

Chapter 10

Electrophoresis in Microfluidic Systems

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1. Introduction

Many chemical and biochemical analysis methods involve performing a sequence of processes that can be broadly classified in terms of sample preparation, reactions, and product analysis. Since the reaction products often contain mixtures of multiple chemical species, subsequent analytical steps must be capable of separating and identifying the individual components. Electrophoresis, which relies on inducing detectable differences in migration behavior between charged species under the influence of an applied electric field, has proven to be a highly versatile analytical technique owing to a favorable combination of characteristics including relatively simple hardware design and compatibility with a wide range of analytes including biological macromolecules (e.g., DNA, proteins). More recently, there has been considerable interest in adapting electrophoresis technology to miniaturized microfluidic formats with the aim of producing portable low-cost versions of conventional benchtop-scale instrumentation. Ultimately, it is envisioned that these efforts will enable electrophoresis to become an integral component of self-contained “lab-on-a-chip” devices capable of putting the power to perform a variety of sophisticated chemical, biological, and biomedical assays directly in the hands of those who need the information most.

On the macroscale, the development of capillary electrophoresis (CE) marked a breakthrough that overcame many limitations of early slab gel

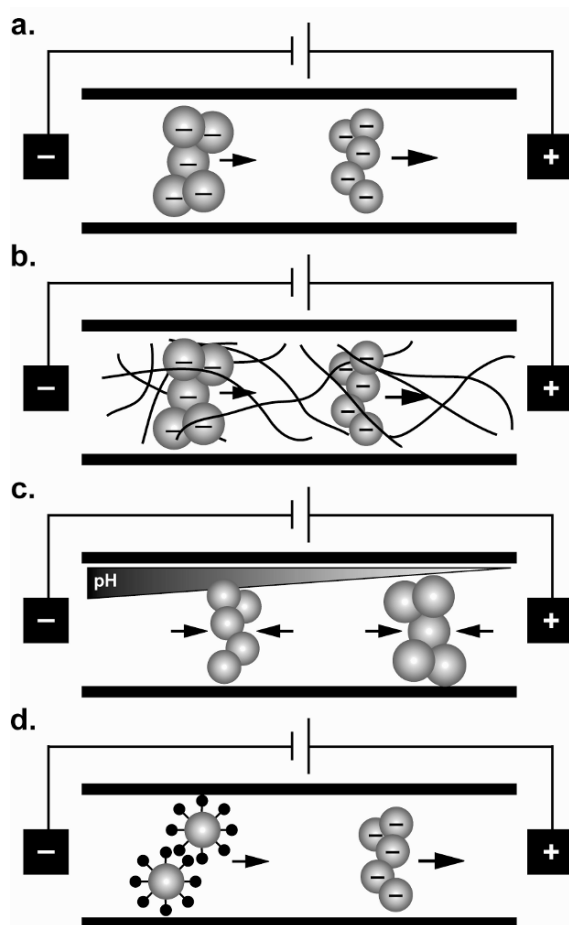


Fig. 1. Electrophoresis modes employed in miniaturized systems include (a) free solution electrophoresis, (b) gel electrophoresis, (c) isoelectric focusing, and (d) micellar electrokinetic chromatography (negatively charged analytes are depicted)

instruments. The use of ultra-narrow capillaries (typically 50–100 μm inner diameter) provided more efficient heat dissipation and allowed higher electric fields to be applied while minimizing temperature nonuniformities arising from Joule heating effects. This helped make it possible to achieve faster analyte mobilities and shorter run times without sacrificing separation performance. In addition to these benefits, the capillary format inherently requires reduced sample and reagent quantities and offers a greater capacity for automation. Since capillary cross-sectional dimensions are on the same scale as typical microfluidic channels, it is not surprising that many miniaturization efforts have focused on direct scale-down of proven

CE technologies. A number of different microscale implementations of this fundamental phenomenon have been explored in order to suit the requirements of specific analytes and applications, including adaptations of slab gel and capillary-based techniques as well as chromatographic methods [16, 30, 59, 61, 91, 106, 112, 146, 153, 175, 200, 206, 301, 342]. Some of the most common variations that have been reported include the following (Fig. 1).

1.1. Free Solution Electrophoresis

This technique involves separation of molecular analytes on the basis of their migration speed in response to an applied electric field (typically expressed in terms of electrophoretic mobility $\mu = v/E$ where v is the migration speed and E is the electric field strength). When analytes are suspended in an ionic buffer environment at a specific pH, each species migrates with a different mobility allowing them to be resolved as distinct zones and separated on the basis of size and charge (Fig. 1a). Depending on the substrate material used to construct the separation channel, surface charge effects may also induce a bulk electroosmotic flow component superimposed on the analytes' electrophoretic migration. This can be advantageous or detrimental to the separation depending on the relative magnitudes of electrophoretic and electroosmotic effects. Consequently, the ability to precisely control surface charge and buffer pH is critical to achieving optimal separation performance.

1.2. Gel Electrophoresis

This approach differs from free solution methods by the introduction of a sieving matrix material (often a polymer gel) into the separation channel, and is frequently employed for separation of DNA and proteins. The use of a sieving matrix is essential in the case of DNA, where the free draining molecular configuration adopted in free solution results in mobilities that are independent of fragment size. The gel matrix reintroduces a size dependence to the electrophoretic migration as analytes travel through the porous gel network, with smaller fragments experiencing less resistance and eluting faster (Fig. 1b). Gel electrophoresis also offers advantages associated with decreased diffusional broadening of the separated zones and a reduction in electroosmotic flow due to adsorption of the gel matrix along the microchannel walls that neutralizes surface charges. The need to load or cast a viscous polymer gel into a small-diameter microchannel, however, can pose challenges.

1.3. Isoelectric Focusing (IEF)

This method is often applied in protein separations and involves a process whereby analytes are separated on the basis of their isoelectric points. Here, migration occurs in free solution through a pH gradient established along the length of the separation channel. Electrophoretic migration continues until each analyte reaches a location where the local pH renders it neutrally charged (Fig. 1c). The quality and reproducibility of the pH gradient are key factors that determine achievable separation performance associated with IEF techniques.

1.4. Micellar Electrokinetic Chromatography (MEKC)

This is a hybrid technique involving a combination of electrophoretic and chromatographic principles that can be applied to the separation of both neutral and charged species. Here, negatively charged micelles are formed by adding an appropriate concentration of surfactant to the buffer solution. Since the micelles are formed by association of the hydrophobic and hydrophilic groups comprising individual surfactant molecules, the hydrophobic or hydrophilic character of the analyte dictates the extent of interactions with the micelles. Consequently, an analyte's mobility is determined by an interplay between charge, size, and hydrophobicity. Hydrophobic analytes will preferentially interact with the hydrophobic micellar interior resulting in net migration speeds close to that of the micelles, while the migration of hydrophilic species will not be strongly affected. Separation of neutral species can be achieved by superimposing a bulk electroosmotic flow.

It should be emphasized that the techniques described above, while encompassing the majority of methods adapted to microfabricated systems, represent a subset of the much broader field of electrophoresis technology. Miniaturized electrochromatography techniques represent another important class of analytical techniques, and are reviewed separately in an accompanying chapter. Here we focus on developments reported in refereed journals, with the understanding that additional studies may be documented in sources such as conference proceedings and patent literature.

2. Electrophoresis in Microfabricated Systems

The design of most microfabricated electrophoresis systems is relatively simple, consisting of the following fundamental elements: (1) a sample

injection zone, (2) an electrophoresis separation channel, and (3) a system for detection of the migrating analytes (Fig. 2). Despite this underlying simplicity, advances in micro- and nanofabrication technology have enabled greater sophistication to be incorporated through integration with other on-chip processes to achieve enhanced throughput and efficiency.

In terms of economics, the benefits of miniaturization include reduced reagent consumption and an increased capacity for automation so that the costs associated with performing chemical and biochemical reactions can be dramatically lowered. In terms of hardware, the use of batch photolithography-based microfabrication and micromachining technology allows hundreds or thousands of devices to be produced simultaneously at virtually the same cost per wafer. Consequently, as has been repeatedly demonstrated in the microelectronics industry, the cost benefits of microfabrication become most compelling when the device size becomes as small as possible. For electrophoresis applications, this means that the ability to construct separation columns of sufficient length to deliver the required level of resolution and sensitivity while occupying the most compact allowable on-chip area is of critical importance.

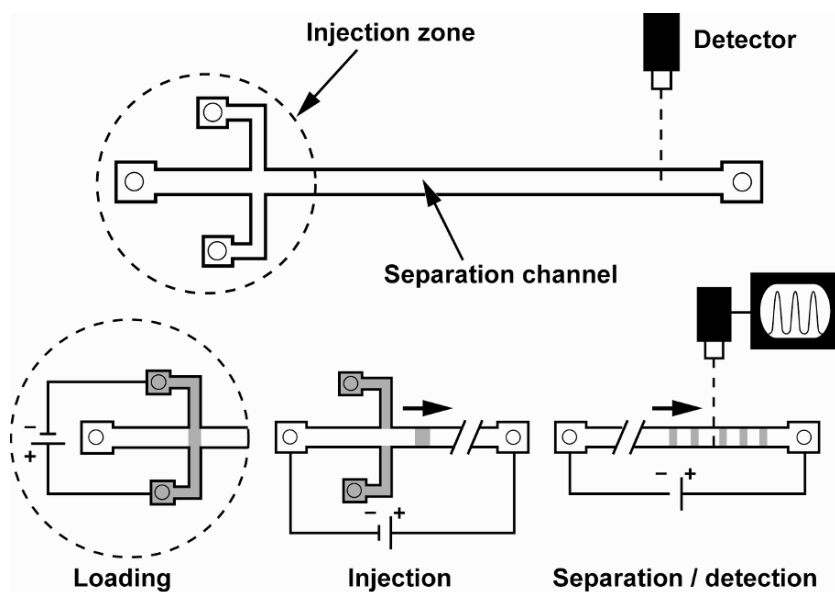


Fig. 2. A typical microscale electrophoresis run begins by electrokinetically introducing a sample into the device, after which the voltage is switched so that a narrow band is injected into the separation channel. Different species migrate with different mobilities and separate into distinct zones that are detected downstream

2.1. Injection and Separation

To effectively separate comigrating species, the difference in their electrophoretic mobilities must allow them to move apart and separate into distinct zones at a faster rate than the zones broaden due to the cumulative effects of diffusion and dispersion during the elution time. Often, a finish-line mode of detection is employed whereby an optical or electronic signal is generated as the migrating species travel past a fixed downstream detection point. The ability to distinguish neighboring zones or peaks can then be quantified in terms of a parameter called the *separation resolution* R that expresses the ratio of the distance between peaks ($t_2 - t_1$) to the sum of their half-widths at the base [95] (Fig. 3). If the zones follow a Gaussian profile, the half width of each peak can be taken as twice its standard deviation σ , yielding the following expression

$$R = \frac{t_2 - t_1}{2(\sigma_1 + \sigma_2)}. \quad (1)$$

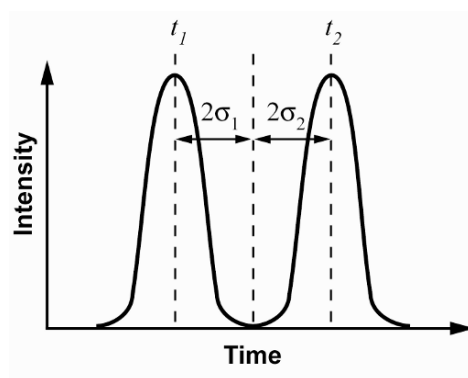


Fig. 3. In a typical electrophoresis experiment, the intensity of fluorescently labeled migrating analytes is recorded as they travel past a fixed detection point in the separation channel. The ability to distinguish two neighboring zones can be expressed in terms of the separation between peaks relative to their widths

Peak widths may also be expressed in terms of their full width at half maximum (FWHM), which can be related to the standard deviation according to $\text{FWHM} = [2\sqrt{2\ln 2}] \sigma$ such that (1) becomes

$$R = \left[\sqrt{2\ln 2} \right] \frac{t_2 - t_1}{(\text{FWHM}_1 + \text{FWHM}_2)}. \quad (2)$$

By convention, a value of $R \geq 0.5$ is often taken as a criterion to indicate that two neighboring peaks are clearly distinguishable.

The observed widths of the migrating zones reflect contributions from a number of factors including diffusional broadening, the initial width of the injected sample plug, and the finite detection volume. Considering only the diffusional contribution, the quantities in (1) can be expressed in terms of mobility (i.e., the migration speed) and a diffusion coefficient (i.e., the rate of band broadening during electrophoretic migration) yielding the following equivalent expression for separation resolution [18, 188]

$$R = \frac{1}{4} \left(\frac{\Delta\mu}{\mu} \right) \frac{L}{\sqrt{2D(L/\mu E)}}. \quad (3)$$

Here, the term $\Delta\mu/\mu$ is the *selectivity* (i.e., the relative mobilities between neighboring zones), μ is the average mobility of the neighboring zones, and L is the separation length (i.e., the distance between injection and detection points). D is a coefficient characterizing the rate of longitudinal zone broadening and is generally larger than the field-free diffusion coefficient. An important point to note from (3) is that resolution scales with separation length as $R \propto \sqrt{L}$, establishing a limit on the extent to which the length of a separation column can be reduced. Separation lengths can vary widely (millimeters to tens of centimeters) depending on the specific application, sample type, and resolution requirements. In cases where L cannot be reduced without adversely affecting performance, longer separation columns can be folded into spiral or serpentine geometries, often with specially designed turns to minimize dispersion (Fig. 4). These designs permit a more compact arrangement on the chip surface (Table 1).

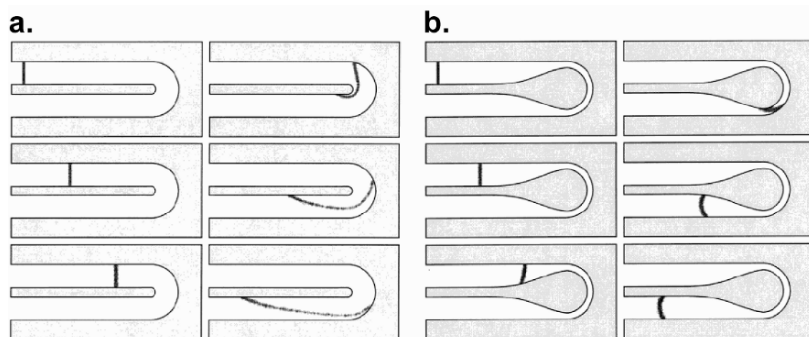


Fig. 4. Numerically simulated analyte transport through a U-shaped microchannel segment with (a) a uniform cross-section and (b) a low-dispersion turn geometry to minimize distortion of the migrating zone [100] (reproduced with permission, copyright 2001 American Chemical Society)

Table 1. Electrophoresis microchips incorporating separation channels folded into compact geometries

Compact geometry method	References
Serpentine	[21, 44, 126, 131, 135, 136, 143, 187, 215, 238, 269, 273, 287]
Serpentine (low dispersion geometry)	[15, 58, 99, 100, 166, 207, 226–228, 236, 268, 297, 337]
Serpentine (surface modification)	[139, 169]
Spiral	[45, 98]

The process by which samples are injected into the separation channel is also important. Injection of a nonconcentrated and unfocused sample zone not only requires a long separation distance in order to distinguish each component, but the corresponding signal from each species may fall below the detectable range as the zones spread by diffusion. Injection of a concentrated and focused sample zone allows each component to be detected in a considerably shorter separation distance. A variety of schemes are possible, the majority of which involve a perpendicularly crossed channel geometry where analytes are electrokinetically transported across the separation channel after which the voltage is switched such that only the sample volume at the intersection is injected [71, 107, 108, 131, 135, 140, 151, 154, 159, 167, 179, 194, 239, 241, 272, 305, 339] (Fig. 2). A sampling of other techniques includes bulk flow [123], capillary [271], diffusion-based [270], pressure-driven [170], hydrodynamic [8], dielectrophoretic trapping [2, 3, 40], nanocapillary array interconnects [28], combined electrophoretic and electroosmotic processes at microchannel–nanochannel intersections [49, 56, 318], and on-chip microelectrode arrays [19, 65, 177, 178, 262].

2.2. Sieving Gels

A variety of sieving matrix formulations have been employed in electrophoresis microdevices, most notably in applications involving DNA and protein separations where analyte mobilities in free solution are either not size dependent or only weakly so [1, 330] (Table 2). Polyacrylamide gels (both

Table 2. Sieving matrix materials used in electrophoresis microchips

Gel matrix	References
Agarose	[119, 120, 155, 300]
Bacterial cellulose fibrils	[283]
GeneScan polymer	[264, 286, 303]
Hydroxyethyl cellulose (HEC)	[77, 118, 125, 142, 144, 163–165, 202, 203, 217, 226, 249, 263, 265, 271, 285, 288–291, 321, 322, 324–326]
Hydroxypropyl cellulose (HPC)	[70, 74, 250, 251]
HPC/HEC combination	[313]
Hydroxypropylmethyl cellulose (HPMC)	[316, 328, 329]
HPMC/latex nanoparticles	[284]
Methylcellulose	[52, 235, 274, 294–296, 341]
Pluronic	[278, 300]
Polyacrylamide (noncrosslinked; LPA)	[15, 27, 34, 72, 73, 96, 101, 151, 157, 166, 183, 184, 187, 204, 205, 207, 211, 220, 221, 227, 228, 239, 240, 248, 253–256, 271, 273, 287, 309, 310, 323, 332, 337]
LPA- <i>co</i> -alkylacrylamide	[38]
LPA- <i>co</i> -dihexylacrylamide	[39]
LPA nanogel	[58, 261]
Polyacrylamide (crosslinked, photopolymerized)	[19, 32, 115, 116, 177, 178, 222, 229, 262, 298–300]
Polyacrylamide (crosslinked, chemically polymerized)	[24, 306]
Polydimethylacrylamide (PDMA)	[68, 75, 152, 190, 192, 252, 292, 319, 320]
Polyethylene glycol (PEG)/polylactic acid (PLA) nanospheres	[281]
Polyethylene oxide (PEO)	[293, 331]
POP-6	[6, 7, 85–87]
Polyvinylpyrrolidone (PVP)	[12, 154, 217, 235, 244, 297, 344]
SDS 14-200	[260]
SNAP solution	[44]

crosslinked and noncrosslinked) are widely used owing to favorable properties including optical transparency, electro-neutrality, and overall separation performance. Crosslinked gels generally yield a denser pore network however, the necessity to polymerize a gel inside the separation channel means the matrix is generally not replaceable, limiting device reusability. Photopolymerization techniques have been used to precisely position gels inside microchannel networks by using a photomask to selectively illuminate the device with UV light after which the unpolymerized reagents can be easily removed. Noncrosslinked polyacrylamide gels (i.e., linear polyacrylamide; LPA) that form entangled networks at concentrations exceeding a critical threshold are also useful for electrophoretic separations and are replaceable. Since formation of this entanglement network is accompanied by an increase in viscosity, the pressure required to inject the gel matrix into the microseparation channel is one factor that limits the available range of polymer concentrations. Thermoreversible gels such as agarose (a polysaccharide) and Pluronic (an amphiphilic block copolymer) have also been investigated as a means to aid loading and allow for replacement of the sieving matrix. These formulations undergo a thermally induced transition from gel-like to liquid-like behavior over a specific temperature range. Other sieving gels that have been studied include hydroxyethyl cellulose, hydroxypropyl cellulose, methylcellulose, polydimethylacrylamide, and polyvinylpyrrolidone.

2.3. Detection

Another critical component of electrophoresis microdevices is the ability to detect migration of the separated zones (Table 3). Typically, a laser-induced fluorescence (LIF) system is employed whereby fluorescently labeled species are illuminated by a laser (e.g., argon ion) that excites fluorophores conjugated with the migrating analytes. The resulting fluorescence signal is filtered to block background illumination from the excitation source and recorded using a photodetector (e.g., photomultiplier tube). In some cases, optical microscope systems are employed whereby the electrophoresis chip is mounted on a stage and the fluorescently labeled migrating zones are observed and recorded under magnification using a digital (e.g., CCD) camera. Under sufficiently high magnification, it is even possible to observe the dynamics of individual DNA molecules as they migrate through the separation channel (Fig. 5).

Table 3. Detection techniques employed in electrophoresis microchips

Detection technique	References
Absorbance	[122, 176, 197]
Chemiluminescence	[124]
Electrochemical	[8, 11, 77, 93, 94, 150, 155, 168, 193, 198, 199, 279, 326]
Infrared	[231]
Laser-induced fluorescence (LIF)	[4, 6, 7, 9, 12, 15, 21, 22, 27, 34–39, 42–48, 51, 52, 58, 68, 70–75, 78–88, 92, 96–98, 101, 102, 107–109, 113, 116, 118, 125, 126, 130–138, 142, 143, 144, 147, 149, 151, 152, 154, 157, 160–167, 181, 183–187, 190, 192, 194–196, 201, 203–205, 207, 211, 215, 217, 218, 223, 224, 226–228, 230, 235–237, 239, 240, 244–246, 248–258, 260, 261 263–265, 268, 269, 271, 273, 274, 285–293, 303, 306, 309–313, 315, 316, 319, 320, 322–325, 332, 333, 335–337, 340, 344, 345]
Microscope/digital camera	[5, 10, 19, 25, 26, 29, 32, 41, 64, 104, 105, 114, 115, 119–121, 141, 156, 177–179, 202, 208, 213, 214, 220, 221, 229, 238, 242, 243, 262, 266, 267, 276, 278, 294–296, 298–300, 317, 327, 334, 338]
Mass spectrometry	[55, 145, 173, 174, 182, 219]
On-chip photodiode	[24, 222, 321]
Raman spectroscopy	[314]
Single molecule imaging	[39, 66, 69, 103, 127, 209, 297, 307]
Two beam fluorescence cross correlation spectroscopy	[20]

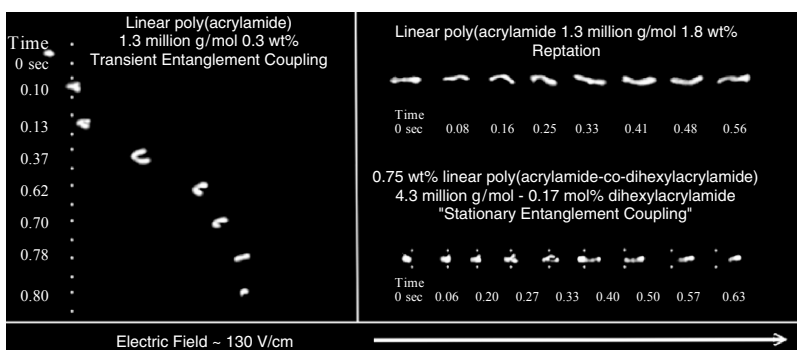


Fig. 5. Images of single λ -DNA molecules migrating through three different gel matrices [39]. The gel concentration and composition both influence the dynamics of interactions with the matrix during electrophoresis (reproduced with permission, copyright 2006 American Chemical Society)

Optical detection techniques generally require an illumination source and photodetection components that in many cases contribute significantly to the overall size of the system. These issues have stimulated interest in the development of miniaturized detection technology, as has been demonstrated through construction of silicon-based microelectrophoresis chips incorporating on-chip integration of photodiode circuitry. Nonoptical detection techniques have also been investigated as a means of providing more compact device designs. Electrochemical detection, for example, involves monitoring electrochemical potential variations as analytes migrate past a working electrode positioned within the separation channel [304].

2.4. Device Construction

The majority of electrophoresis microchips are constructed using silicon or glass substrates (Table 4). Typical microchannel cross-sectional dimensions range from tens to hundreds of microns in width to 5–100 μm in depth. The substrate containing the microchannel network is then bonded to a corresponding flat piece of glass or silicon in order to form a sealed enclosure. In the case of electrophoresis, at least one of the substrates is typically glass or quartz in order to provide optical transparency for analyte detection. Access holes are drilled in order to inject surface treatments, sieving gels, and samples into the microchannel. Subsequent packaging may involve adding connections to external liquid handling hardware and electronic voltage or temperature control components. The use of silicon substrates can be advantageous by offering the potential to incorporate on-chip electrodes, heaters, temperature sensors, and photodetection circuitry.

Plastic substrates have also been explored for use in electrophoresis. One of the most widely used plastic substrates in microfluidics is polydimethylsiloxane (PDMS), a silicone rubber possessing excellent optical transparency and the ability to form strong bonds with both glass and PDMS surfaces. The use of plastic substrates can considerably simplify fabrication by allowing molding or *soft lithography* processes to be employed whereby microchannel structures are cast against a rigid master mold. PDMS is an elastomeric material, a property that can also be exploited to construct mechanical fluidic control components such as on-chip valves and pumps. Unfortunately, many plastics are gas permeable making it difficult to polymerize gels inside the microchannel because any oxygen present within the substrate inhibits the reaction.

Table 4. Substrate materials used to construct electrophoresis microchips

Substrate material	References
Acrylic	[114, 202]
Calcium fluoride	[231]
Glass, fused silica	[4, 6, 7, 9, 11, 12, 17, 21, 22, 27, 34–39, 42–48, 55, 58, 68, 71–73, 75–82, 84–88, 90, 92, 96–98, 101, 102, 107, 108, 115, 116, 118, 121, 125, 126, 128–133, 136–138, 142, 142–144, 150–152, 154, 157, 160–169, 173, 174, 176, 181–186, 190, 191–196, 201, 203–205, 207, 211, 215–218, 223, 226–228, 230, 236–240, 242–244, 248–251, 253–258, 263–268, 271, 276, 279, 280, 285, 286, 288–292, 303, 309, 310, 314–316, 319, 320, 322–326, 332, 333, 336, 337, 340, 343, 344]
Glass/polyester film	[122]
Polydimethylsiloxane (PDMS)	[64, 94, 127, 198, 199, 208, 209, 213, 214, 224, 327]
PDMS/glass	[8, 15, 69, 70, 74, 113, 119, 124, 147, 155, 156, 162, 269, 334]
Polyethylene terephthalate glycol (PETG)	[111]
Polymethylmethacrylate (PMMA)	[50–54, 89, 139, 149, 179, 187, 219–221, 235, 246, 252, 260, 261, 273, 274, 287, 293, 295, 311–313, 328, 329, 331, 335, 341]
PMMA/glass	[20]
PMMA/PDMS	[120]
Polyvinyl chloride embedded capillary	[306]
Quartz	[10, 13, 42, 83, 93, 134, 135, 141, 197, 294, 296, 297, 345]
Silicon	[26]
Silicon/glass	[5, 19, 23–25, 29, 32, 66, 103–105, 109, 177, 178, 222, 225, 229, 262, 298–300, 307, 338]
Silicon/parylene	[321]
Silicon/silicon oxide	[41]
Thermoplastic elastomer	[278]
Vivak	[317]
Zeonor	[145]

While glass substrates are desirable for use in electrophoresis applications due to their optical transparency, they also possess a characteristic negative surface charge at pH values above ~ 3 due to deprotonation of surface silanol (Si-OH) groups to form silanoate (Si-O⁻). The resulting negative surface charge attracts positively charged counterions dispersed in the buffer solution such that a thin layer near the channel walls is formed where their concentration is locally in excess of the bulk value. When an electric field is applied, this positively charged counterion layer migrates toward the negative electrode in a sheath-like manner, transporting the bulk liquid with it (Fig. 6). This electroosmotic flow (EOF) phenomenon may be advantageous in terms of providing a means to pump liquids and reagents in microchannels, but is generally undesirable for DNA separations because the EOF direction is opposite to that of the electrophoretic migration of negatively charged DNA.

The magnitude and reproducibility of EOF can also be challenging to precisely control because it is highly sensitive to surface chemistry and buffer pH. Electroosmotic flow phenomena have been extensively studied in conventional CE systems where glass and fused silica capillaries are routinely used. These efforts have resulted in the development of robust coating procedures capable of effectively neutralizing surface charges [14, 57, 60] (Table 5). The most widely used process, originally developed by Hjertén [117], involves covalently polymerizing a thin layer of polyacrylamide or other passivating polymer along the inner surface of the capillary or microchannel. Electroosmotic effects are not as problematic in gel electrophoresis because the gel matrix often acts to neutralize or screen the negative surface charge. Characterization and control of EOF is less well studied in other substrate materials (e.g., plastics), but is an active area of ongoing research.

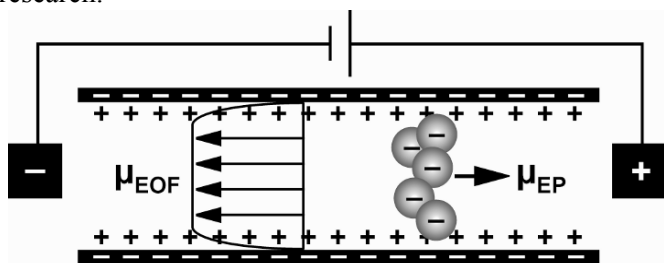


Fig. 6. The intrinsically negative surface charge along the walls of a glass microchannel induces formation of a positively charged counterion layer that is transported toward the cathode when an electric field is applied. This layer acts as a sheath around the bulk liquid, generating an electroosmotic flow with characteristic speed μ_{EOF} . These EOF effects are superimposed on an analyte's electrophoretic migration (μ_{EP}) and may act to either reinforce or oppose it

Table 5. Surface passivation techniques used in electrophoresis microchips

Surface passivation technique	References
[Acryloylamino]propyl] trimethylammonium chloride (BCQ)	[55, 173, 174]
Bio-Rad run buffer	[152]
HCl	[119]
HCl, NaOH	[92, 113, 264]
Hydroxyethyl cellulose (HEC)	[249]
Hjertén process	[15, 27, 34, 58, 68, 75, 77, 96, 101, 125, 134, 136, 142, 144, 151, 157, 163–166, 183, 184, 197, 203–205, 207, 211, 217, 218, 227, 228, 248, 253–256, 263, 265, 285, 292, 294, 296, 319, 320, 322, 336, 337]
HNO ₃	[70]
HNO ₃ /NaOH	[43]
Hydroxypropylmethyl cellulose (HPMC)	[261]
LPA (in PDMS microchannel)	[327]
LPA (photopolymerized)	[115, 116]
Methanol	[224]
Methyl hydroxyethyl cellulose (MHEC)	[260]
NaOH	[21, 22, 35, 42, 48, 102, 138, 143, 147, 154, 162, 167, 181, 182, 185, 213, 214, 230, 242, 276, 317, 332, 333, 345]
O ₂ plasma	[120]
Polydimethylacrylamide (PDMA)	[44, 64, 84]
PDMA/alkyl glycidyl ether	[208, 209]
Polydimethylsiloxane (PDMS)	[9]
PDMS/Pluronic	[201]
Polyethylene glycol (PEG)	[220]
Polyhydroxyethylacrylamide	[38, 39]
Polyvinylpyrrolidone (PVP)	[12, 118, 141, 244, 288–290, 344]
Silane	[323]

3. Applications of Microchip Electrophoresis

Microfabricated electrophoresis systems have been used to analyze samples ranging from small molecules, to DNA, to proteins (Table 6). Analysis of both single- and double-stranded DNA is of particular interest

because of the central role it plays in a variety of biomedical and molecular biology applications. Separation of single-stranded DNA fragments labeled with covalently attached fluorophores are typically performed under denaturing conditions generated by addition of chemical denaturants and/or running at an elevated temperature ($\sim 50^{\circ}\text{C}$) to inhibit secondary structure formation that would alter migration behavior. Fragment sizes typically range from oligonucleotides tens of bases in length up to around one kilobase. Double-stranded DNA separations are not performed under denaturing conditions and fragments can be labeled with intercalating dyes that do not require covalent attachment. Fragment sizes that can be separated extend from around 100 bases to the kilobase size range. DNA molecules in the 40–50 kilobase vicinity and longer are large enough to be directly observable using an optical microscope, enabling migration of individual molecules to be recorded. Protein separations differ somewhat from DNA because they possess a variable charge to size ratio. Two dimensional configurations are often employed to deal with this added level of complexity whereby species are first separated in one dimension

Table 6. Analytes separated using electrophoresis microchips

Analyte separated	References
DNA (double-stranded)	[5, 7, 10, 12, 19, 24–26, 29, 32, 34, 39, 41, 44, 52, 64, 66, 68–70, 74, 75, 77, 78, 85–88, 101, 103–105, 118–121, 125, 127–129, 136, 141, 142, 144, 148, 151, 152, 154, 155, 163–166, 177–179, 190, 202, 203, 208, 209, 212, 216, 217, 222, 226, 229, 233, 235, 240, 244, 250–252, 263–265, 271, 274, 278, 281–288, 290, 291, 293, 295, 297, 300, 307, 311, 313, 316, 319–322, 324–326, 328, 329, 331, 338, 341, 343, 344]
DNA (single-stranded)	[6, 15, 58, 71, 72, 76, 78, 96, 157, 183, 184, 187, 192, 204, 205, 207, 211, 227, 228, 239, 248, 253–256, 261, 271, 273, 289, 292, 294, 296, 298–300, 302, 303, 323, 332, 337]
Proteins	[9, 17, 27, 35, 38, 42, 84, 90, 97, 98, 114–116, 122, 124, 138, 156, 185, 186, 197, 220, 221, 234, 236, 249, 260, 327, 335]
Small molecules	[4, 8, 20–22, 36, 37, 43–48, 50, 51, 53–55, 71, 79–83, 92–94, 102, 107–109, 113, 126, 130–135, 137, 143, 145, 147, 149, 150, 155, 160–162, 167, 168, 173, 174, 176, 181, 182, 193–196, 198, 199, 201, 213–215, 218, 219, 223, 224, 230, 231, 237, 238, 242, 243, 246, 257, 258, 266–269, 276, 279, 306, 309, 310, 312, 314, 315, 317, 326, 333, 334, 336, 340, 345]

according to charge (e.g., using isoelectric focusing in a pH gradient), after which each constant-charge zone is separated according to size. Finally, applications involving separation of neutral or weakly charged analytes can be accomplished using MEKC techniques.

3.1. Advanced Electrophoresis Methods

Recent advancements have resulted in the development of separation technologies offering capabilities beyond those found in adaptations of conventional electrophoresis techniques [180] (Table 7). One notable example is the use of micro- and nanofabricated pillar arrays as separation matrix structures in place of polymer gels (Fig. 7a). These post arrays can be easily mass produced using micromachining technology and possess inherently uniform monodisperse two-dimensional pore morphologies. By manipulating the size, shape, and spacing of the pillars, separation properties can be tuned to make them compatible with a wide range of samples and analyte sizes. In addition, since the sieving structures are prefabricated inside the microchannel, the gel loading process is eliminated. The detailed physics associated with collisions and interactions that occur between the migrating analytes and the array of obstacles are responsible for introducing size-dependent mobilities. The size of the nanostructured pillars is limited by the resolution of photolithographic patterning, typically in the vicinity of a few hundred nanometers. Consequently, these designs are most effective for separation of large analytes (e.g., kilobase sized DNA). Another class of micromachined sieving structures that have been employed for electrophoresis involves patterning of periodically spaced nanometer size gaps between the floor and ceiling of the separation channel (Fig. 7b). Unlike pillars, the gaps are vertically spaced and can be fashioned relatively straightforwardly by controlled etching. The physics of DNA electrophoresis through these nanogap arrays can be described in terms of an entropic trapping mechanism whereby excursions into the nanogaps produce migration characterized by rapid hops between gaps, with larger fragments experiencing a higher probability of excursions into the nanogaps and thereby eluting faster than smaller ones.

A novel and entirely different class of fabricated sieving structure consists of magnetic microspheres that become assembled into a packed matrix upon application of an external magnetic field (Fig. 7c). Here, the pore network morphology depends on an interplay between the size and concentration of the particles and the separation channel geometry. This arrangement allows sieving matrices with tunable reproducible pore sizes to be formed in-situ, and the aggregated particle network can be instantaneously

dispersed once the magnetic field is removed. Another novel separation phenomenon of interest to miniaturized systems is surface electrophoresis of DNA. Here, size dependent mobility is induced via interactions between the substrate (typically silicon) and DNA chains adsorbed on its surface. In this way, surface electrophoresis can be used to perform size selective fractionation in the absence of conventional sieving gels.

Table 7. Variations of electrophoretic separation adapted to the microchip format

Separation mechanism	References
Atomic force microscope (AFM)	[302]
Electric field flow fractionation (EFFF)	[33]
Entropic recoil	[26]
Entropic trapping	[31, 62, 103–105, 247, 277]
Isoelectric focusing (IEF)	[114, 122, 124, 197, 249]
Isotachopheresis (ITP)	[314]
Magnetic bead array	[63, 64, 208–210]
Micellar electrokinetic chromatography (MEKC)	[45, 160, 215, 236, 238, 243, 260, 279, 310, 315]
Microfabricated pillar array	[5, 10, 25, 29, 41, 65–67, 121, 127, 141, 225, 232, 307, 308, 334, 338]
Microstructured periodic cavities	[69]
Optical fractionation	[191]
Single molecule fluorescence bursts	[88]
Surface electrophoresis	[171, 172, 189, 233, 259]

Finally, an intriguing adaptation of electrophoresis for separation of short oligonucleotide fragments has been demonstrated using an electric field imposed parallel to an atomic force microscope (AFM) tip [302] (Fig. 7d). The DNA fragments to be separated are first electrokinetically collected at the base of the AFM cantilever, then released by a periodically reversing electric field applied between the cantilever and substrate. The DNA fragments display a size-dependent mobility as they migrate along the length of the AFM tip, and the inherently small dimensions allow very high electric fields to be applied with minimal Joule heating. By tuning the frequency at which the electric field is reversed, desired fragment sizes can be transferred from the tip to the surface of a substrate while slower moving fragments are driven back to the reservoir before reaching the tip.

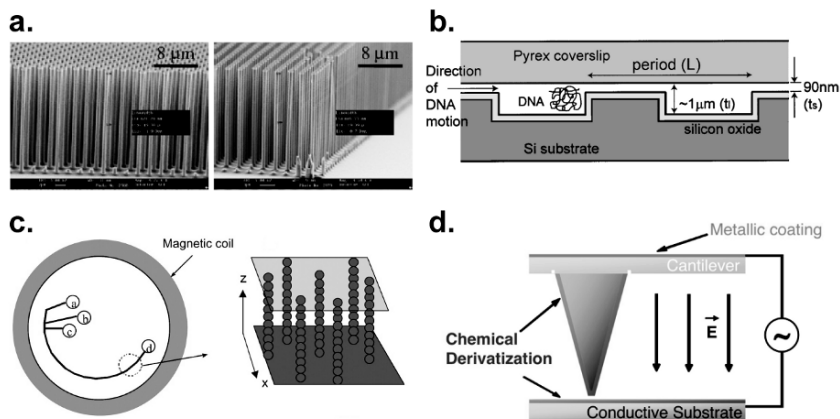


Fig. 7. (a) Scanning electron micrograph of microfabricated high-aspect ratio pillar arrays in two different arrangements [29]. The structures are etched into a silicon substrate using a deep reactive ion etching (DRIE) process capable of producing pillar diameters and spacings of order 500 nm (reproduced with permission, copyright 2006 IOP Publishing LTD). (b) Illustration of a typical geometry used to perform separations based on entropic trapping effects [103] (reproduced with permission, copyright 1999 The American Physical Society). (c) Schematic of an arrangement incorporating a separation channel inside a magnetic coil (left) [64]. A columnar network morphology is formed in a suspension of 1 μm dia superparamagnetic particles when a magnetic field is applied (right) that can function as a sieving matrix for DNA separations (reproduced with permission, copyright 2002 American Association for the Advancement of Science). (d) Concept of separating DNA using atomic force microscopy [302]. When an electric field is applied between an AFM cantilever and a substrate, DNA fragments initially at the base of the AFM tip migrate toward the substrate with size-dependent mobilities and can be selectively deposited by tuning the electric field reversal frequency (reproduced with permission, copyright 2006 American Institute of Physics)

3.2. Integrated Systems

Considerable efforts have also been directed toward combining electrophoresis-based analysis with other operations to produce integrated lab-on-a-chip systems (Table 8). Many genomic analysis applications, for example, involve using the polymerase chain reaction (PCR) to chemically amplify minute DNA samples to detectable levels prior to analysis. The PCR process involves repeatedly cycling a reagent mixture (template DNA, primers, dNTPs, a thermostable polymerase enzyme, and other buffering additives) through temperatures corresponding to *denaturation* of the double-stranded template ($\sim 95^\circ\text{C}$), *annealing* of single-stranded oligonucleotide primers at locations adjacent to the target region ($\sim 50\text{--}65^\circ\text{C}$), and enzyme

directed synthesis (*extension*) of the complementary target strand ($\sim 72^\circ\text{C}$). The inherently high efficiency of this process, yielding an exponential increase in the number of copies with each cycle, has helped make PCR one of the key enabling technologies in molecular biology. Thus, it is not surprising that considerable efforts have been directed toward integrating PCR with electrophoretic separation of the amplified DNA fragments. Miniaturization of PCR is challenging, however, due to the potential for evaporation when minute volumes of aqueous reagents are repeatedly heated to temperatures in the vicinity of 95°C , and due to the potential for non-specific adsorption of reagents at the reactor walls in high surface to volume microchannels that can inhibit the reaction [158, 245, 275].

Table 8. Integrated microfluidic devices incorporating electrophoresis

Integrated functions	References
2-D separation	[98, 236, 238, 260]
Band capture	[73, 177, 178]
Cell lysis	[201, 319]
Immunoassay	[37]
Isothermal amplification	[24, 110, 285]
Labeling	[35, 42, 83, 97, 102, 132, 133, 186, 264]
Polymerase chain reaction (PCR)	[68, 70, 119, 152, 163–166, 228, 229, 319, 324, 344]
Purification	[15, 228]
Restriction digest	[97, 136, 229]
Sanger sequencing	[15]

Examples of other operations integrated with microchip electrophoresis include cell lysis, sample purification, multi-dimensional separations, labeling, and hybridization. Progress has also been made toward incorporating multiple sample processing and analysis steps in a single microfluidic device, as demonstrated in a hybrid glass–silicon design developed in the Burns group capable of amplifying a 106 bp DNA target from a bacterial genomic template via an isothermal strand displacement amplification (SDA) process followed by gel electrophoresis with integrated photodetection of the fluorescently labeled reaction products [24]. Subsequent work

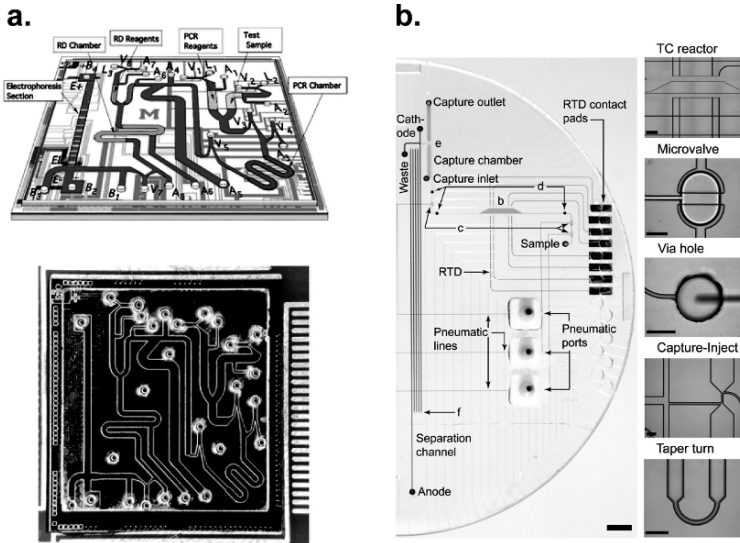


Fig. 8. (a) Schematic (upper) and photograph (lower) of a 1.5×1.6 cm microfluidic device capable of performing a sequential PCR, restriction enzyme digestion, and gel electrophoresis [229] (reproduced with permission, copyright 2006, The Royal Society of Chemistry). (b) Layout of a microfluidic bioprocessor for performing Sanger cycle sequencing of DNA (scale bar = 5 mm) [15] (reproduced with permission, copyright 2006, The National Academy of Sciences of the USA)

has resulted in development of an ultra-compact 1.5×1.6 cm hybrid glass/silicon microfluidic chip capable of performing a PCR-RFLP assay for influenza A virus detection involving two sequential reactions followed by an electrophoretic separation [229] (Fig. 8a). Most recently, the Mathies group has reported a multilayer glass/PDMS design capable of performing integrated Sanger cycle sequencing of DNA (a reaction requiring similar thermal cycling parameters as PCR) followed by product purification and electrophoretic separation in a 30-cm long folded channel [15]. Read lengths of 556 bases were achieved with 99% accuracy (Fig. 8b).

Commercial DNA analysis systems based on microchip capillary electrophoresis technology have also appeared on the market (Table 9). For example, the Agilent 2100 Bioanalyzer, the most widely used commercial chip-based DNA analysis device, is based on a Caliper LabChip design incorporating arrays of glass electrophoresis microchannels that can be loaded with a low viscosity gel-dye mixture. This system uses interchangeable electrophoresis chips that interface with a benchtop power supply and optical detection system. The Hitachi SV1100 Microchip CE system is based on a similar concept, but the electrophoresis microchips are constructed using PMMA. The BioMEMS-768 DNA sequencer from Network Biosystems/Shimadzu takes a slightly different approach by using microfabrication technology to construct arrays of hundreds of 40 cm long separation channels in 50×25 cm glass substrates to provide higher throughput and integration with conventional automated liquid handling systems.

Table 9. Commercial microchip electrophoresis systems

Commercial system	References
Agilent 2100	[17, 76, 90, 128, 129, 212, 216, 343]
Hitachi SV1100	[50, 51, 53, 54, 76, 110, 129, 148, 234, 281–284, 328, 329, 331, 341]

4. Summary and Outlook

Considerable strides have been made since microfabricated electrophoresis devices were first developed in the early 1990s [194]. These advancements have been made possible through a combination of improvements in micromachining technology, sieving matrix materials, and instrumentation. Despite these advancements, the current generation of miniaturized systems generally have yet to demonstrate benefits in cost or performance that are compelling enough to make them seriously competitive with conventional benchtop-scale CE technology. Some of the challenges that remain to be addressed include reducing device size to the point where the enormous cost savings associated with photolithographic microfabrication can be fully realized, enhancing integration, improving the capability to interface with the external macroscale environment, and developing miniaturized detection technology. Systematic fundamental studies are also important in order to provide a more complete understanding of the physics of electrophoresis in micro- and nanoscale environments. Future developments in these areas over the next few years are likely to lay the foundation for a new generation of rapid, sensitive, and inexpensive instrumentation

with separation performance exceeding that in many of the conventional benchtop-scale analytical systems available today.

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