup allowed to determine the speed of migration, which is constant in CE separations, as well as the migration direction of the analytes [51]. The time at which an analyte should pass the OC4D was calculated from the speed based on the signals and positions of the CDCDs and the distance between the OC4D and the CDCD next to it. On average, depending on the analyte, the measured time was 0.16 to 0.61 s shorter than the calculated time and the SD was 0.10 to 0.18 s (n = 5). Spatially, this means that the analyte has exceeded the position of the OC4D by only 49 to 111 μm on average (corresponding to a SD of 21 to 51 μm). The precise determination of the location of analytes along the separation path is necessary for setups where the analytes are transferred, for example, to an additional separation dimension, for fractionation or for stopped-flow experiments. Similar to our results, excellent linearity (R² = 1.0) was reported for the evaluation of the detector position as a function of the detection time by Caslavská et al. [52]. Multidetector setups with up to 16 C4Ds were described in literature but were mainly applied to validate simulations of CE separations. The C4D setups used in literature were more spacious. A direct comparison of LODs was not possible due to missing statements. Also, it was not stated if any interferences between the detectors were observed [53]. Further, multidetector setups were used to record concurrent CE separations of anions and cations using different sample injection modes [54].

### 3.4 Quantification of glyphosate in a herbicide formulation

To demonstrate the applicability of the CDCDs to real samples, the content of glyphosate and potassium was determined in the herbicide Roundup PowerFlex via external calibration, see Fig. 4 for electropherograms. A BGE of 20 mM MES/His (pH 6.1) proved suitable for the separation of
glyphosate because it was doubly charged at pH 6.1 (pK\textsubscript{a} values: 2.0, 2.6, 5.6, and 10.6 [55]). For detection, the CDCD 2×10-SA was used (see discussion in Section 3.1.4). The results obtained for both analytes showed excellent linearity (R\textsuperscript{2} > 0.99) in the concentration range 62.5 to 250 \mu M for glyphosate and 125 to 1500 \mu M for K\textsuperscript{+}. The LOD was estimated based on S/N = 3 to 10 \mu M for glyphosate and 7 \mu M for K\textsuperscript{+}. The migration time precision was <1.2\% RSD (n = 3). The RSD of the peak area was <10\% (n = 3). The concentration of K\textsuperscript{+} and glyphosate in the herbicide formulation was determined via a calibration curve in triplicate at two dilutions (1:20 000 and 1:10 000). The results were: 4.6 M ± 3.4\% for K\textsuperscript{+} and 3.2 M ± 1.3\% for glyphosate. According to the datasheet, the nominal concentration was approximately 2.84 M of the glyphosate potassium salt, which is 11\% lower than measured for the sample. The deviation is possibly due to the high dilution of the samples, the high viscosity of the herbicide formulation, possibly some matrix effects or simple deviations between labeling and actual content.

4 Concluding remarks

In this study, we presented different setups of portable CD-CDs combined with an operational amplifier. To obtain best LODs and a compact detection head, a systematic study was conducted regarding electrode length, the use of a differential measurement mode, and different excitation voltages. To judge the performance of the CDCDs, a direct comparison to the OpenC\textsuperscript{4}D and a commercial C\textsuperscript{4}D was carried out. For the fully optimized CDCD with two electrodes of 10 mm length and a square wave excitation voltage with a frequency of 32 kHz and an amplitude of 24 V, LODs (S/N = 3) for K\textsuperscript{+} and Li\textsuperscript{+} were approximately 4 \mu M. Similar results were obtained for the commercial C\textsuperscript{4}D. The LODs for the OpenC\textsuperscript{4}D were twice as high. Depending on the measurement conditions, LODs between 0.1 and 3.7 \mu M (LOQs of 0.3 to 12.3 \mu M) (mostly for K\textsuperscript{+}) were reported for C\textsuperscript{4}Ds in literature [20,39–50].

Compared to the other C\textsuperscript{4}Ds used in this study, the detection head had a low weight of only 2.6 g. Therefore, the detection head can easily be carried by the CE capillary itself so it can be freely positioned along the separation path. To enhance handling compared to currently available detectors, the CDCD setups were battery powered and used wireless data transmission. With their compact design, low weight of less than 200 g including batteries, low power consumption of the detection device of approximately 680 mW (less than 250 mW when LODs above 40–60 \mu M were sufficient) it was well suited for portable systems, even with multiple detectors for timing events. Additionally, the CDCD was low priced with 80 EUR, and the simple assembly proved beneficial. For convenience, full automation for measurements with commercial CE systems was implemented. The hardware and software were optimized for real time data plotting and is provided as open source. It was also shown that multidector setups to enable spatial tracking of analytes during separation were possible.

The authors have declared no conflict of interest.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

5 References

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