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In-Plane Biocompatible Microfluidic Interconnects for Implantable Microsystems

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Abstract

Small mammals, particularly mice, are very useful animal models for biomedical research. Extremely small anatomical dimensions, however, make design of implantable microsystems quite challenging. A method for coupling external fluidic systems to microfluidic channels via in-plane interconnects is presented. Capillary tubing is inserted into channels etched in the surface of a Si wafer with a seal created by Parylene-C deposition. Prediction of Parylene-C deposition into tapered channels based on Knudsen diffusion and deposition characterizations allows for design optimization. Low-volume interconnects using biocompatible, chemical resistant materials have been demonstrated and shown to withstand pressure as high as 827 kPa (120 psi) with an average pull test strength of 2.9 N. Each interconnect consumes less than 0.018 mm³ (18 nL) of volume. The low added volume makes this an ideal interconnect technology for medical applications where implant volume is critical.

Keywords

Implantable biomedical devices; Parylene-C; microfluidic interconnections; vapor deposition

I. Introduction

Implantable micropumps have begun to be used for site-directed delivery of gene vectors and/or therapeutic compounds [1]. In space-constrained applications such as implantation into the human mastoid cavity, or subcutaneous implantation in small animals, the form factor and volume of the fluidic interconnects are of critical importance. Coupling to microfluidic systems is generally achieved with fluidic ports formed with hard polymers, metal, or Si [2]–[6] or by coupling into soft polymers such as Polydimethylsiloxane (PDMS) [7], [8]. For medical implant applications, additional coupling structures and out-of-plane approaches add unacceptable volume. In-plane interfaces exit from the side of the device and therefore offer the potential to significantly reduce overall fluidic interconnect volume, but often require complex processing [5] or are incompatible with small diameter tubing (<150- μ m OD) [9]. Coupling approaches relying on adhesives (epoxies and elastomers) can result in either blocked capillaries [2] or gap formation and dead volumes depending on the material viscosity and gap width. Existing microfluidic interconnect technologies fail to reliably meet the combined space and biocompatibility requirements of implantable

microsystems that are needed for many clinical applications and for use in small animal model systems, such as mice.

Here, we present a robust interconnect technology requiring only a single mask level and deposition of Parylene-C (chlorinated poly-para-xylylene) onto room temperature surfaces to capture small diameter capillary tubing. Parylene-C provides the requisite controlled deposition of a sealing material into the small spaces between the capillary and the microfluidic channel. It is an attractive material for biomedical fluidic interconnects due to its biocompatibility and chemical resistance [10]. Parylene has been used for conformal coating [11], pore-filling [12], microchannel formation [13], and channel penetration [14], [15]. Polyimide, USP Class VI compliant, has been used for implants as medical probes [16], and microchannels [17] and is well suited as small diameter tubing for use as cannulae [18] in the implanted microsystems for which these interconnects are targeted.

This paper presents the interconnect concept, fabrication, and testing with an emphasis on added interconnect volume, dead volume, resistance to leakage from internal pressure, and robustness to applied force on the extending capillary. The characterization of Parylene-C deposition into channels was used in conjunction with equations describing molecular flow and diffusion to spatially model monomer concentration and estimates the polymer deposition within tapered channels. This deposition prediction permitted optimization of channel geometries for full gap filling without voids at the tubing/channel interface.

Device fabrication is described with testing on several designs bracketing the predicted optimum channel dimensions. Testing includes measurement of deposited Parylene-C and void characterization along the length of the interconnect, burst/leakage pressure, and pull-strength. These results along with overall interconnect volume, dead volume, and fabrication complexity are compared with commercial and other research devices.

II. Interconnect Concept

The microfluidic interface consists of capillary tubing inserted in-plane into the widened end of an on-chip microchannel. The tubing is held in place with deposition of Parylene-C, which polymerizes into the space between the capillary tubing and the microchannel, and effectively secures the tubing. The entire device is simultaneously encapsulated in Parylene-C, enhancing device biocompatibility. Fig. 1 is an illustrative diagram of the interconnect concept showing the capillary tubing coupled directly to a microchannel in a glass-covered Si wafer. The long mean-free path of Parylene-C during deposition (20 °C, 42 mtorr) allows penetration into micro-gaps resulting in a pseudoconformal coating with deposition thickness decreasing with depth inside microgaps [14], [19].

The channel shape was designed to leverage this effect such that the narrow region at the tip of the inserted tubing would occlude first during deposition to provide a fluidic seal and reduce the potential for dead volumes. Continued Parylene deposition filled the space between the capillary tubing and the microchannel, effectively securing the tubing in place. A deposition thickness profile was estimated to design the interconnect channels with optimal width and taper for complete fill without creation of voids and dead volumes.

Fig. 2 is a drawing of capillary tubing inserted 500 μm into the channel and shows the two types of voids that may occur with this design. The first (void type 1) results from a channel taper that is too broad and occludes at the tubing/microchannel interface leaving a void at the channel entrance. This void is not in contact with the fluid flow path and would not contribute to dead volume, but could impact pull-strength or burst tests. The second (void type 2) results from a channel taper that is too narrow and occludes at the channel entrance resulting in dead volume at the tubing/microchannel interface. Dead volume is a concern for

implantable microfluidic systems for drug delivery where precise measurement of delivered fluids is important and fluid exchange may be required. Unswept volumes, areas of stagnation within the flow path, are not as critical as dead volume for these applications.

This simple processing method can provide a low-volume, low-dead volume interconnection between the capillary tubing and the microchannel while encapsulating the entire device with a biocompatible, chemical resistant material. Unswept volumes are minimal, being dictated by the wall thickness of the capillary tubing.

III. Parylene-C Channel Penetration Characterization

The deposition of Parylene-C into narrow constant-width channels was characterized to gain an understanding of the deposition profile. Characterization devices consisting of glass and Si were fabricated with isotropically etched constant width channels (50 μm). The glass and Si were clamped together to enable easy removal for deposition thickness measurement.

Parylene-C was deposited into the channels, using a deposition system fabricated locally at Rochester Institute of Technology, Rochester, NY (deposition rate $\sim 5.3 \mu\text{m/h}$, 20 $^{\circ}\text{C}$, 42 mtorr). The wafers were separated, and the thickness of the deposited polymer was measured with a profilometer. The characterization of Parylene-C channel penetration (see Fig. 3) demonstrated a reduction in deposition thickness with depth into the channel consistent with results presented by Broer and Luijks [14] for 56- μm channels. This initial characterization data indicated that constant width channels would not be completely filled with polymer, and that channels with tapered ends would need to be designed for tubing capture and gap occlusion. The behavior of the Parylene-C monomers is dependent on the type of interactions within the interconnect gap as shown in Fig. 4. The monomers can interact with other monomers [see Fig. 4(a)] or with the gap walls [see Fig. 4(b)]. They can adsorb directly on the channel walls, polymerize to an existing polymer at the adsorption site [see Fig. 4(c)], or continue to migrate along the surface until they arrive at another polymerization site [see Fig. 4(d)].

This paper used the characterization of Parylene-C deposition into straight channels to understand how these interactions relate to deposition thickness, and to develop a method of estimating the polymerizing deposition into tapered channels. The governing equations for polymer deposition in tapered channels will depend on the transport regime of monomers in the system. This transport is characterized by the Knudsen number (see Table I) which is the ratio of the mean free path to the characteristic length in the system.

For low Knudsen numbers, the mean free path of the monomer is much smaller than the dimensions of the system and intermolecular interactions predominate. High Knudsen numbers indicate that wall/molecule interactions will predominate. In this paper, the mean free path, calculated using (1) and the parameters for this deposition configuration in Table II, is 1.47 mm

$$\lambda = \frac{k_B T}{\sqrt{2} \pi d^2 P}. \quad (1)$$

The characteristic length is defined by the width of the gaps around the polyimide tubing which is less than 100 μm yielding $K_n > 14.7$. This indicates that the transport of the Parylene-C monomer is in the free molecular regime, Knudsen flow, where intermolecular collisions may be ignored. This result agrees with the work by Broer and Luijks [14], who state that the deposition due to molecular flow dominates that of viscous flow for a system of similar dimensions and pressures.

Calculation of Fickian diffusion for Knudsen flow into the channels was used to determine a time-dependent monomer concentration and an estimate for the deposited film thickness along the length of the tapered channels. This estimate was used to generate a width profile for the tapered channel, designed to prevent the formation of voids during the polymerizing deposition.

IV. Fabrication and Testing

A. Device Fabrication

Interconnect devices were fabricated as shown in Fig. 5 for use with polyimide capillary tubing (140- μm OD, Microlumen, Tampa, FL). An aluminum hard mask was used to pattern the channels in the surface of the Si with an isotropic etch (Drytek Quad SF_6 : 130 sccm, O_2 : 10 sccm, Pressure: 30 mtorr, and RF power: 130 W) to a depth of 140 μm . Once the hard mask was removed in a wet etch, the wafers were diced and treated in a piranha clean. Borofloat glass (Addison Engineering, San Jose, CA) was diced, cleaned, and anodically bonded to the Si substrate to enclose the channels and provide optical access to the interface. The anodic bonding was performed at 1000 V_{DC} (F15, EMCO, Sutter Creek, CA) and 400 $^\circ\text{C}$ for 10 min.

Three designs were produced to bracket the optimized channel taper width of 215 μm (angle 5.88°) by $\pm 10\%$ with widths at the opening of 193 μm , 215 μm , and 236 μm . All channels had a length of 500 μm and narrowed to 112 μm to match the ID of the polyimide capillary tubing; having a smaller overall diameter than the tubing assures that the tube will stop against the channel walls during insertion. To facilitate pull-testing, polyimide-coated fused silica capillary tubing (153- μm OD, Polymicro Technologies, Phoenix, Arizona) was used for some of the devices. To accommodate their larger diameter, channels were overetched to a depth of 155 μm . This created a nonoptimal gap geometry not designed to fill completely with Parylene-C.

B. Interconnections

Polyimide capillary tubing was inserted in-plane until the tubing end interfaced with the channel walls. A fixturing setup, as shown in Fig. 6, was used to keep the tubing aligned in the channel. The free ends of the tubing were covered with Parafilm (Structure Probe, Inc., Westchester, PA) to prevent unwanted Parylene-C deposition. A 40- μm layer (50 μm for polyimide-coated fused silica capillary devices) of Parylene-C was deposited (rate = 5.3 $\mu\text{m}/\text{h}$) to capture the tubing, create a fluidic seal, and fully encapsulate the device to provide a biocompatible surface suitable for medical implantation.

C. Fill Percent and Deposition Thickness

The thickness of the Parylene-C deposited within the original gaps was measured by cross sectioning the devices using an edge polisher and imaging the sections under a microscope. The edge polisher was used to remove a precise amount of material, and produced clean images. The images were measured for Parylene-C thickness, void area, and original gap width at various depths into the channel. These measurements were used to calculate the percent of the original gap volume filled with Parylene-C. Fill percent FP is calculated from the area of the gap to be filled g and the void area v : $[FP = (g - v)/g]$. Fill percent is a measure of how well the polymer has penetrated into the gap, which is a useful metric for the type of interconnect presented here. The volume of the original gaps to be filled and the volume of the voids in the Parylene-C were extrapolated using the measured area and the thickness of each slice, $\sim 50 \mu\text{m}$.

D. Leak-Burst Pressure/Leakage Test

The interconnects with polyimide-coated fused silica tubing were connected to the pressure test setup using NanoTight fittings (Upchurch, Scientific, Oak Harbor, WA). One side of the device was connected to compressed argon with a luer connector, while the other side was connected to a valve. Compressed argon with maximum pressure of 120 psi was applied. Pressure was measured with a gauge on the gas regulator. The devices were submerged in water and viewed through a microscope to detect air bubbles. The downstream valve was opened to confirm flow through the devices and then closed for pressure testing.

E. Pull Test

A pull-test load cell was designed using a strain gauge (1.5/120-LY11, Omega Engineering, Inc., Stamford, CT) in a Wheatstone bridge configuration with weights from 50 to 500 g used for calibration prior to testing. A micromanipulator was used to pull the polyimide-coated fused silica tubing out of the interconnect channel, while a multimeter was used to record the strain signal.

V. Results and Discussion

Devices using polyimide tubing were fabricated and measured for fill percent. The designs for these devices bracketed the optimized design: four interconnects with the optimal geometry, four with 10% wider geometry, and four with 10% narrower-than-optimal geometry. Fig. 7 is an image of a cross section 50 μm into the channel showing the areas that were measured, the original gap area g , the void area v , and the thickness of the deposited Parylene-C film for a 10% narrower design. The results from the cross sectioning show that the four optimized and four wide channels filled 100% with Parylene, as predicted by the estimation, whereas the four narrow channels had an average fill percent of 97.9 % ($\sigma = 0.7\%$). The narrow channels occluded at the opening before filling completely resulting in a type 2 void. Cross sections of the interconnect area demonstrate the formation of voids at the entrance of the gap, type 1 voids, and type 2 voids in the middle of the channel, but type 2 voids near the interior end of the tubing proved difficult to expose as cross sections through that portion of the interconnect caused damage to the soft materials of Parylene-C and polyimide. The dead volume for the 100% filled, optimized interconnects is zero and the unswept volume is calculated to be 0.0004 mm^3 (0.4 nL). The calculated unswept volume is the result of the difference between the inner and outer diameters of the tubing and not a result of any voids in the deposited polymer.

Interconnects were tested for leakage using polyimide-coated fused silica and held to the maximum available pressure of 120 psi for all devices ($N = 8$). The interconnects were subjected to the pull test with an average recorded force of 2.9 N ($\sigma = 0.6$ N, maximum = 4.1 N, minimum = 2.3 N) required to pull the tubing cleanly out of the Parylene-C in the interconnect channel. The nature of the observed pull-test failures, where the tubing pulled cleanly from the polymer, suggests that the failure mechanism is polyimide to Parylene-C adhesion. For these interconnects with rigid polyimide-coated fused silica tubing, the average fill percent was 87.5% ($\sigma = 5.7\%$). These nonoptimized channels occluded at the entrance leaving a type 2 void (see Fig. 2) at the tube end as a dead volume of 0.00115 mm^3 (1.15 nL).

The characteristics and performance of the microfluidic interconnects presented herein are compared with commercial and other research devices in Table III. Interconnect volume is the volume added to the device for the interconnect system. Numbers for this metric are not normally reported and have been calculated from the dimensions of the fabricated devices, but do not include the effective added volume of an out-of-plane connection. An order of

magnitude improvement was achieved in total interconnect volume over the best out-of-plane designs, with over two orders of magnitude improvement over other in-plane designs. Burst or leak pressure tests measure the maximum internal pressure of air or liquid in the microfluidic system that the interconnect can withstand before failure. If interconnect failure does not occur, then the maximum tested pressure is reported. The in-plane, Parylene-C captured interconnect pressure performance exceeded all reported maximum pressures for research devices. Test setup limitations prevented testing to the 435-psi pressures reported for the commercial device. Pull-test results are comparable to those reported in the literature with the exception of the flanged thermoplastic approach [3] which achieved 39 N. This strength is attributed to the significantly larger volume of the interconnect ($>50 \text{ mm}^3$).

Both pressure and pull-test performance are related to the available surface area for the interconnect and either adhesion or applied force to generate the seal. The achieved performance with an interconnect length of $500 \mu\text{m}$ and a total capillary contact area of $<0.24 \text{ mm}^2$ speaks to the robustness of this polymer deposition approach for in-plane fluidic interconnects. The completed interconnect is shown in Fig. 8 and demonstrates the low added volume aspect of this technique.

Future characterization to further prove the suitability of this device for biomedical implantation could include testing for aging in aqueous media.

VI. Conclusion

An in-plane microfluidic coupling scheme has been demonstrated that allows for low-volume interconnects to small diameter polyimide tubing with simple Si processing techniques and low-temperature Parylene-C deposition. These interconnects are not removable, but this is not a requirement for implantable biomedical devices. The low volume of the interface, 0.018 mm^3 (18 nL), is important for medical applications where implant volume is critical and enables a system form factor consistent with subcutaneous implantation in mice.

This method can produce designs for a range of tubing sizes with the only limitations set by the required amount of polymer deposited and the etch profile at the tubing/channel interface. The size of the tubing would not affect the utility of this method as much as the size and shape of the resultant gap between the tubing and the channel. The favorable results of the pull test and burst test for the nonoptimized channels indicate that the optimized interconnects would perform as well as, if not better than those tested here. In light of these positive results, future designs could focus on shorter taper lengths that require less deposited Parylene-C while still maintaining sufficient contact area for robust performance. The low dead volume makes these interconnects suitable for drug delivery.

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Biography

Dean G. Johnson (S'05) received the B.S. and M.S. degrees in electrical engineering from Michigan State University, East Lansing, MI, in 1988 and 1990, respectively.

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Robert D. Frisina received the A.B. degree in experimental psychology and economics from Hamilton College, Clinton, NY, in 1977, and the Ph.D. degree in bioengineering, psychology, and neuroscience from Syracuse University, Syracuse, NY, in 1983.

He joined the Chemical and Biomedical Engineering Department at the University of South Florida in 2010 as a Professor. He holds adjunct appointments at the National Technical Institute for the Deaf, Rochester Institute of Technology, Rochester, NY, in communication sciences, and the University of Buffalo, Buffalo, NY, in communication disorders and sciences. At the University of Rochester School of Medicine and Dentistry, he served as a Professor in the Otolaryngology Department, from 2004 to 2010, and in the Department of Biomedical Engineering, from 1999 to 2010. His research interests include the determination of brain mechanisms responsible for encoding of speech and complex sounds in young and aged toward biotherapeutic interventions.

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David A. Borkholder (M'91–SM'06) received the B.S. degree in microelectronic engineering from the Rochester Institute of Technology, Rochester, NY, in 1992, and the M.S. and Ph.D. degrees in electrical engineering from Stanford University, Stanford, CA, in

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In 2004, he joined the Rochester Institute of Technology, where he is currently an Associate Professor of Electrical and Microelectronic Engineering. He holds adjunct appointments at the University of Rochester, Rochester, MD, in the Department of Otolaryngology and Biomedical Engineering. He served as the Director of Hardware Engineering at ZONARE Medical Systems, Inc., the Director of Electronic Systems and the Technical Lead for new products at Cepheid, and worked on the manufacture and characterization of charged-coupled device image sensors within Eastman Kodak Company. His research interests include biosensors, biomedical microelectromechanical systems, medical devices, and auditory dysfunction and treatment, with currently funded research on murine inner ear drug delivery, noninvasive glucose detection, cuff-less blood pressure monitoring, and blast dosimetry for soldier traumatic brain injury.

Dr. Borkholder is a member of the Tau Beta Pi, the Eta Kappa Nu, the Phi Kappa Phi, the Association for Research in Otolaryngology, the Biomedical Engineering Society, the American Association for Engineering Education, and the IEEE Engineering in Medicine and Biology Society.

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Fig. 1. In-plane fluidic interconnect concept. (a) The $140\text{-}\mu\text{m}$ OD polyimide tubing is inserted $500\text{ }\mu\text{m}$ into tapered channel end, $215\text{ }\mu\text{m}$ wide at opening. (b) Top view showing designed gap taper in red. Parylene-C will fill this gap while encapsulating the entire device. Not drawn to scale.

Fig. 2.

Potential voids resulting from Parylene-C deposition into gap between polyimide tubing and Si microchannel. Voids of type 1 result from a taper angle that is too large and requires additional polymer deposition. Voids of type 2 result from a taper angle that is too small and creates dead volume. The 70- μm gap between the channel wall and the tube at the channel entrance is typical for the fabricated interconnects.

Fig. 3. Measured thickness of Parylene-C along the 50-μm wide channel within the characterization devices. Shown with exponential curve fit $y = 7.396e^{-0.004x}$.

Fig. 4. Diagram of different molecular interactions within a tapered channel. (a) Monomer–monomer interaction. (b) Monomer–wall interaction, not adsorbed. (c) Monomer–wall interaction, adsorbed. (d) Monomer–wall interaction, surface migration.

Fig. 5. Fabrication Process. (a) $0.36\text{-}\mu\text{m}$ Al hard mask used to pattern Si wafer. Isotropic etch in SF_6 and O_2 in Drytek Quad result in an approximately hemispherical microchannel. (b) The aluminum was removed, the devices were diced and cleaned, and borosilicate glass was anodically bonded to create the channels.

Fig. 6.

Illustration of a Si fixture used to align tubing with tapered channels for deposition of Parylene-C. Reusable fixtures fabricated from the Si during device fabrication process. Parafilm protects free ends of tubes, Si fixture provides support and alignment, and glass capped device chip accepts tube ends for Parylene-C deposition.

Fig. 7.

Optical image of cross section of Parylene-C penetration into channel around polyimide tubing. Original designed gap (outlined) which has been filled with Parylene-C. Small triangular void area is also outlined. Deposited film thickness shown by double pointed arrows. Cross section 50 μm from edge of the wafer.

Fig. 8. SEM of the side of the microfluidic chip with small diameter (140- μm OD) tubing exiting in-plane.

TABLE I

Flow Regimes

Knudsen Number	Regime
$K_n < 0.01$	Continuum Flow
$0.01 < K_n < 0.1$	Slip Flow
$0.01 < K_n < 3$	Superposition of Viscous Flow and Molecular Flow
$K_n \gg 3$	Molecular Flow

Adapted from [20]

TABLE II

Parameters Used to Determine the Mean Free Path

Symbol	Quantity	Value/Units
k_B	Boltzmann constant	1.38E-23 J/K
T	Temperature	473 K [†]
P	Pressure	5.6 Pa (42 mtorr)
d	Average diameter of molecules	4.22E-10 m (0.422 nm) ^{††}

[†]Temperature of gas in deposition chamber (surface temperature: 293 °K)

^{††}Approximated by using a weighted average molecular diameter [19, 20] of nitrogen, oxygen, and benzene [22] (the basis of Parylene).

TABLE III

Comparison of Microfluidic Interconnect Devices

Materials	Volume [†]	Max Pressure	Pull Test	Dead Volume	Fabrication Complexity	In-Plane	Tubing OD	Ref
Silicon and Epoxy	0.667 mm ³ ^{††}	60 psi	1-2 N	0.002 mm ³	high	no	0.425 mm	[2]
Flanged Thermoplastic Tubing/glass/Polycarbonate	>50mm ³	NR	39 N	NR	high	no	0.25 mm	[3]
Needle/Epoxy into Acrylic	5 mm ³	67 psi	NR	NR	medium	no	2.38 mm	[4]
Silicon	6 mm ³	20 psi	NR	NR	high	yes	0.84 mm	[5]
Heat Shrink Tube/Silicon	4.7 mm ³	29 psi	3 N	NR	high	no	0.9 mm	[6]
PDMS/Needle/luer fitting	>50 mm ³	102 psi	NR	NR	low	no	1 mm	[7]
PDMS/Epoxy	33 mm ³	100 psi	2 N	NR	medium	no	1.02 mm	[8]
Metal/Plastic (commercial)	>1500 mm ³	>435 psi	NR	<0.1 mm ³	low	yes	1.6 mm	[9]
Parylene Captured Polyimide	0.018 mm³	120 psi	2.9 N	0 ^{†††}	low	yes	0.140 mm	This work

[†] Volume calculated from published drawings, not reported.

^{††} Volume without epoxy = 0.089 mm³

^{†††} Calculated Dead Volume, Calculated unswept volume = 0.0004 mm³

NR = Not Reported