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Flow sampling in capillary electrophoresis with a pneumatically driven computerized sampler

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Abstract. Developments in sample introduction from liquid flow in capillary electrophoresis are reviewed. We have focused on the description of a pneumatically driven sampler that enables to force the sample stream to pass the inlet of the separation capillary. The advantages of such an input device are absence of a voltage rise and/or drop time during sampling, ease of operation because no vial manipulations are involved, and simple automation and computerization. However, the main advantage of such input devices seems to be that they facilitate easy, multiple inputs from a single sample vial. This opens the possibility of monitoring the concentration changes taking place inside the vessel, which is an important task in analytical biotechnology. This article describes some possible applications of such samplers in coupling capillary electrophoresis with flow injection analysis and high performance liquid chromatography in multiple input experiments (with or without stacking) for the reduction of detection limits and for monitoring reaction kinetics.

Key words: capillary electrophoresis, sample introduction, computerization, bioprocess monitoring, detection limits.

INTRODUCTION

Modern analytical laboratories are equipped with commercially available high-performance miniaturized and computerized instruments. Although this approach has many advantages, it has also an obvious drawback: the direction of a research project may be determined by the data that the instrument can deliver, rather than the importance of the project. As S. Hjertén, one of the most eminent persons in contemporary separation science, pointed out recently: "There is, accordingly, great risk that new, fundamental urgent areas which require design and construction of new apparatus and synthesis of new chemicals will not be explored" [1].

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Sampling has been a procedure in capillary electrophoresis (CE) that still requires radical ideas for the study of new unexplored fields in chemistry. Although two basic procedures, hydrodynamic and electrokinetic sample introduction, are extremely simple to implement just by raising an input vessel or applying high voltage during sampling those procedures lack reproducibility and convenience. Search for more sophisticated but reliable procedures has been of interest in CE since the beginning of its application until now. Commercial instruments usually provide robotic arms or autosamplers for manipulating sample and buffer liquids. Usually the cost of the sampler makes up a significant part of the cost of a particular instrument. Despite all refinements used in samplers of commercial instruments they are not very well suited for fulfilling a large class of analytical tasks where otherwise CE could perform an important role. Those tasks involve situations where analysis of a sample whose composition varies in time is needed. On-line monitoring of the course of chemical reactions or bioprocesses occurring in fermenters belongs to this class of tasks. A typical feature of those tasks is the need for multiple sampling from the same vessel whose composition changes in time. Convenient means for multiple sampling are needed also for making judgements about a new assay or separation protocol performance (estimating its accuracy and precision). A more exotic class of tasks is performing experiments with multiple pseudo-random sample introductions into capillary for the reduction of detection limits.

Although commercial instruments could be used in the cases described above, these are too troublesome for multiple sample introduction purposes. Application of microchips might be a possible solution. Computerized, sophisticated control of sample and buffer flows is easy to perform on microchips just by switching voltages between different channels formed on the chip. Microchips definitely belong to the future of analytical separations. Presently their use is restricted to a few laboratories where advanced technology of microchip production is available. Also, commonly microchips require the usage of laser fluorescence detectors that involve derivatization procedures.

Developments in nonconventional sample introduction in CE have been of interest during the last decade. A review with 79 references [2] focuses on the possibility of forcing the sample stream to pass the separation capillary inlet. The easiest approach to multiple sampling seems to be combination of CE with flow injection analysis (FIA). Sampling from the flow can be implemented by rejecting the use of sample and buffer vials common in commercial instruments. Instead, the capillary inlet is placed into a narrow inlet channel, which can be filled with buffer or sample by any of the possible flow-controlling devices. The sampling process can be controlled by peristaltic or high performance liquid chromatography (HPLC) pumps, which force the buffer flow through the inlet channel. The sample can be introduced via a common HPLC rotary valve as a plug into this flow, which carries it further past the capillary inlet. During this passing, part of the sample is introduced electrokinetically into the capillary.

This approach allows of using a variety of detectors and is very simple to implement in virtually every laboratory where multiple sampling is needed. Kuban and co-workers [3, 4] were the first to perform coupling of flow injection analysis (FIA) and CE. They were followed by Fang et al. [5]. Characteristically, CE equipment in FIA experiments performs the role of a detector for this method, i.e. in the simplest form of coupling separation the capillary together with the electrode is simply inserted into the output flow of the FIA equipment (see Fig. 1). In typical cases the input flow line consists of a common 6-port HPLC valve for sample introduction into the buffer flow. Many other arrangements are possible. For a special application, in comprehensive two-dimensional HPLC & CE, Lemmo & Jorgenson suggested the idea of "flow gating" [6] where the sample is an effluent flowing out of the HPLC column. By interrupting the buffer flow by closing the solenoid valve a portion of the effluent is allowed to penetrate before the capillary and the sample introduction takes place. Restoring the buffer flow before the capillary by opening the solenoid valve completes the sampling procedure.

A computerized, pneumatically driven sampler allowing manipulation of up to four flows under computer control was developed at the Institute of Chemistry, Tallinn Technical University [7]. Initially designed as a device for generating sophisticated sample and buffer flow successions before the capillary it found an application in demonstrations that a reduction of detection limits in CE could be achieved by simply changing sampling procedures. It was shown that the sampler is capable of performing thousands of pseudo-random sample injections with high frequency (sample introduction after every 0.5–1 s) [8]. This technique, known as correlation CE, was first proposed by Smit's group at Amsterdam University [9, 10] and was recently transferred to microchip format by Fister et al. [11], Kaneta et al. [12, 13], and Zhang et al. [14]. Correlation CE enables a reduction of the detection limit by an order of magnitude. Even lower detection limits can be achieved using sample stacking [15], especially in the field amplified head column mode [16]. Computerized manipulation of sample and/or buffer flows before the capillary enables to use this technique in "dynamic" mode and to reduce detection limits several thousand times [17, 18].

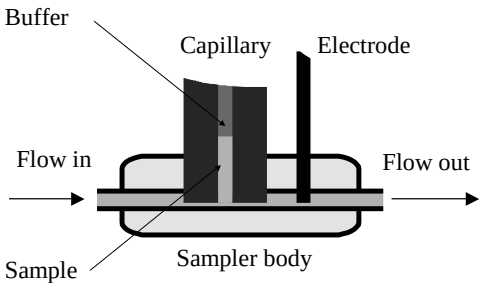

Fig. 1. Principle of sampling from the flow.

In this paper various applications of the sampler are reviewed. First, it is demonstrated that, due to the possibility of manipulating liquid flows without switching off the high voltage applied to the capillary, the sampler enables to improve reproducibility of sampling many times. Particularly, this is illustrated for an electrospray ionization condensation nucleation light scattering detector (ESI–CNLSD). Secondly, possible applications of the sampler in bioanalytical chemistry are demonstrated. These include on-line monitoring of bacterial processes and monitoring of enzymatic kinetics.

FLOW SAMPLER

Sampler description

The sampler schematic is presented in Fig. 2. The sampler operates by a rapid exchange of the buffer to sample and vice versa in a narrow inlet channel. The buffer/sampler interchange is performed by application of pressure pulses to the sample and buffer vessels. The vessels act as gas displacement pumps. Pressure to the vessels and sampler channels is delivered by several computer controlled two-way solenoids. The solenoids SV1 and SV2 are used for buffer and sample rinse, respectively. Solenoid SV3 is used for closing the inlet channel. If SV1 delivers simultaneously pressure to the inlet channel a hydrodynamic sampling can be performed. One inlet channel is not shown in Fig. 2 for simplicity. It

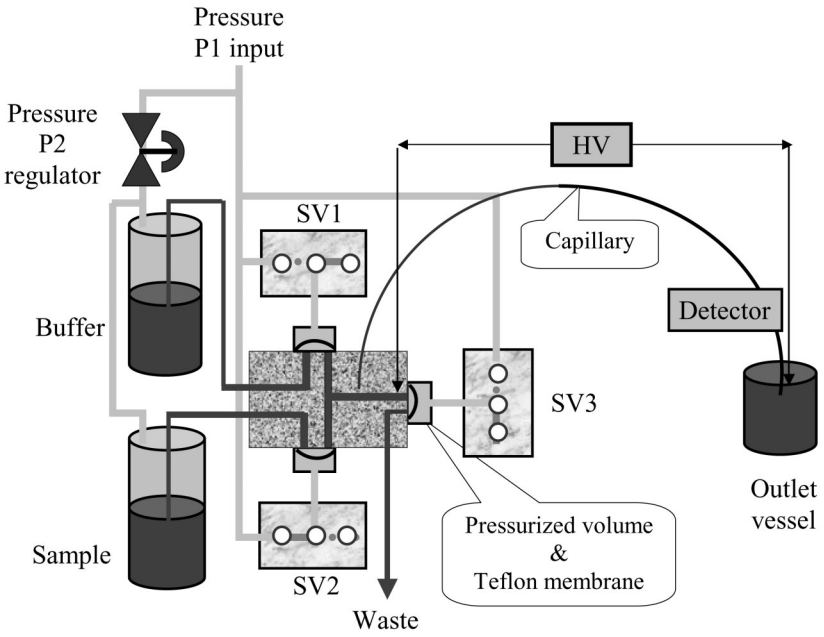

Fig. 2. Pneumatic sampler. SV1, SV2, SV3 are solenoid valves (dot – voltage applied to the valve, bar – voltage not applied to the valve).

Table 1. Sampling sequence logic

Action	SV1[a]	SV2[a]	SV3[a]	SV4[ab]
Buffer rinse	1	0	0	0
Sample rinse	0	1	0	0
Hydrodynamic sampling	0	1	1	0
Capillary rinse with NaOH	0	0	1	1
Electrokinetic sampling	0	0	0	0
Pherogram run	0	0	0	0

[a] 0 – no voltage applied to the valve, 1 – voltage applied to the valve.
[b] Valve not shown in Fig. 2.

performs similarly to the buffer or sample channels and is used for rinsing the capillary with the necessary washing liquid (if SV3 closes the waste channel at the same time). The sampling logic is presented in Table 1.

The sampler body is made of Plexiglas or polyether ether ketone (PEEK). Its dimensions are $3.5 \times 1.5 \times 1.5$ cm. The input channel has a length of 30 mm and 1.0 mm I.D. Thus, the total volume of the input channel is about 30 μL. Channels are opened by Teflon films by liquid pressure and closed by air pressure delivered through solenoid valves or opened to the atmosphere by them. Correct balancing of the liquid and air pressure is important and can be performed easily. It is evident from Table 1 and Fig. 2 that to execute the sampling process pressures must satisfy the following relationship: $P1 > P2$. The applied pressure $P2$ ranged between 0.3×10^5 and 0.8×10^5 Pa and $P1 = 1.0 \times 10^5$ Pa. Experiment control and detector signal acquisition are performed via "ADAM-4060" relay output module and "ADAM-4017" analogue input module (Advantech Ltd., Taipei, Taiwan) under control of LabView 4.1 (National Instruments, Austin, TX) installed into a Pentium PC.

As pointed out above, the flow sampler has several properties that can be considered advantageous as compared to the samplers that appear in commercial instruments. First, the high voltage should not necessarily be interrupted during the sampling process. Although no special investigations have been performed, this should improve the sampling process reproducibility since the voltage rise and/or fall during the sampling has been recognized to be the least reproducible part of the sampling procedure [10]. Secondly, flow samplers can be very simply computerized. Indeed, as demonstrated by us, sophisticated sample sequences can be generated easily [8]. Thirdly, contrary to samplers included into commercial instruments, flow samplers are very useful for process monitoring. On-line sample preparation devices (such as membrane separators) can easily be implemented into the flow line. Forthly, flow sampling devices are very cheap and can be manufactured in the lab by investigators themselves from the materials and parts available in every lab. This feature differentiates flow samplers advantageously from the CE devices manufactured on the silicone or polymeric substrate. Although the latter devices can in principle perform any of the operations that flow samplers are designed for, microchip CE samplers are manufactured frequently by

using an extremely sophisticated technology requiring special rooms, procedures, and human skills. This means that the microchip technology is not very widely available. As a disadvantage it should be noted that flow samplers are inconvenient to use if there are very many different samples requiring frequent manipulation with different sample vials. Also they consume larger amounts of sample and buffer than common samplers.

Evaluation of sampler performance in improving the precision of ESI–CNLSD

ESI–CNLSD description

ESI–CNLSD was developed as a rugged all-purpose detector for CE and chromatography at the Department of Chemistry and Biochemistry, Southern Illinois University (Carbondale, Illinois, USA). It is an improved detection technique of evaporative light scattering detection. CNLSD is a universal detection method since light scattering is not compound selective and has detection limits comparable to those of fluorescence detection [19, 20]. The operation of the detector has been thoroughly described in several publications [21, 22] and only a brief outline is given here. CNLSD operates so that the effluent from the capillary outlet is nebulized by electrospray to an aerosol from which the mobile phase is evaporated, leaving behind particles of analytes. Desolvated particles serve as nuclei for heterogeneous nucleation when exposed to saturated butanol vapour, where they can grow to large droplets. The number of particles is then measured using a light scattering technique. This detection method is very universal and in comparison with evaporative LSD has 100–200 times higher sensitivity [23]. Although the excellent performance of ESI–CNLSD has been demonstrated on the analysis of a wide class of compounds, it has not received wide acceptance yet, but reportedly it will soon be commercially available [24].

As follows from the description of the detector, its response is universal and independent of the nature of the analytes other than volatility, and is thus valuable for the detection of compounds that lack chromo- or fluorophores or are electrochemically inactive. The major drawback of this detection method with CE is its cumbersome practical implementation. CE needs HV applied to the ends of the quartz capillary and another HV should be applied between the outlet end of the capillary and the counter electrode for creating electrospray. These two voltages have to be precisely adjusted for obtaining good ES. In order to inject a new sample, however, the electrophoretic HV and electrospray HV must be switched off, and after the introduction of the sample plug into the capillary, both HVs have to be quickly adjusted again. Voltage adjustment in each run may lead to electrospray with different characteristics resulting in aerosol droplets of different size. Also, the fraction of particles lost in the detection system may vary with adjustments. This makes manual sampling with CE–ESI–CNLSD slow, inconvenient, and irreproducible. For the same reason ESI–CNLSD turns out to be an excellent system for testing the performance of the flow sampler.

Notably, the operation of CE–ESI–mass-spectrometry (MS) also typically involves steps for adjusting separation and spray voltages described above. This may explain why interfacing CE to MS is sill under research and a developing stage despite the obvious importance of the possible outcome. This is in sharp contrast with the rapid maturing of another separation method – HPLC–ESI–MS.

The problem could be overcome by introducing the sample into the capillary by a sampler operating via pneumatic pulses. The described sampler could be a good candidate for such a task because in the inlet channel the flow pulses of buffer and sample solutions can rapidly replace each other without bubbling or interrupting the electric current through the capillary. The performance of the improvement should be expressed in terms of reduction of the standard deviation of the determination of the analytes compared to the sample introduction used commonly in CE. Also, an improvement of the overall stability (in other words, the "routine" of the analysis procedure) should result from this combination due to the fact that electrospray conditions can be set up before the measurement and no further adjustments are needed during each measurement.

Interfacing the sampler to CE–ESI–CNLSD

To test the hypothesis that not switching off HV during the sample introduction will lead to performance improvement of the CNLSD, the flow sampler was interfaced with the CE–ESI–CNLSD system [25, 26]. To fabricate the electrospray emitter, 2–3 cm of the outlet capillary was painted with a gold paint (OG 805 Premium Gold, Duncan Enterprises, Fresno, CA, USA). The gold paint was then heated using a heat gun to form a smooth coating on the capillary surface, which is required for stable electrospray operation. An additional 5 cm (from the gold painted part) of the capillary was painted with a copper paint (Quick Grid Repair Resin, Loctite, Cleveland, OH, USA) for connection to the power supply. The outlet of the transfer capillary with a fabricated electrospray tip at its terminus was placed in the cylindrical glass spray chamber (1.5 cm I.D., 5 cm long) through a length of a stainless steel tubing, which was used to position the capillary within the spray chamber. The aerosol was carried with a 0.9 L/min flow of carbon dioxide. A cylindrical flow-through neutralizer (model P-2021SS Nuclecel in-line ionizer, NRD, Grand Island, NY, USA) was placed directly at the end of the spray chamber. The negative HV necessary for the electrospray process was directly applied to the neutralizer. The neutralizer contains polonium-210 (alpha emitter) of 10 mCi activity whose decay creates a weak bipolar plasma. The electrons from the plasma neutralize the charges from the highly charged droplets resulting from the electrospray process. The schematics of the experimental setup is presented in Fig. 3.

The CNLSD system included a TSI (St. Paul, MN, USA) Model 3025A Ultrafine condensation particle counter (CPC) operated in low-flow mode (aerosol uptake at 300 mL/min). The CPC provides output of the number of detected particles per unit gas-phase volume (mL), here represented as No./mL. A HV power supply (Series 230, Bertan, Hicksville, NY, USA) was used to power the electrospray.

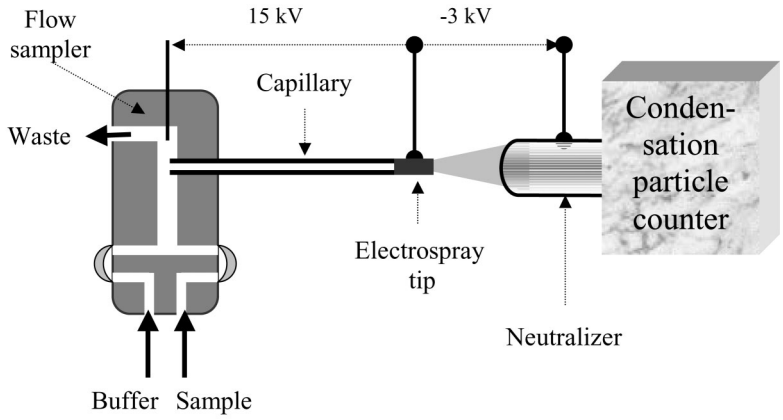

Fig. 3. Experimental set-up of the CE–ES–CNLSD system.

Testing sampler performance in a FIA–CE–ESI–CNLSD experiment of artemisinin determination

Previous tests of sampler performance revealed the sampler precision to be about 2–3% relative standard deviation (RSD) of peak area measurements using UV detection [7]. The reproducibility of the ESI–CNLSD set-up performance, measured from the peak areas, was 5–6% [25]. This is in accordance with our recent measurements [26]. For comparison of the reproducibility between manual and computerized samplings a challenging task was set up by an on-line determination of artemisinin by converting it to negatively charged products using a FIA–CE–ESI–CNLSD system. Atremisinin is a traditional Chinese antimalarial drug, which is difficult to determine because it does not adsorb UV light. A rapid and simple CE method has been developed for its determination by on-line treatment with alkaline [27]. In this treatment artemisinin was automatically and reproducibly converted to the products (one product, known under the abbreviation “Q292”, was detected by a UV detector). In our test of reproducibility a similar approach was used: a 200 mM artemisinin sample was mixed with 500 mM NH_4OH solution in a tubular (“serpentine”) reactor with 48 turns per 3 min at 40 °C. The reaction mixture was periodically sampled into the CE system and peak areas of products were measured.

Figure 4 depicts electropherograms obtained by manual sampling versus electropherograms recorded using computerized flow sampling. An experienced operator performed the manual sampling. It follows from Fig. 4 that computerized sampling guaranteed reproducibility of peak area determination with RSD = 10%. This is in accordance with previous measurements using the same CE–ESI–CNLSD system [26]. In contrast, manual sampling failed to introduce the sample in three occasions (first, third, and sixth sampling). Even when the sample was successfully introduced the product peaks are difficult to recognize among many phantom peaks whose appearance is typical of working with unstable

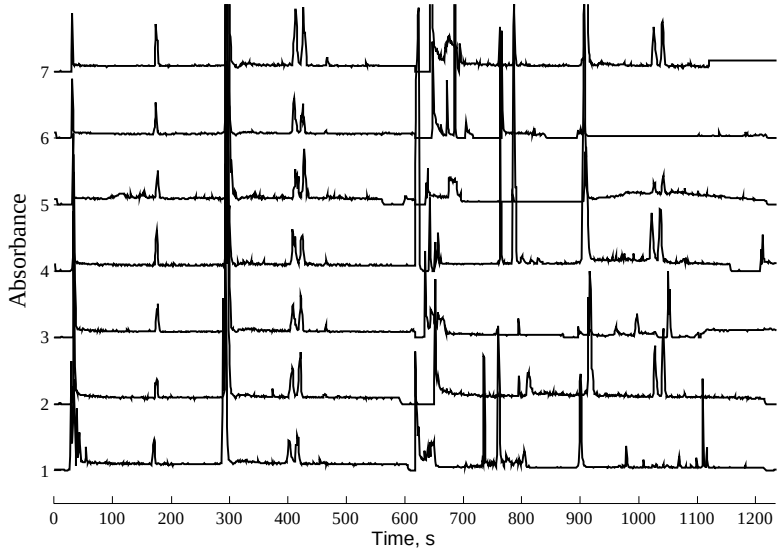

Fig. 4. CE–ES–CNLSD performance. Comparison of series of electropherograms obtained by computerized (first 600 s) versus manual (from 600 to 1200 s) sampling. Buffer: 5 mM ammonium acetate; sample: reaction mixture of artemisinin and ammonium hydroxide (200/500 mM) mixed at 40 °C for 3 min. Identification of peaks: at 150 s unknown, at 290 s and 900 s – artemisinin and neutral reaction products, at 400 s and 1050 s – products.

CE–ESI–CNLSD. In addition, RSD was as high as 50%. Thus, being three times better, the flow sampler performance is indeed superior to manual sampling, which is evident even without any statistical scrutiny.

MISCELLANEOUS APPLICATIONS OF FLOW SAMPLERS

In the following part of this review various applications of the sampler will be described. This includes experiments in generating specific sample and buffer sequences before the capillary for reducing detection limits, monitoring bio-processes and enzymatic kinetics, and coupling HPLC to CE for comprehensive separation of samples. In the following examples the dimensions of the particular sampler used differ somewhat (1 to 2 mm) in channel diameters. Still, the overall construction of the samplers was similar to that described in the paragraph Sampler description.

Improvement of signal-to-noise ratio of electropherograms and analysis reproducibility with digital signal processing and multiple injections

Poor signal-to-noise ratios and analysis reproducibility in CE were improved by application of multiple injections of the same sample at (pseudo) randomly chosen time moments [8]. Experimental electropherograms appear as traces of a

random signal, but due to the precisely known input sequence, experimental electropherograms can be transformed to “normal” using proper mathematical operation. One order of signal-to-noise ratio improvement was achieved in practice. It was demonstrated that better realization of the capabilities of multiple input requires that the detector noise be “pre-whitened”, i.e. spikes, baseline drift, oscillations, etc. must be removed from the detector signal before transforming it to an electropherogram of a common form. Such filtering of the detector signal was accomplished using iterative, menu-driven software written in Matlab, a high-level programming language.

The pneumatically driven sampler facilitates sample stacking from the sample stream by the head-column field amplification technique [17, 28]. It was demonstrated that the sampler makes possible the combination of two classical injection methods – the electrokinetic and hydrodynamic modes. Detection limits obtained were approximately 0.1 ppb (i.e. 9 nM) for alkylbenzylamine cations with common UV detection. The stacking performed by combined injection mode is referred to here as “dynamic” stacking. Dynamic stacking from the sample stream avoids electrolysis degradation and overheating of the sample. It also supplies the input channel with fresh sample, keeping the concentration of the sample constant. However, it was observed that sample plug drifts due to the EOF will reduce dynamic stacking performance, and the method was later improved by stabilization of the sample plug position by using backpressure. It was demonstrated that the sample plug length could be kept constant by monitoring the current in the capillary, which, in turn, controls a feedback system based on backpressure at the capillary outlet [18].

Monitoring the kinetics of various processes

Capillary electrophoresis can be a valuable tool for on-line monitoring of bioprocesses. This was demonstrated in examples of model processes of the production of organic acids by phosphorus-solubilizing bacteria [29] and degradation of various phenols by *Rhodococcus* bacteria [30]. Disappearance of substrates and appearance of products were monitored and controlled with a membrane-interfaced dialysis device. No additional sample preparation was required. The time resolution of monitoring in this particular work was approximately 2 h, but it could be reduced to 2 min. Analytes were detected at low μg/mL levels with a reproducibility of approximately 10%. To demonstrate the potential of CE in processes of biotechnological interest, results from monitoring were submitted to qualitative and quantitative analysis.

A computerized pneumatic sampler connected to CE was used for monitoring the degradation process of L-ascorbic acid (L-AA) [31]. The decrease in the concentration of L-AA in the samples (orange juice and orange fruits of which the squash was prepared by squeezing the fresh fruit) could be monitored between the runs as well as within the test cycles consisting of 10 injections with 10 min injection intervals. A significant decrease in the L-AA concentration after

72 h storage in a dark and dry room at 17 °C was observed in orange juice, but not in orange squash. The RSD of the migration time was less than 1% and the intraday and interday RSD of peak areas were respectively 2.1% and 2.8%. The limit of detection was 1 ppm. Automated sampling for the CE method was found to be highly suitable for the detection of L-AA in fruits and fruit products as well as for the monitoring of L-AA degradation process.

The enzymatic conversion of nucleotide adenosine triphosphate (ATP) to adenosine diphosphate (ADP) by hexokinase was monitored in the bioreactor interfaced via the pneumatic sampler to a capillary electrophoresis unit [32]. The method of micellar electrokinetic chromatography, employing reversed electro-osmotic flow by cationic surfactant and reversed polarity mode provided a good resolution and short analysis time of less than 5 min. The samples were injected electrokinetically, using −25 kV voltage for 3 s and detected by their UV absorbance at 254 nm. The analytes were detected at a μg/mL level with a reproducibility of about 7%. A popular method for measuring enzymatic processes is electrophoretically mediated microanalysis (EMMA) [33]. In contrast to EMMA the use of the pneumatic sampler enabled on-line monitoring of the reaction, which is not possible by EMMA. A typical time course of the ATP conversion is represented in Fig. 5. To demonstrate the potential of CE in understanding the processes of biological interest, such as nucleotide degradation and metabolism, investigations of the efficiency and the time course of the enzymatic transformation were carried out in several hexokinase and ATP concentrations. The data were subjected to the Michaelis–Menten analysis. The Michaelis constant K_m was 0.2 mM, which agrees well with the published K_m values, which are between 0.2 to 0.4 mM.

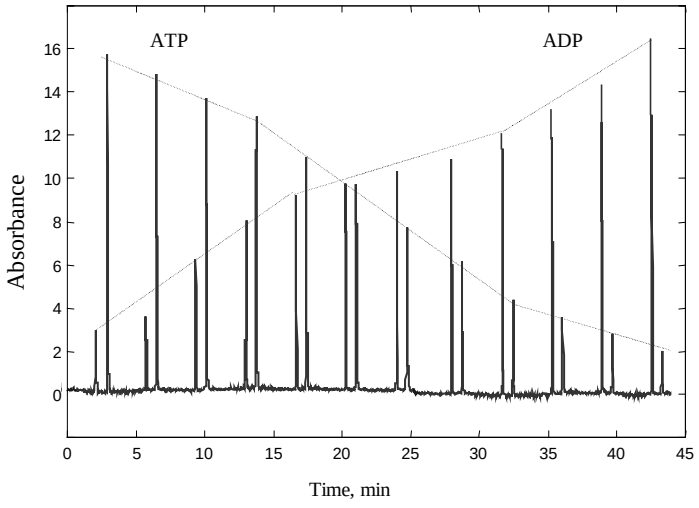

Fig. 5. Electropherograms recorded during the conversion of ATP to ADP catalysed by hexokinase.

Comprehensive HPLC–CE

A new approach was proposed to solve the problem of a long separation time in the second dimension in the comprehensive two-dimensional chromatography [34]. This approach overcomes the need for a rapid separation in the second column by repeating the analysis of a sample many times. In each of these individual analysis cases the sample is injected into the first dimension

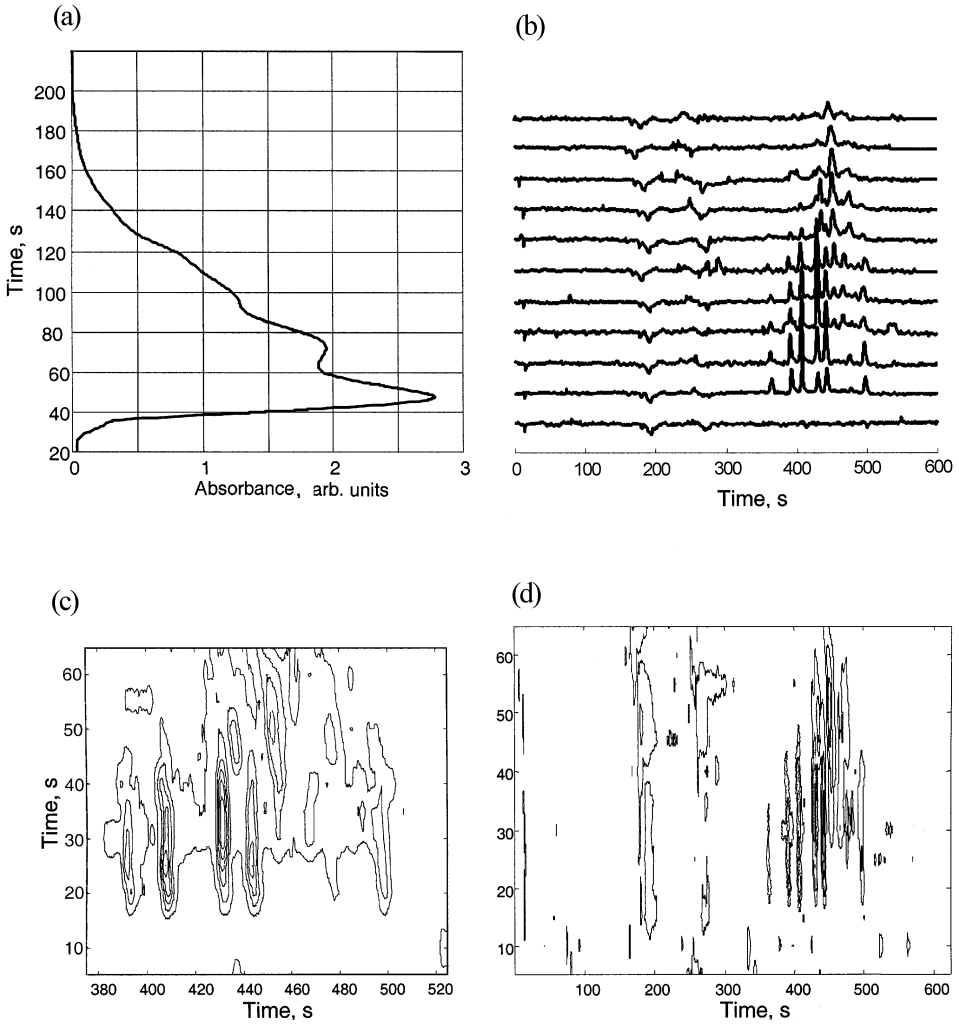

Fig. 6. Comprehensive two-dimensional analysis of a tannin sample (0.5 mg/mL). HPLC column: BIO-RAD HI-PORE RP-304; HPLC eluent: 12.5 mM potassium dihydrophosphate water (72.5%)–acetonitrile (25%)–methanol (2.5%) solution; CE buffer: 20 mM sodium tetraborate. (a) – CE detector signal; (b) – electropherograms recorded at particular time moments, approximately corresponding to the time axis in Fig. 6a; (c) – zoomed in part of the contour plot presented in Fig. 6d; (d) – contour plot.

column and after a delay a small amount of the effluent at the end of the first column is sampled to the second dimension column. The time interval between the samplings from the first column to the second column increases constantly. Thus, the system enables a comprehensive analysis of the effluent emerging from the first into the second column. This approach, which was called *stroboscopic sampling*, was tested for coupling HPLC to CE. An interface for connecting HPLC to CE was developed. The interface operates on the principle of transporting the effluent from the HPLC column to the capillary inlet by small pressure pulses (0.5 MPa). The performance of the interface for accomplishing the comprehensive HPLC–CE analysis was demonstrated for an on-line connection of a short ion-exchange column and an ion-exclusion column to the CE capillary. A comprehensive separation of a tannin sample is illustrated in Fig. 6.

CONCLUSIONS

The review above shows that the pneumatically driven computerized sampler developed at the Department of Chemistry, Tallinn Technical University, enables reproducible, precise, and flexible manipulation of liquid flows before the separation capillary inlet. It appears that a large number of rather different experiments can be set up using the sampler. Besides the determination of low levels of analyte concentrations, this device is useful for monitoring both bacterial and enzymatically catalysed processes and for coupling different analytical devices to CE separations.

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Voogsisestus kapillaarelektroforeesis arvuti juhitud pneumosamplerit kasutades

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Artiklis kirjeldatakse vedelikuvoost võetud proovi sisestamist kapillaarelektroforeesis. Tähelepanu all on proovi sisestaja, mis kasutab õhurõhu impulsse proovivoo suunamiseks kapillaari ette. Sellise sisestusseadme eeliseks on kõrgepinge muutuste vältimine proovi sisestamise ajal. Ka puudub vajadus proovianumatega manipuleerimiseks. Sisestusprotseduuri automatiseerimine on lihtne. Peale nimetatud eeliste tekib ka võimalus proovi paljukordseks sisestamiseks ühest ja samast anumast. See avab võimaluse mitmesuguste protsesside seireks, mis on analüütilise biotehnoloogia tähtis ülesanne. Artiklis kirjeldatakse mitmeid proovi sisestusseadme rakendusi voogsisestusanalüüsis, vedelikkromatograafias, detekteerimispiiride alandamisel ja protsesside kineetika seires.