# PACKAGING OF BIOMEDICAL ANALYSIS SYSTEMS

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## ABSTRACT

Packaging is a critical component of biomedical analysis systems that is often overlooked, and continues to be relatively primitive. Biomedical applications offer several unique challenges for packaging systems including: biocompatibility, sample injection into pressurized channels, a variety of energy transfer modes, platforms, and interfaces, and often a hostile environment. Several packaging methodologies are presented here with application to biomedical analysis systems as well as other microfluidic systems. Of special interest are the methods for interfacing microanalysis systems with the external user and the manipulation of samples at these dimensions. Specifically, packaging methods for miniature field flow fractionation systems, micropipettes, microneedles, and microreactors are presented.

## INTRODUCTION

Packaging for biomedical analysis systems offers several unique challenges, that in many cases, have not yet been addressed. Of major concern is the biocompatibility of these analysis systems. The definition of biocompatibility will vary with the application of the microsystem, but in general requires the use of surfaces with low protein adsorption, non-leaching materials, and other "non-interactive" features. Thus, the biological material must be protected from the device. These requirements will vary significantly depending on whether cells, DNA, proteins, or other biological materials are the primary analytes or actors. On the other hand, many biological environments and liquids can be damaging to microsystems, so the sensitive components of the microanalysis system must be protected from the harsh environment.

Interfaces between biomedical devices and modules are also of critical interest. Most biomedical analysis system currently rely on large, inefficient wells for sample handling and interfacing. While this interface method is often functional, it often eliminates some of the advantages of microsystems such as the cost savings associated with small sample sizes. In other systems, a sample must be injected into a pressurized channel, so the well structures are unacceptable. In some bioreactors, high pressures and temperatures are required for optimal function, and seals become a major issue. Accordingly, this paper will address several possible methods for solving these unique problems.

Another important need is to be able to link to current standard methods for interfacing chromatography and other fluidic systems. Systems that cannot connect meaningfully with existing equipment will require an entire new industry to develop and will therefore be accepted much more slowly.

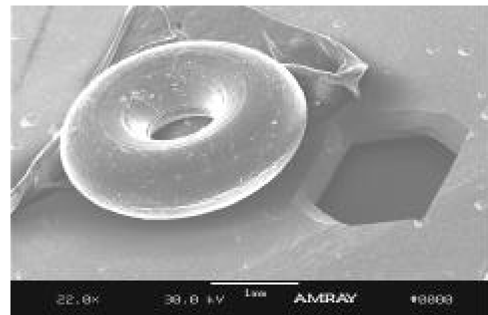


Figure 1. Original via design compared to 001 o-ring used for sealing.

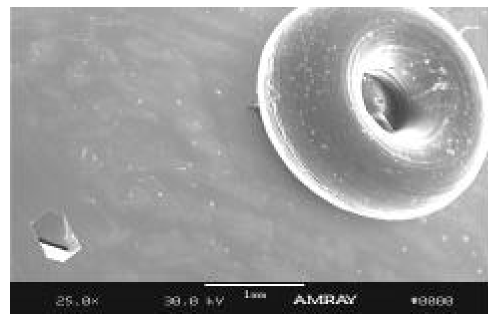


Figure 2: Reduced-size via giving robust sealing with 001 o-ring.

## MICROFLUIDIC SEALS FOR MICROREACTORS

Recent work at the Institute for Micromanufacturing developed microfluidic devices for performing gas-solid heterogeneous catalytic chemical reactions [1,2], with seal technology applicable to a wide range of microanalysis devices. These reactions are conducted over a range of conditions of temperature and pressure. To date, these conditions have covered 20ºC to 300ºC and $10^{-2}$ to $10^{4}$ torr. For full utilization of these reactors, we anticipate the need to reach temperatures of 500ºC and pressures near $10^{5}$ torr. Leak-tight seals for gaseous fluids at these conditions provide significant challenge relative to typical seals on microfluidic devices.

The silicon microreactor has via holes that penetrate the wafer on which it is made. These holes are aligned with a passage drilled in a

metal plate that is aligned with the via in order to supply gas-phase reactants and to release gas-phase product. The plate is sealed to the chip with a compressed o-ring of standard size 001, measuring about 2 mm in diameter. Figure 1 shows the original via design next to an o-ring that was glued to the chip to make the size comparison. It is obvious by inspection that this combination will not result in a reliable, leak-tight seal.

Figures 2 and 3 show a new via design. The size reduction (400 µm vs. 1.5 mm) resulted in a reliable seal that can tolerate variations in final via size as well as small misalignments in the assembly. The opening in the small via is actually an elongated orifice or gap. This geometry is acceptable since the low flow rates of our microsystem cause no significant pressure drop at this gap. Although this improvement resulted in a system that operates at temperatures up to 300ºC, a new approach is needed for higher temperatures due to the inherent limitations of elastomeric seals.

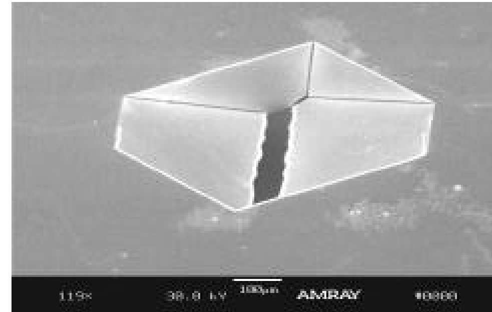


**Figure 3**: Close up of reduced-size o-ring showing gap originating from silicon crystal planes.

## MICROMACHINED NEEDLE ARRAYS

One rapidly growing area of interest is biomedical instrumentation where significant efforts worldwide are being made to develop micro biochemical analysis systems, physiological systems, and drug delivery systems [3,4,5]. Since the application of micromachining technologies to biomedical problems is still relatively new, there is an increasing set of manufacturing techniques and critical applications still to be addressed. One application of interest to the biomedical industry is the development of microneedles. Some of the smallest hollow needles that are available today have inner diameters of over 200µm.

Consequently, it is clear that a demand exists for a hollow needle device that can withstand typical handling and subcutaneously deliver medication without the usual discomfort associated with current needles. A schematic representation of such a device, a fluid coupled hollow metallic micromachined needle array, is presented in Figure 4.

Each array is composed of hollow metallic microneedles fabricated on top of a silicon substrate using micromachining surface fabrication techniques [6]. Every microneedle of the array consists of input shafts and cantilevered output shafts. A novel cross-flow design (needle coupling channels) is incorporated to equalize pressure distribution and minimize the effects of clogged passages within the needles [7]. A scanning electron micrograph of a micromachined needle array released from silicon substrate is shown in Figure 5. The needle coupling channels are positioned at the center of each needle and are 100 µm wide. Two sets of 60×100 $\mu m^2$ structural supports are 250 µm from each needle end. The needle wall thickness is approximately 20 µm of electroformed palladium. Each needle channel is 2 mm long, while the total width of the 25-needle array is 5.2 mm. The center-to-center spacing of individual needles is 200 µm.

The quality of the fabrication of the tip of each needle is especially important, since this is the part that will be

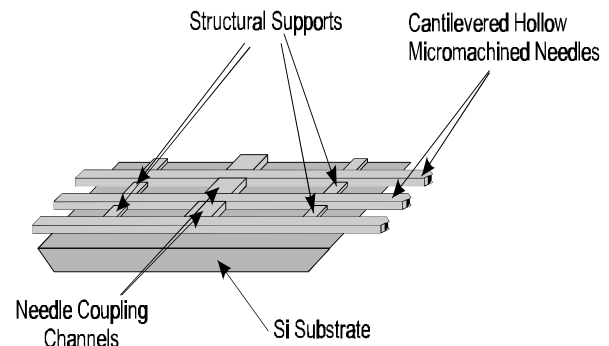


**Figure 4.** Schematic representation of the fluid coupled micromachined needle array.

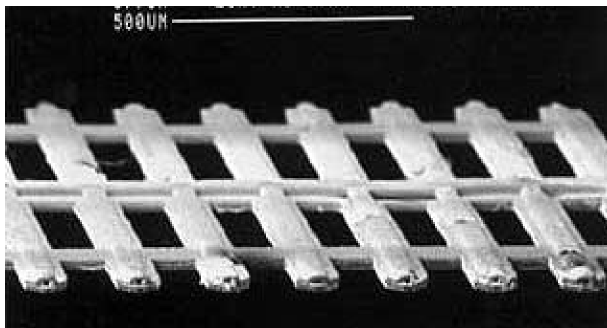


**Figure 5.** SEM of micromachined needle array. The inner dimensions are approximately 20×40 µm.

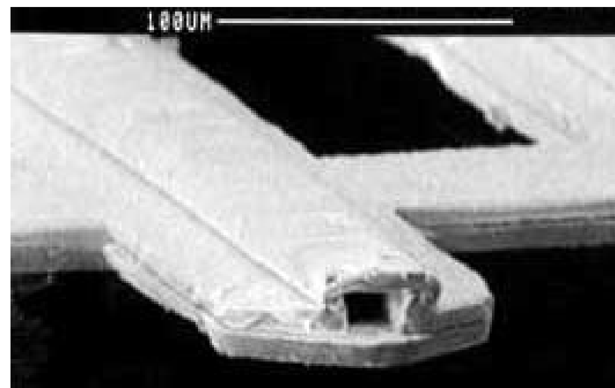


**Figure 6**. SEM of a micromachined microneedle output tip. The inner dimensions are approximately 30×20 µm, while the outer dimensions are approximately 80×60 µm.

inserted through skin for drug delivery. Figure 6 is a SEM showing a close-up of one of the needle tips. The inner dimensions are approximately 30×20 $\mu m^2$, while the outer dimensions are approximately 80×60 $\mu m^2$. The distance from the needle tip to the structural supports is 250 μm. The needle tip is formed by a 45° angle for ease of penetration.

Packaging of the micromachined needle arrays is accomplished using machined acrylic that serves as an interface between a standard syringe and the array. A schematic representation of the machined acrylic interface is shown in Figure 7. The input end of the interface has a tapered luer fitting that allows connection to a standard syringe. The midsection of the interface contains a region that serves as a fluid reservoir that allows development of flow into individual microneedles and ensures an equal pressure distribution between microneedle inputs. The output end of the interface contains a machined slot in which the micromachined needle array is inserted and permanently mounted using a biocompatible polymeric adhesive.

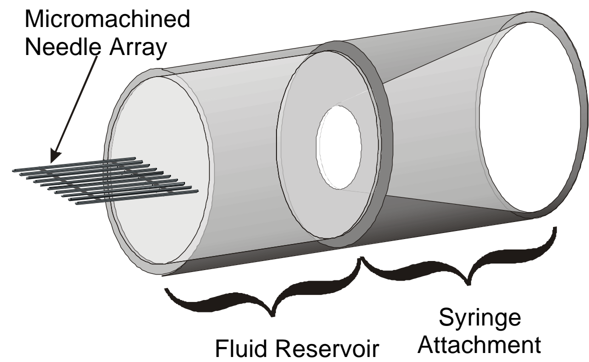


**Figure 7**. Schematic representation of the machined acrylic interface that is used to adapt a standard syringe to the micromachined needle array.

A photograph of a packaged two-dimensional (linear) metallic micromachined needle array is shown in Figure 8a. The machined acrylic interface has a diameter of 9.5 mm and a length of 13 mm. Figure 8b shows a photograph of the same interface connected to a standard 1 cc syringe to form the completed assembly used for drug delivery or fluid extraction. This entire assembly measures only 10 cm in length and is shown compared to a penny.

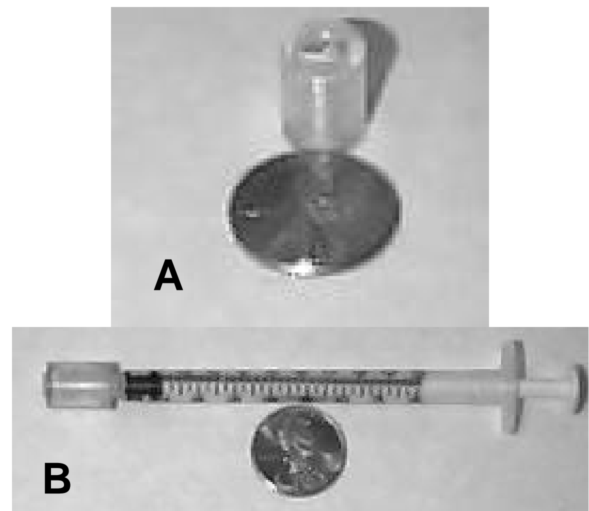


**Figure 8**. **A:** A photograph of a packaged two-dimensional (linear) metallic micromachined needle array. **B:** A photograph of the interface connected to a standard 1 cc syringe.

## MICROMACHINED PIPETTE ARRAYS

One challenge of future miniaturized biological/chemical analysis laboratories is to manipulate small (sub-μL) samples on a macro-scale in a parallel fashion. Today's commercially available sample handling systems for biochemical analysis are limited to wide center-to-center spacing (3.0 mm) and cannot handle sample volumes less than approximately 0.5 μL. In addition, these systems dispense in the range of 6 to 12 pipettes at one time. With the current trends toward miniaturizing biochemical analysis techniques and the drive toward the development of a μ-TAS, techniques must be developed to allow precise macro-scale manipulation of pL to nL range sample volumes in a highly parallel manner. Therefore, it is important to develop a method for highly parallel macroscale sample loading of pL to μL volumes that would allow precise handling of samples in the pL to μL range and still be compatible with the size dimensions (center-to-center spacing) of the micromachined biochemical analysis systems. One technique that addresses these problems uses micromachined pipette arrays for sample loading of miniaturized biochemical analysis systems. A schematic diagram of a micromachined pipette array is illustrated in Figure 9.

The micromachined pipette arrays are fabricated using extensions of previously reported surface micromachining fabrication technologies [8,9]. An example of a micromachined pipette array fabricated on top of a silicon substrate is shown in Figure 10. These pipettes are 11.75 mm in length with 2 mm extending from the substrate, while 3 mm separates the pressure ports from the pipette ends. The inner width of individual pipettes is 150 μm while the inner height (the thick photoresist thickness) is 22 μm. The electroplated nickel walls are 20 μm thick.

Individual pipettes are accessed using a backside etch. A cross-section schematic of the micromachined pipette input ports and interface is shown in Figure 11. The use of

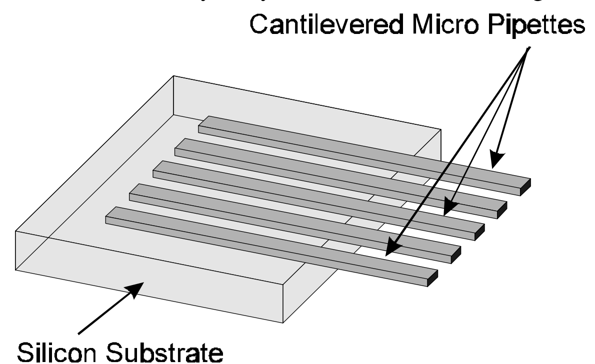


**Figure 9.** Schematic drawing of a micromachined pipette array (MPA).

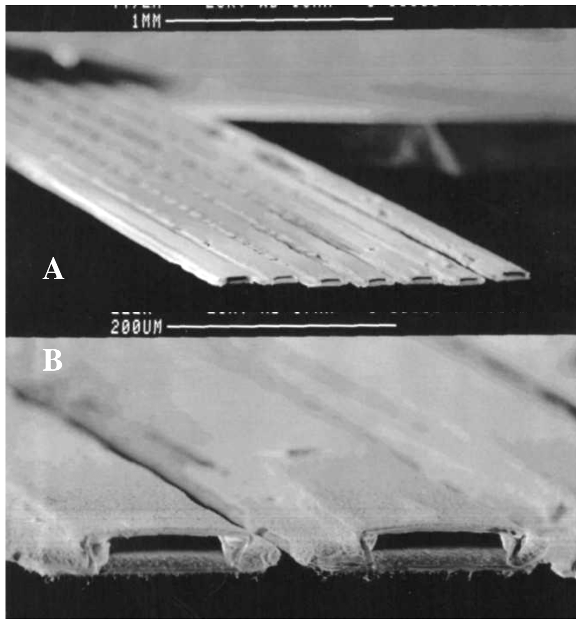


**Figure 10.** SEM micrographs of an array of pipettes extending from the substrate. A. Individual pipettes are 11.75 mm in length, 190 μm in width, and 50 μm in height. Pipettes extend 2 mm off the substrate edge. **B**: The inner cross-sectional dimensions of pipettes are 150 x 22 μm. The structural material is electroformed nickel.

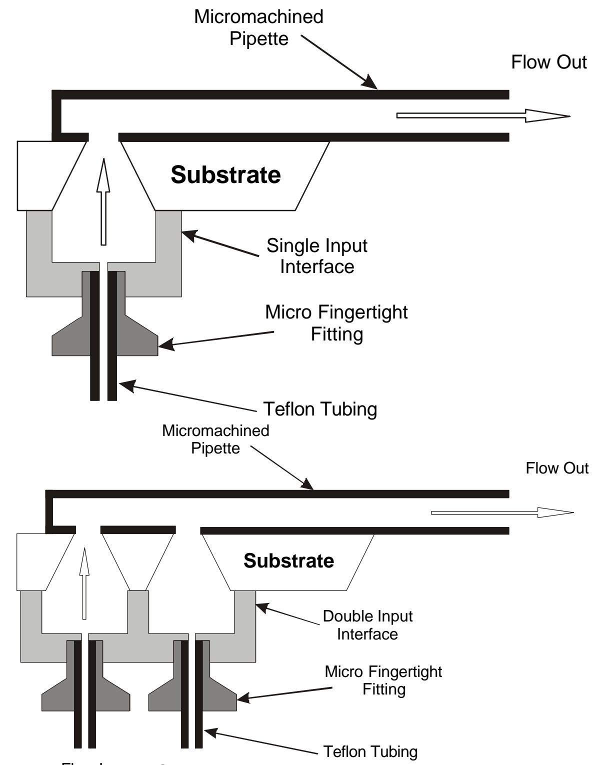


**Figure 11.** Schematic of the back-side interface for single-input and double-input pipette arrays.

bottom input ports allowed the macroscale interface between microchannels and macro-tubing to be moved from the front of the device to the back, resulting in a more robust interconnect. The interface can also be modified to provide downstream ports for static pressure measurement in addition to the inputs for fluid flow.

Each array typically consists of 5 or 7 pipettes. While each pipette had an individual input port, the acrylic interface provides a single pressure source through a manifold. The volume of the manifold is many times greater than the volume of each pipette, allowing a uniform pressure distribution across input ports of the entire array. Thus, the flow through each pipette is assumed to be equal.

Interfaces machined from acrylic are used to connect the fabricated micromachined pipette arrays with 397 μm inner diameter Teflon tubing. The acrylic interfaces are attached to the micromachiend pipette arrays using an ultra-violet (UV) curable adhesive. Teflon tubing connects the acrylic interfaces to either a pressure source or a pressure transducer. Photographs of single-input and double-input micromachined pipette arrays are shown in Figure 12.

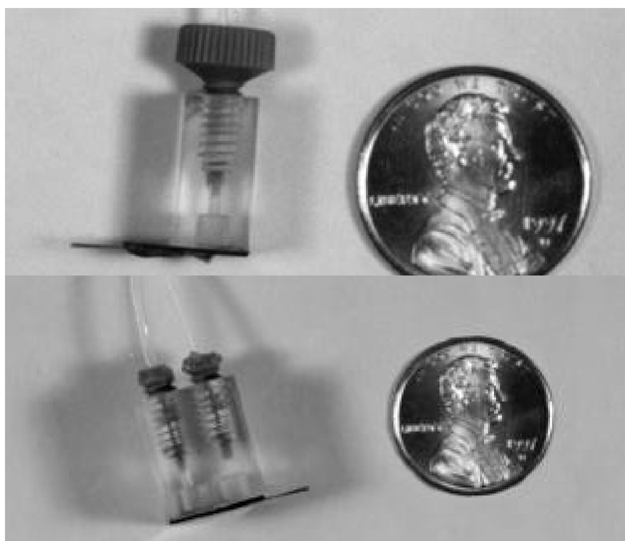

**Figure 12. A.** Photo of a single-input micromachined pipette array interfaced from the backside. **B.** Photograph of a double-input micromachined pipette.

## Micromachined EFFF System

Another system that has some unique packaging requirements with which we have been working is the micromachined electrical field- flow fractionation system (μ-EFFF). Electrical Field-Flow Fractionation is a

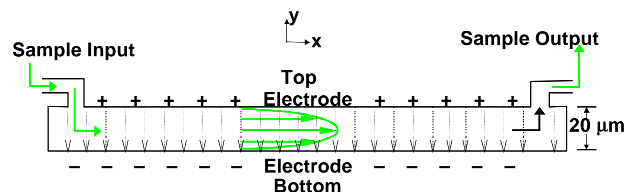


**Figure 13**. Schematic diagram of the operation of an EFFF system.

particle separation technique that relies on an electric field perpendicular to the direction of flow and separation as shown in Figure 13.

The channels for the miniaturized EFFF system are shown schematically in Figure 14. Fabrication and other information about the system has been reported previously [10]. The system also has an integrated electrical impedance detector that has been incorporated at the exit end of the channel [11,12].

The μ-EFFF system, therefore, requires both electrical and liquid connections. The electrical connections are rather straightforward with the only complication being that connections must be made to two parallel substrates separated by a very small distance and covered by polyimide. The fluid flow connections are much more demanding and include a need for sample injection into the system. The electrical and fluid connections will be covered separately.

### *Electrical Connections*

The electrical connections for the prototype μ-EFFF system were made by bonding small diameter wire to the metal bond pads using an electrically conducting adhesive. This was a simple process for connections made to the electrodes on the silicon substrate since the electrode material extended beyond the polyimide spacer and left a significant area for electrical contact. Bonding the wires to the glass substrate was somewhat more difficult. The first requirement was that the metal forming the channel and detector electrodes be continuous with the metal film on the sidewall of the glass substrate as shown in Figure 14a, since the substrate surface would be inaccessible after bonding. This continuous coverage was accomplished by using a sputter deposition system to apply the electrode material, and then while the electrodes were being photolithographically patterned, photoresist was specifically applied to the sidewall of the glass substrates in the areas where electrical connections would need to be made. This process left an electrical connection to the channel and detector electrodes on the sidewall that could then be easily bonded to using the conductive adhesive. The resistance of the connection was typically 2-3 Ω with very good strength and flexibility. A diagram of the completed electrical connections is given in Figure 15.

### *Fluid Flow Connections*

The requirements for the fluid flow connections in the μ-EFFF were much more demanding and included: an ability to withstand up to 20 psi (140 kPa), a flow area match with the channel, accurate positioning of connections, and flexible connections to allow changes to the connected components. In addition, the two ends of the channel do not have identical requirements. At the entrance of the channel there is a requirement for sample injection while the exit of the channel connects only to a drain or fraction collector. The ideal though, we be to have the same basic configuration that can be modified for either purpose.

A schematic of the basic fluid flow connection is shown in Figure 16. The connection is made by bonding a polypropylene ferrule for 1/16” tubing from Upchurch Scientific over the port using a biocompatible UV cured adhesive (Loctite 3301). Just a small amount of adhesive can be used to position the ferrule since further bonding will be

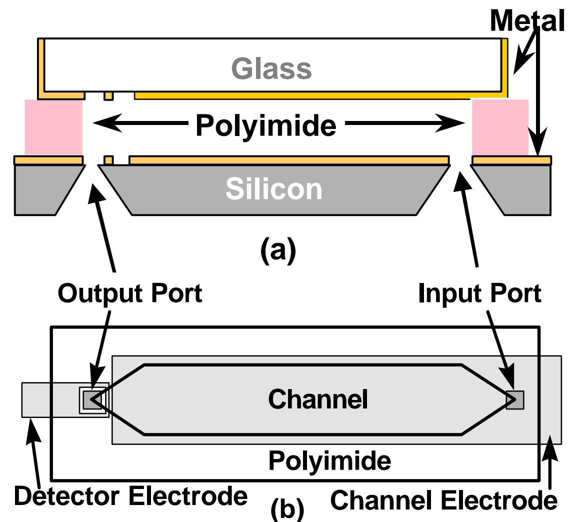


**Figure 14.** Schematic of channel and detector layout (a) Side view of channel (b) Top view of channel

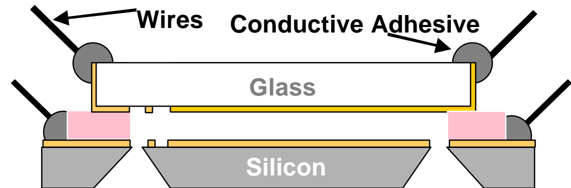


**Figure 15.** Diagram showing electrical connections

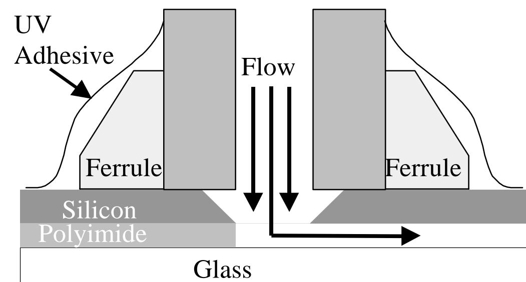


**Figure 16**. Schematic of basic fluid connections.

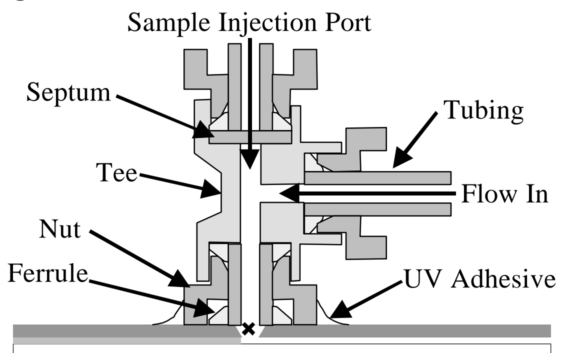


**Figure 17**. Cross section of the sample injection system. The X marks the point of sample injection.

performed later. This step is critical in that the position of the ferrule determines the position of the tubing later on. Once the ferrule has been adequately positioned, tubing can be placed into the ferrule and seated against the silicon substrate. At low pressures the friction fit is sufficient to prevent leakage, but for most applications additional adhesive can be applied to prevent leakage even at high pressures.

The tubing of choice for this application is PEEK tubing from Upchurch Scientific. PEEK can be securely bonded using most adhesives while Teflon tubing is nearly impossible to bond with any strength. Steel and titanium tubing have also been used in this application, but they tend to transmit torque and bending moments very well which can cause loss of adhesion or outright fracture of the adhesive or the silicon (due to the small diameter and long moment arms, the torques can be very high even at low applied forces).

This setup meets all of the requirements specified earlier and can be assembled in about five minutes due to the fast curing of the UV-cured adhesive. Additionally, for instances when tubing needs to be changed, acetone can be applied to dissolve the adhesive (a cyanoacrylate) and start over again.

An external sample injection system is used since the flow into which the injection is made is pressurized and the addition of valves would greatly increase the complexity, cost, and losses in the system. Additionally, the external system eliminates losses in analyte and still functions adequately, though and on-chip injection system would likely improve the resolution of the separation system.

A schematic of the injection system is shown in Figure 17. The injection system begins with the same basic setup as shown in Figure 16, but with additions to allow quick connection of a tee-connector for injection. A short nut from Upchurch Scientific is bonded directly to the silicon substrate over the previously bonded ferrule such that the threaded portion points away from the surface. The tubing is cut such that it matches the height of the nut and the required ferrule. A tee-connector, also from Upchurch Scientific, with a large enough thru-hole such that a needle will fit completely through the tee, is then attached to the nut bonded to the substrate. A nut, ferrule, and septum along with tubing to guide the injection needle is attached to the tee at the vertical opening. Injection is made through the septum and the needle from the injection syringe is inserted until the tip reaches the point marked with an “X” in Figure 17. The pump or flow source is connected to the perpendicular opening of the tee.

This configuration has several advantages including ease of setup and reconfiguration for other attachments, sample injection in or very near the entrance of the channel (which improves resolution in the system and eliminates the time required for sample transport to the channel), there is no flow blockage during injection which eliminates pressure buildup, and the connections are very robust with high resistance to applied forces.

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