

MICROMACHINED METALLIC PIPETTES AND BIOANALYSIS SYSTEMS

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In this paper, we discuss miniaturized biochemical analysis system components, micromachined metallic pipette arrays (MPA) and the micromachined electrical field-flow fractionation system (μ -EFFF). The design, fabrication, and characterization of the MPA and μ -EFFF are detailed. In addition, the integration of the components using mechatronics technologies is discussed.

INTRODUCTION

One rapidly emerging application field for micromachining technologies is biomedical instrumentation. Micromachining technologies are of interest to the biomedical instrumentation industry because the manufacturing technologies offer an avenue to produce miniaturized instrumentation systems with sub-micron precision. Miniaturization of instrumentation is of interest for a variety of reasons, dependent on the application. For example, in the case of surgical instrumentation, micromachining technologies can be used to develop precision surgical tools for endoscopic and delicate surgical procedures. The need for precision surgical tools is driven by the need for less invasive surgical procedures as well as by the number of specialized microscopic procedures under study and in practice today. Another example of miniaturized biomedical instrumentation is biological/chemical analysis systems. In the case of miniaturized analysis system, scaling down of the system dimensions from "macro" to "micro" scale dimensions has several advantages. The key advantages of miniaturization are faster analysis times, highly parallel analysis systems, smaller sample/reagent volumes, and the opportunity to manufacture disposable analysis systems using batch fabrication technologies.

As is similar to other application areas of micromachining technologies, micromachining enables the realization of biomedical instrumentation previously unattainable using conventional manufacturing techniques. Therefore, micromachining technologies can be used to advance biomedical instrumentation development by enabling the development of novel instrumentation and by enabling miniaturization of existing biomedical instrumentation. Examples of novel biomedical instrumentation manufactured or under development using micromachining technologies include multi channel neural stimulation and recording

systems, whole cell systems, and artificial sensory systems. Examples of miniaturized instrumentation developed as alternatives to larger "macro" scale instrumentation include biological/chemical analysis systems and medical monitoring systems.

The number of biomedical applications for micromachining technologies is rapidly growing. Since micromachining technologies are a relatively new set (and increasing set) of manufacturing technologies, there are many critical applications still to be addressed. To date, many advances have been made in biomedical instrumentation development as a result of using micromachining technologies to fabricate (or partially fabricate) the total instrumentation system. The main types of biomedical instrumentation which utilize micromachining technologies are neural stimulation/recording systems [1-13], biological/chemical analysis systems [14-29], whole cell systems [30-35], surgical instrumentation [36-38], medical monitoring systems [39], prosthetic devices (e.g., artificial limbs) [40], and tactile sensors [41-44].

During the past 10 years, a large number of biological analysis techniques have been demonstrated using micro-scale systems and have been implemented using the micromachining technology. Currently, these systems include electrophoresis [21-24], free flow fractionation [19,20], electric field flow fractionation (EFFF) [25], polymerase chain reaction (PCR) [26-29], and liquid chromatography [17,18]. For these systems to be practical, the systems must integrate sample handling, data processing, and data acquisition, preferably in a totally automated system. This paper will look at examples of processing and sample loading.

Today, micro samples are loaded primarily by two methods: pipetting and electromigration. In pipetting, small sample volumes are transferred into the loading ports of the separation microchannels. The major disadvantage of this method is the lack of fine control (sub μ L) over the actual sample volumes. In electromigration, samples are loaded into a channel perpendicular to the separation microchannel. Application of electric field along this channel results in electromigration of the sample and the loading of precise sample volumes. This method requires additional micro channels for sample loading operation.

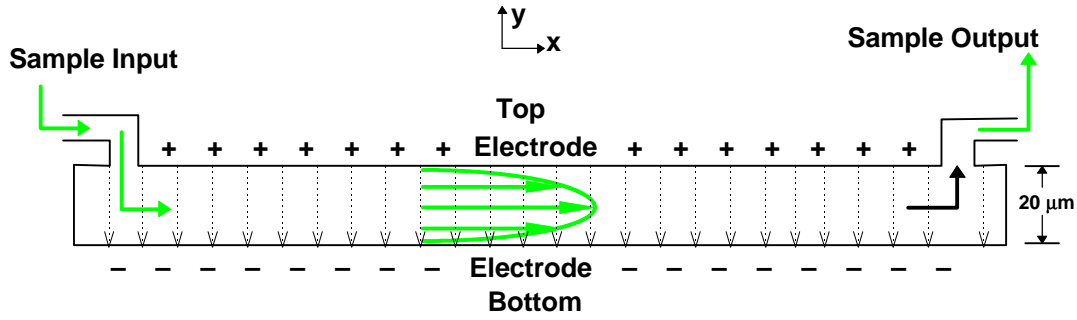


Figure 1. Diagram of EFFF function showing parabolic flow profile, configuration of electrodes, and sample input and output ports.

Two primary advantages of the micromachined pipette arrays (MPA) are (a) the ability to transfer precise volumes of samples in the pL to μ L range, and (b) the ability to handle samples in a highly parallel fashion, with a possibility of manipulating hundreds of samples simultaneously. In addition to the use as a passive element for sample handling, the MPA's can be used for multiple operations (passive and active). One clear example is the use of MPA's in PCR, as the reaction can be performed while samples are inside the pipettes. An electrical current through the pipettes will uniformly heat samples to the required temperatures, while convective air cooling and conductive cooling through bulk silicon (high thermal conductivity) substrate will cool the pipettes during the cooling stage of the PCR thermal cycling.

The micromachined pipette arrays are designed to work with a wide range of biochemical analysis systems. Our group has been working specifically with electrical field flow fractionation (EFFF). EFFF is a separation technique that relies on an electric field perpendicular to a flow field in a high aspect ratio channel with the electric field formed across the thinnest dimension of the channel as shown in Figure 1.

In current EFFF systems, the channel thickness is about 120-200 μ m [45], while micromachined versions have channels with a height of 5-40 μ m [25]. The separations are performed in a low-viscosity liquid (typically an aqueous buffer solution) which is pumped through the separation channel. The EFFF process is based on controlling the relative velocity of particles by forcing particles towards the wall of the channel [46]. Particles with high electrophoretic mobility or “ ζ -potential” will pack close to the wall while particles of lower ζ -potential will form a more diffuse cloud that extends further into the flow stream. Since the flow in the channel is laminar and the associated velocity profile is parabolic, the particles will move through the channel at distinct rates based on ζ -potential and particle size. Since the particle size is easily determined using other techniques, the effect of the EFFF process is to separate particles by ζ -potential [47].

EFFF systems are used to separate particles in colloids, emulsions, and other suspensions, and to measure

characteristics of these particles including electrophoretic mobility, ζ -potential, and diffusion coefficient. Particles of biological interest that can be separated and tested using a μ -EFFF system include proteins, DNA, liposomes, organelles, cells, viruses, polymers, and other particles modified by these biological molecules. Additionally, the system can be used to make measurements of protein adsorption, adsorbate activity, and close packing of proteins, DNA, or other molecules (i.e. surface modified particles) on colloidal particles, monitor environmental water conditions, and determine the polydispersity of colloids with respect to size, charge, and stability [48]. Fields expected to be interested in a system such as this include biochemistry, cell biology, bioengineering, biomaterials, chemistry, the separation sciences, pharmaceuticals, medicine, and environmental engineering.

The resolution of an EFFF system is given by Equation 1 where R_s is the resolution of the system, Δd is the difference in diameters for the particles being resolved, d is the average diameter of the particles being separated, D is the average diffusivity of the sample, w is the plate separation distance, L is the channel length, μ is the electrophoretic mobility of the particles, V_{eff} is the effective voltage in the channel, and $\langle v \rangle$ is the average velocity of the carrier in the channel [49]. When examining Equation 1 closely, it becomes apparent that the best method for improving resolution for a given sample is by decreasing the channel width since raising the applied voltage is difficult due to electrolysis of the buffer solution. Thus, EFFF is an ideal system for the application of micromachining technologies. Figure 2 is a graph of Equation 1 and shows the increase in resolution with decreasing channel height and increasing applied voltage. The use of micromachining technologies will give the next generation of EFFF systems several significant advantages over its larger relatives including faster separation times,

$$R_s = \frac{\Delta d}{d} \sqrt{\frac{L m^3 V_{eff}^3}{6 \langle v \rangle}} \quad (1)$$

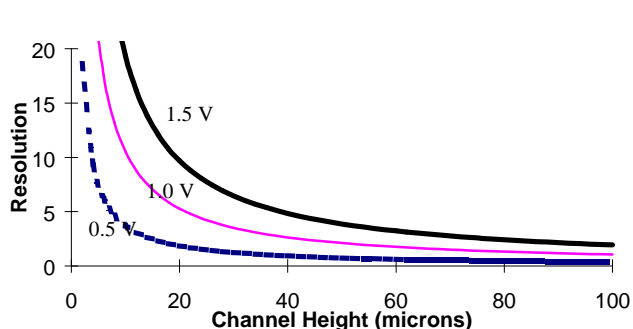


Figure 2. Graph of equation 1 showing increase in resolution for decreasing channel height for various applied voltages. The particles are 40 and 50 nm polystyrene in a NH_4HCO_3 buffer with a flow rate of 0.9 cm/s. The simulated channel is 6 cm long.

increased resolving power, smaller sample sizes, reduced system cost, smaller system size, and parallel channel capability. Recent work has shown the feasibility of a micromachined EFFF system and demonstrated the applicability of the literature to a channel of these dimensions.

The development of miniaturized biological/ chemical analysis systems is one of the rapidly growing application areas for micromachining technologies. In order to realize these miniaturized systems, there are many technological hurdles to be overcome. Some of the primary issues are: a) interfacing samples and reagents from the macro scale to the micro scale, b) detection of output from the micro analysis system, and c) manipulation of pL-nL sample volumes. In this paper, the development of miniaturized micro analysis system components discussed. First, a method for interfacing/delivering small (pL- μL) sample volumes is discussed, the micromachined pipette array. Second, a miniaturized analysis system, the micro electrical field flow fractionation system, is discussed.

MICROMACHINED PIPETTE ARRAYS (MPA)

The micromachined pipette arrays (MPA) are fabricated using extensions of previously reported micromachining fabrication technologies [11,50, 51]. The fabrication process is low temperature and is compatible with integrated circuit (IC) technology as a post process.

Initially, a $\langle 100 \rangle$ silicon wafer is RCA cleaned and one side is heavily doped with boron using high temperature thermal diffusion to form a 4-6 μm p^+ layer. A layer of silicon nitride deposited using plasma enhanced chemical vapor deposition (PECVD) is used as a mask during the subsequent anisotropic etching of silicon in 20% KOH at 60°C [53]. The diffused p^+ boron layer serves as an effective etch stop; forming a sacrificial membrane upon which portions of the pipette shafts are fabricated and subsequently released (Figure 3a). Next, a metal system of adhesion layers and an electroplating

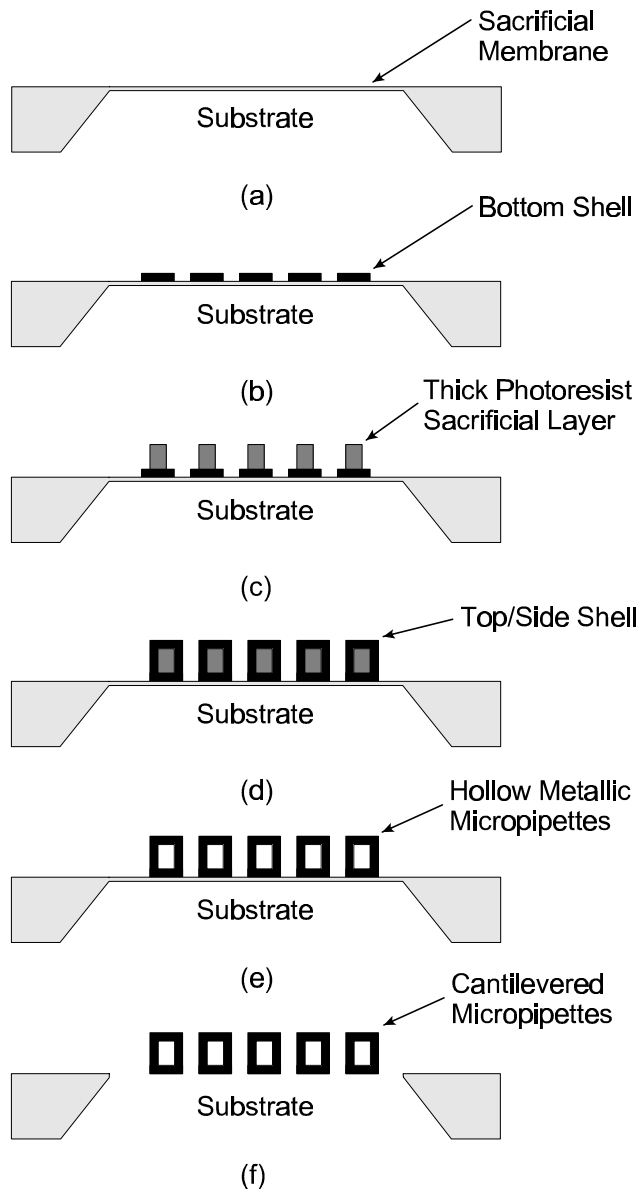


Figure 3. Micromachined pipette array fabrication procedure. (a) Create silicon membrane using high temperature p^+ doping and KOH etching; (b) microelectroform bottom shell; (c) apply and pattern thick photoresist; (d) microelectroform side walls and top shell; (e) remove thick photoresist using acetone bath; (f) release pipettes by etching p^+ membrane.

seed layer is deposited over the substrate and the micro molding layer (photoresist) for defining the bottom wall of the pipette is spin coated and patterned using standard photolithographic techniques. The bottom wall of the pipette is formed using micro electroforming technology (Figure 3b). A variety of metals can be used as the primary structural material in pipette fabrication (e.g., nickel, gold, copper). Once the electroforming is complete, the micromolding photoresist is removed using acetone, methanol, and water consecutively, and adhesion and seed metal layers are removed using wet etching. Next, 5 to 50 μm of



Figure 4. Scanning electron micrograph of a micromachined pipette array. The wide sections are $12750 \times 1500 \times 30 \mu\text{m}^3$ (L×W×H). The microchannels extend 1.5 mm from the silicon substrate and are 500 μm wide. The structural material is electroformed nickel with wall thickness of 15 μm .

commercially available thick positive photoresist (AZ4620) is spin coated and lithographically patterned on top of the electroformed metal [52]. The thick photoresist is used to precisely define the inner dimensions of the pipette and serves as a thick sacrificial layer to be removed later in the process (Figure 3c). An electroplating seed layer is then sputter deposited over the thick photoresist. The sputtering process is used due to its superior side wall coverage. After the deposition, top and side walls of the pipette are micro electroformed using a commercially available positive photoresist to form micromolds (Figure 3d). Once the walls are formed, an acetone bath is used to remove the micromolding photoresist and the sacrificial thick photoresist from the inside of the structure forming the hollow pipette (Figure 3e). To electrically isolate pipettes, reverse sputtering or wet etching is used to remove the remaining adhesion and seed layers. The p^+ membrane is removed from the membrane regions by SF_6 dry etching from the backside of the wafer. Thus, the shafts of the pipettes are released and freely suspended,

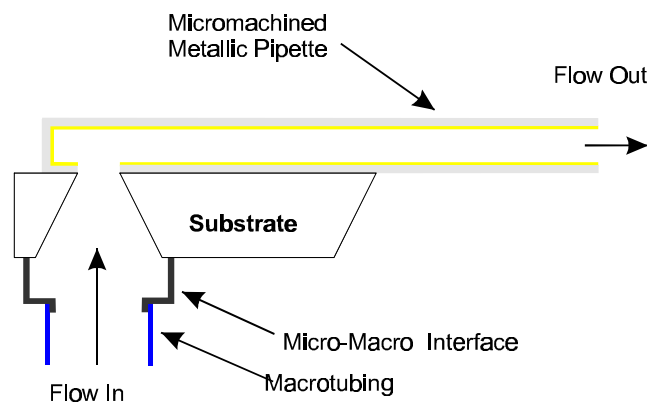


Figure 5. Micromachined pipette array (MPA) interfacing scheme via the back-side input ports.



Figure 6. Photograph of a micromachined pipette array interfaced from the back side. A 1/8 in tubing and 1/8 inch swagelock adapter are used to connect micro-interface to the macro pressure source

projecting outward from the substrate (Figure 3f).

A micromachined pipette array fabricated on a silicon substrate is shown in Figure 4. The wide sections of these pipettes are 12750 μm long and 1500 μm wide. The pipette shafts extend 2 mm from the silicon substrate and are 500 μm wide. The inner thickness of the pipettes is 30 μm . The structural material is electroformed nickel with wall thickness of 15 μm .

The input ports of the pipettes are fabricated by etching through the substrate for backside access (Figure 5). A central or an isolated pressure interface is used to interface the macro pressure of fluid source with an array of microchannels. A photograph of an interface attached to the MPA is shown in Figure 6.

MICROMACHINED ELECTRIC FIELD FLOW FRACTIONATION (μ -EFFF)

The prototype μ -EFFF systems was fabricated using micromachining technologies as outlined in Figure 7 [25]. Initially, Si_3N_4 is deposited on both sides of a 76 mm $\langle 100 \rangle$ silicon wafer. Bulk anisotropic etching in KOH [53] is used to define 200 μm square input and output ports as demonstrated in Figure 7a. Next, titanium and platinum are deposited on the polished side of the wafer. Metals are

patterned to form channel electrodes, detection electrodes, and contact points using a photoresist mask and a mixture of 8 parts H₂O, 7 parts HCl, and 1 part HNO₃ to etch the platinum and a 1% HF solution to etch the titanium as shown in Figure 7b. Thick photosensitive polyimide is used to define the micro flow channels (10-40 μm in height) as indicated in Figure 7c [54]. Once polyimide is spun on to the wafers, UV patterned and developed, then it is completely cured in an oven. The thin Si₃N₄ membranes are then removed (Figure 7d). Titanium and platinum are sputtered on a glass substrate that has been cut to fit over a group of μ-EFFF channels (Figure 7e). The titanium and platinum are subsequently patterned to form the second set of electrodes. The glass and silicon substrates are bonded together using a UV curable, biocompatible adhesive (Figure 7f). A cross-section at this point is shown in Figure 7g.

Plastic ferrules are bonded over the input and output ports of the silicon substrate using the same UV cured adhesive. Teflon tubing with an inner diameter of 254 μm is inserted into the ferrules and bonded in place. The Teflon tubing provides an attachment point for the buffer pumping system and allows sample injection. The μ-EFFF devices fabricated to date range from 4 to 6 cm in length with channel heights of 10 to 40 μm and aspect ratios between 50 and 600. A picture of the μ-EFFF system and two macro scale EFFF systems is shown in

Figure 8. The macro EFFF systems are both single channel systems, one with a length of 64 cm and the other with a length of 30 cm and both are similar to systems now in the midst of commercial development. There are 10 μ-EFFF devices on the wafer pictured. Notice that the μ-EFFF devices are less than 0.5 cm in overall thickness while the macro channels are well over 10 cm thick.

Polystyrene particles were separated according to the theory found in the EFFF literature, both demonstrating the accuracy of mathematical models for an EFFF system of this size and proving the ability to fabricate a system of these dimensions. Sample injection and detection were both performed off-chip and contributed to limiting the possibilities of this EFFF device due to their size mismatch with the μ-EFFF channel. While, this model served to prove the concept of a micromachined EFFF system, there is still much work to be done before a commercial system could be made available.

A typical separation run through the μ-EFFF system is shown in Figure 9. The 130 nm particles are clearly separated from the supporting medium expressed in the void peak, while the wide peaks are a result of high band broadening. The predicted elution time using the mathematical model is about 21 min for these particles, while the actual elution time for these particles is 2.6 min after taking into consideration the 30 second stop time and the transport time delay of 3.5 min at this flow rate. This discrepancy can be rectified by observing

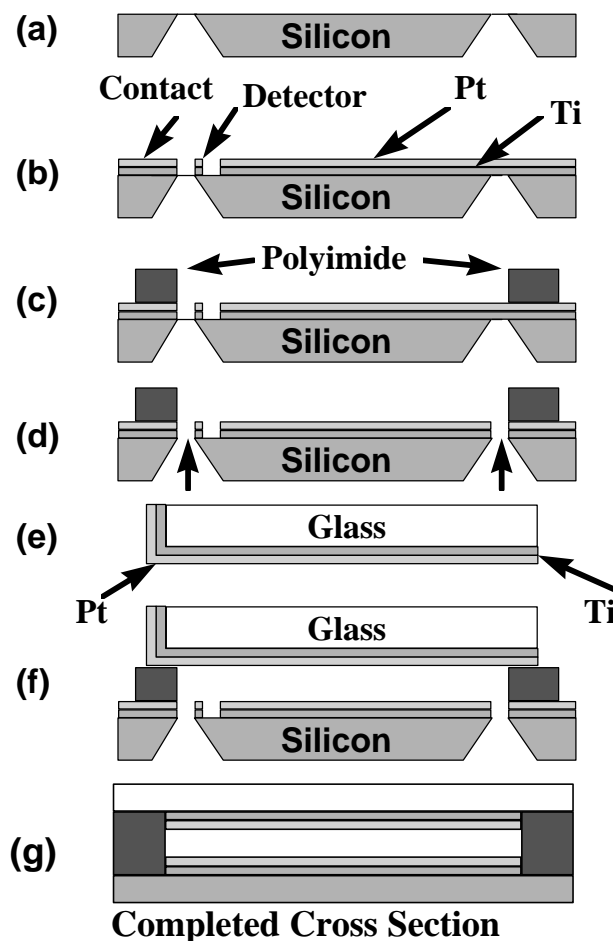


Figure 7. Flow diagram of fabrication of μ-EFFF system. (a) Etching of input and output ports in silicon (b) Deposition and patterning of titanium and platinum electrode (c) Application and patterning of polyimide (d) Removal of Si₃N₄ membranes (e) Deposition and patterning of titanium and platinum on glass substrate (f) Bonding of glass and silicon substrates (g) Cross section of completed μ-EFFF system.

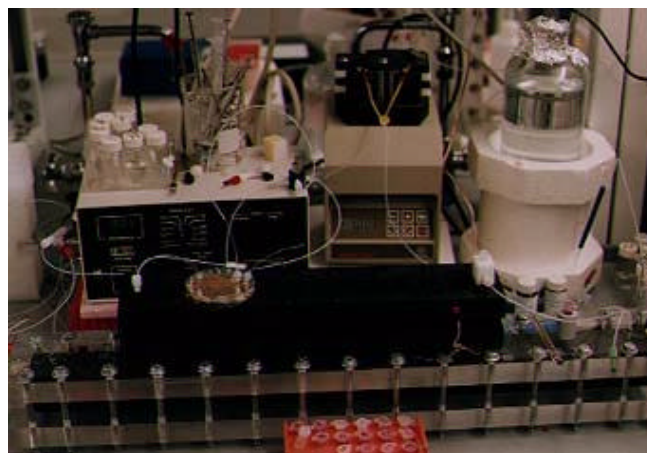


Figure 8. Picture of prototype μ-EFFF system with two macro EFFF systems.

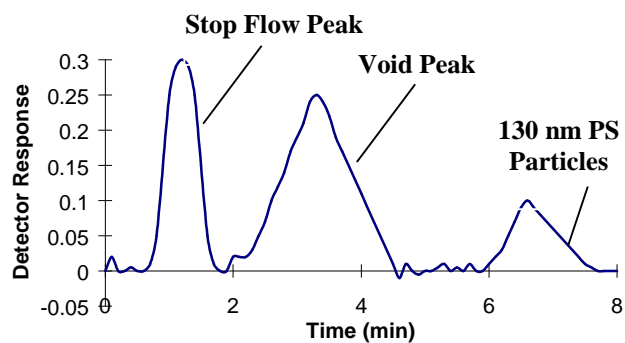


Figure 9. Typical separation run in prototype μ -EFFF system.

the currents flowing in the circuit. The measured current for this run was $38 \mu\text{A}$, about 9 times lower than the predicted current of $324 \mu\text{A}$ using the known conductivity of the buffer and the measured resistance of the circuit. Using the measured current to solve for the actual voltage being experienced across the channel yields a voltage of 200 mV with a predicted elution time for the 130 nm particles of 2.66 min , almost precisely the time taken for the 130 nm particles to elute.

Table 1 gives a comparison of the parameters for typical macro EFFF systems compared to the μ -EFFF system demonstrated here. Note the great improvements in system size, aspect ratio, relaxation time, sample size, run times, and parallel operation. The reduction in system size should allow for the possibility of portable EFFF systems and a decrease in the laboratory space required for the current systems. The increased aspect ratio should lessen the impact of edge effects in the system and thereby reduce band broadening. The reduction in relaxation times and run times should speed analysis in the laboratory. The reduction in sample sizes alleviates the need to greatly multiply a sample before analysis (as is done in DNA amplification by PCR) or to

Table 1
Comparison of parameters for EFFF systems

Parameter	Macro	μ -EFFF
Channel Length	64 cm	4-6 cm
Channel Thickness	$178 \mu\text{m}$	$20 \mu\text{m}$
Aspect Ratio	100	Up to 400
Relaxation Time	300 s	3 s
Measured Number of Plates at 1 cm/s	160	24
Theoretical Number of Plates	750	1200
Sample Size	$5 \mu\text{L}$	$0.1 \mu\text{L}$
Parallel Channels	None	10
Run Times	40 min	5 min
Nominal Field Strengths with 1.7 V applied	95 V/cm	850 V/cm

reduce the effort needed to collect a sample large enough for analysis. The parallel channels allow for multiple tests to be run at the same time.

MECHATRONICS AND MINIATURIZED BIOCHEMICAL ANALYSIS SYSTEMS

One of the technical milestones being sought by industry interested in miniaturized analysis systems is the development of an automated solution for high throughput analysis. The total analysis may consist of multiple operations in which samples are manipulated from one miniaturized analysis component to subsequent components. A common example of the need for multiple operations is in the case of DNA amplification and sequencing. In this case, samples are first amplified using a polymerase chain reaction followed by electrophoretic separation. There are two general approaches to the development of automated systems. The first approach is integrated systems dedicated to specific analysis sequences.

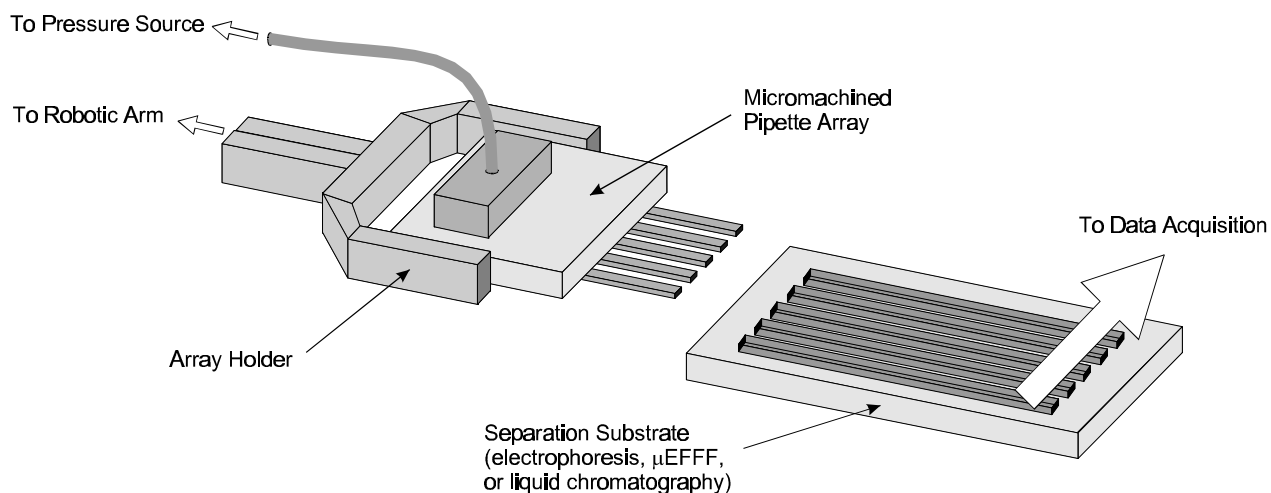


Figure 10. Schematic drawing of a mechatronic bioanalysis system.

The second approach is hybrid systems in which the components are modular and interchangeable. Mechatronics can be utilized eloquently for the development of hybrid miniaturized analysis systems. Figure 10 illustrates the use of micro robotics to realize a hybrid analysis system. In this case, the micromachined pipette array manipulates samples via a robotic arm attached to the array. The analysis chip can be a μ -EFFF system, another miniaturized analysis chip, or a series of analysis chips.

CONCLUSION

In this paper, the development of two miniaturized biochemical analysis system components were discussed. These components, the micromachined pipette array and the micro electrical field flow fractionation system utilize micromachining technologies to develop low cost, highly parallel analysis system components. The design, fabrication, and characterization of the MPA and μ -EFFF system are given. In addition, a performance comparison is given for the equivalent macro scale and micro scale EFFF systems.

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