Bio-microinstrumentation technology: discrete components to modular systems

Bonnie L. Gray*
Microinstrumentation Lab, School of Engineering Science,
Simon Fraser University, Burnaby, BC V5A1S6, Canada

ABSTRACT

The Microinstrumentation Lab group at Simon Fraser University (SFU) develops biomedical nano- and micro-device-based microinstrumentation by combining integrated materials and interconnect technologies with a modular systems approach. A major focus of our research is the development and application of disparate materials, including novel nanomaterials developed in our laboratory, to discrete components, combined with integration and interconnection standards that are designed to be generally applicable to multiple systems in our lab. In this overview, we present a sample of these technologies that have been developed by our lab since its inception, and demonstrate use of these technologies in both discrete components and modular systems towards the realization of complex bio-microinstruments for an ever-expanding group of collaborative projects in biology and biomedicine.

Keywords: microfluidic interconnect, nanocomposite polymers, active polymers, polymer MEMS, magnetic actuation, microvalves, cell research platforms, biosensors, multi-sample microfluidics, design for assembly

1. INTRODUCTION

From the miniaturization of laboratory instrumentation for bed-side rapid diagnosis of disease to bioanalytical instrumentation for studying individual cells or molecules in new ways using micromachined structures, microfluidics is well established as an exciting area of research with great promise and an ever-growing application base. Through the combination of biosensors, microchannel fluid transport, and other micro-mechanical, -optical, -chemical, -electrical and -fluidic components, microfluidic-based microinstrumentation has spawned research into miniaturized instrumentation for, e.g., DNA analysis, proteomics, enzymatic analysis, single cell analysis, immunology, point-of-care medicine, personalized medicine, drug delivery, and environmental toxin and pathogen detection. Other biomedical microinstrumentation, such as wearable or implantable bio-microelectromechanical systems (bio-MEMS), has similarly been investigated for application areas ranging from neuroscience to physiological monitoring.

While such bio-microinstrumentation has the potential to revolutionize laboratory procedures and personalized health care, the adoption of new materials and devices can be slowed by compatibility issues; for example, while polymers have generally been long-recognized as the most appropriate materials for microfluidics development[1], problems with integration of active devices (such as actuation mechanisms, electrodes, or electronic routing) into polymer systems can be surprisingly challenging, especially for flexible systems where the polymers are highly compliant[2]. In addition, while research teams may spend much time and effort in solving materials compatibility issues for individual components, the components must then be integrated or modularly assembled to produce the final instrument. Although the interconnect technology required for such component integration has been widely recognized as an outstanding issue in the practical realization and commercial success of complex microinstrumentation[3], many interconnect technologies have arisen from the need to solve packaging problems for a particular device or instrument, rather than from a systematic and standardized approach. Researchers are increasingly investigating interconnect schemes with a view toward generic structures and standardized methods much as macroscale plumbing or microelectronic packaging is standardized. Despite these advances, a widely adopted microinstrumentation interconnection scheme does not yet exist, a problem which is exacerbated by the constant introduction of new materials, devices, and fabrication techniques, resulting in disparate materials and components for which new integration schemes must be developed.

In the Microinstrumentation Lab (µiL) at Simon Fraser University (SFU), we have attempted a somewhat more systematic approach to the development of biomedical micro- and nano-devices and modular systems with integrated

* bgray@sfu.ca; phone 1 778-782-4371; fax 1 778-782-4951;

Nanosystems in Engineering and Medicine, edited by Sang H. Choi, Jin-Ho Choy, Uhn Lee, Vijay K. Varadan,
Proc. of SPIE Vol. 8548, 854827 · © 2012 SPIE · CCC code: 1605-742/12/$18 · doi: 10.1117/12.979685

interconnect technology. A major focus of our research is the development and application of novel nanomaterials to discrete components, combined with integration and interconnection standards that are designed to be generally applicable to multiple systems in our lab. In this overview paper, we present a sample of these technologies that have been developed by our lab since its inception, and demonstrate use of these technologies in both discrete components and modular systems towards the realization of complex bio-microinstruments for an ever-expanding group of collaborative projects in biology and biomedicine. We begin with a discussion of technologies for combining disparate materials, including the challenges of combining active materials with polymers, and development of new active materials with the goal of easier integration. Next, we discuss technologies for combining disparate components that may be fabricated in different materials, and integrated structural aids for developing modular systems. We then present additional example components and systems that specifically showcase these technologies in collaborative projects associated with the µiL, and demonstrate how generic structures and packaging approaches can aid in new component and system development. Finally, we discuss a few current and future trends for design-for-assembly components and modular system development, both from our lab and promising techniques that we have seen emerging from other researcher groups.

2. TECHNOLOGIES FOR COMBINING DISPARATE MATERIALS

Many contemporary microfluidic and bioMEMS devices have close associations to the fields of molecular biology, biochemistry, cell biology, and health sciences, and employ a wide variety of materials including glass, silicon, metals, and polymers. Despite the range of materials currently used, microfluidics and bioMEMS fabrication methodologies have their basis in silicon microelectronics. While silicon is still often employed especially for, e.g., integrated biosensors and optical detection schemes, and glass is still employed for to its optical properties and familiar surface chemistry, polymers have arguably overtaken these materials as the main materials for realizing microfluidic microinstrumentation such as labs-on-a-chip (LOC) and micro total analysis systems (µTAS). The reasons for this are numerous, and have been covered in many reviews[1,3]. In short, polymers have many potential advantages over other materials including low cost; mechanical properties such as flexibility and mechanical compliance; biocompatibility; ease of inexpensive processing; versatility in terms of size and shape; and many can be bonded to each other, silicon, or glass. Polymers are also being deployed in the emerging fields of flexible microfluidics and bioMEMS. Flexible microinstruments have many potential applications, such as wearable health monitoring for physiological signals or biofluid analysis[4,5,6], sealing for microfluidic systems[7,8], and foldable systems; essentially whenever the device or system must bend or fold, such as in conforming to non-planar objects or space constrained locations. For such highly compliant systems, polymers are essential.

However, despite their advantages, polymers are not necessarily the best choice for all applications, or for all aspects of a microinstrument. Polymer fabrication can be difficult to control, and can be difficult to integrate with other materials. Often a polymer's role in microfluidics or bioMEMS is to act as the "passive" structure, e.g., the substrate, microchannels, fluid wells or reservoirs, or packaging. It is difficult to render them functional, and while great strides have been made in all-polymer electronics, silicon is still the main electronic device material. Other materials are often the best choice for one or more aspects of a microdevice or microinstrument, including: silicon for electronics; metals, for electrodes, electronic routing, or actuation; and glass, for optical detection via fluorescence or transmission surface plasmon sensors[9].

These materials all have very different characteristics and fabrication methods, making combinations of such disparate materials very challenging. Challenges facing integration of disparate materials are compounded further when flexible systems are required. Many research groups are working towards inventive and novel methods to combine disparate materials to produce microfluidic and bioMEMS devices[1,10,11]. Combinations of silicon, glass, polymers, and metals dominate, with other materials such as ceramics, hydrogels, and other materials employed as, e.g., specialized substrates[12], actuation mechanisms[13], or growth media for biological[14]. In general, combinations of disparate materials are facilitated if materials are chosen that: 1) are easily interfaced together for reasons of good adhesion and/or easy integration using batch processing; and 2) possess characteristics that yield long-term compatibility and robustness of interface, e.g., are mechanically similar and/or have an excellent chemical or physical bond.

Metal routing or electrodes can be especially difficult to combine with polymers, especially highly flexible polymers such as the popular prototyping materials SU-8 photoepoxy and polydimethylsiloxane (PDMS) elastomer, due to the inherent materials mismatches between compliant polymers and non-compliant materials employed for active devices such as electronics, sensors, or actuation mechanisms[15]. Thin film metal lines on a polymer substrate may suffer from poor adhesion, development of microcracks, and electrical failure, especially when bent or otherwise strained due to mechanical force or even temperature change. While the problem of combining polymers with metals has been long recognized in the fields of flexible electronics and flexible displays, not all of these materials and techniques are appropriate to microinstrumentation. However, methods can be employed to minimize the materials mismatch. In collaborative work performed at the SFU µiL and between our lab and others in SFU Engineering Science and Chemistry, we have patterned gold electrodes on both SU-8 and PDMS stand-alone and flexible polymer microfluidic devices. These substrates may also contain passive microfluidics, to which thin film metallization has also been integrated to result in metal-on-polymer electronic routing[16] and, together with our collaborators, electrodes for microsensor fabrication[17]. For thin metal film patterning on PDMS and SU-8, two new processes have been developed: 1) a process employing PDMS as a temporary substrate layer upon which layers of SU-8 and Au can be built[18] and 2) a lift-off process employing SU-8 as a sacrificial mask to minimize stress to the metal film during deposition and patterning on PDMS[17]. In each case, these processes rely upon improved matching between the two polymers SU-8 and PDMS (as opposed to a polymer and metal) in order to yield structures with minimized cracking and stress. We have found these methods to be at least as robust as other existing methods, such as the use of specially designed geometries to minimize mechanical strain in metals on polymer substrates[19].

Commercial processes for combining thin film metals with polymers also exist in the form of flexible printed circuit boards (PCBs), although the polymer substrate materials used for flexible PCBs are not nearly as compliant as elastomers such as PDMS. Still, they offer inexpensive and easy prototyping using well-characterized processes and materials such as Kapton™. Other research groups have employed flexible PCBs as substrates for combining silicon components with flexible polymers, by mounting various components for, e.g., physiological monitors, etc.[20] on the metal-patterned PCB surface. At the SFU µiL, we have also investigated flexible PCBs for applications in both wearable sensors and for flexible thermally actuated hydrogel-based microfluidic valves. For the hydrogel based valves, the metal-on-flexible polymer PCB is patterned into heater elements, and then combined with flexible PDMS valve structures and thermally-responsive hydrogels for the actuation mechanism. We have demonstrated hydrogel-based actuation of a plug-type in-plane microvalve[21] employing flexible PCB heaters. The disparate materials of patterned flexible PCB heaters and PDMS are combined using a simple adhesive stacking process, while the hydrogels are integrated into the PDMS microchannels using a micromolding process. The bulk hydrogel is first spin-coated onto a Pyrex™ wafer. The thin film hydrogel is then compressed between two glass plates and a PMMA mold with the negative of the desired features, and then placed in a vacuum chamber for 30 minutes to remove bubbles. This process significantly improves the precision of the hydrogel insertion into the microchannel as the molded hydrogel plugs are already precisely spaced and can be easily aligned to arrays of channels. The devices can be fabricated not just as single devices, but batch processed into arrays.

While such processes can be employed for combining polymers with metals and other functional materials, thin film metal may still produce micro-cracks under flexing and stretching, resulting in a significant reliability issue. Thus, we have investigated the use of conductive nanocomposite polymers (C-NCPs) as alternatives. Such materials enable a promising alternative to polymer-metal hybrid processing by instead replacing the metal with another conductive material with the same characteristics as the polymer with which it is combined, only of high conductivity (this is described more thoroughly in a review of C-NCPs and their applications[22]). This can be accomplished through the introduction of nanoparticles to a base polymer to render it functional, and then combining the functionalized polymer with base polymer substrates, to yield hybrid devices that avoid materials mismatch problems. We have developed a wide range of active SU-8 and PDMS materials that are realized by introduction of conducting and/or magnetic nanoparticles into the polymer matrix, resulting in "nanocomposite polymers" (NCPs). Although we have primarily explored electronic and magnetic functionality to realize microfluidic circuit boards with active elements[2,23,24], other nanoparticles with other functionality are also possible and under development in the µiL. One of the main goals behind development of NCPs is that they retain the flexibility and easy micropatterning of their base polymers while introducing new functionality. Conductive NCPs (C-NCPs) are those materials in which the added nanoparticles cause or enhance conductivity once a certain threshold of nanoparticle percentage is reached, known as the percolation threshold[25]. This percolation threshold is a function of both polymer and nanoparticle properties, and it is advantageous if the percolation threshold is low, as this results in a conductive material which may retain many of the mechanical and other desirable properties of the intrinsic polymer.

To micropattern SU-8 based NCPs, the following general process can be used: clean and dry substrates may be coated with an adhesion layer such as 25 nm chrome, or prior layers of doped or un-doped SU-8. A layer of SU-8 NCP is spin coated, followed by soft baking at temperatures 65-90 °C for several minutes to several hours depending on layer thickness, and ramped cooling to room temperature. The SU-8 layer may also be cast if thicker structures are desired[7]. Structures are patterned using photolithographic UV exposure through a photomask for several seconds to several minutes. Full crosslinking of the SU-8 is achieved by a post-exposure bake at a temperature of 60°C for several minutes to several hours, followed by ramped cooling. The structural layer on each substrate is then developed in SU-8 Developer (Microchem™) for several seconds to an hour in an ultrasonic bath. We have successfully realized conductive SU-8 in film thicknesses ranging from 25 to 200µm, with doping levels ranging from 3% to 65%.

Micromolding of PDMS-based NCPs is accomplished using soft lithography[3] methods similar to those employed for non-conductive PDMS. However, we have developed a modified process that enables hybrid systems with combined micropatterned NCPs and flexible un-doped substrates. Uncured PDMS-based NCP is poured onto SU-8 micromolds, the excess PDMS scraped off with a surgical knife, and the mix de-gassed to remove air bubbles. The samples are thermally cured on a hot plate followed by cooling to room temperature. Undoped PDMS polymer is poured onto the surfaces of the samples, de-gassed, and cured on a hotplate. The resulting hybrid structures composed of micropatterned NCP on undoped PDMS are peeled off from the mold. We have realized structures with multiple levels of NCPs using a similar process[26]. Nanoparticle doping levels have ranged from a few percent for C-NCPs containing carbon nanotubes (CNTs) up to 65% or more for silver C-NCPs.

The resulting hybrid devices (combined NCP and non-functional polymer base materials) can be employed for a wide range of applications. For example, the aforementioned thermally-responsive hydrogels can be combined with conductive NCP microheaters fabricated using tungsten and/or CNT nanoparticles (instead of flexible PCB heaters). In such cases, the hydrogel serves as the active element for a flexible polymer valve diaphragm actuator[27], and is assembled into the valve reservoir using a micromolding process. Other applications range from flexible microfluidic/electronic circuit boards[23] to electrode arrays for impedance-based cancerous tissue detection[26].

Nanocomposite polymers with other functionality, such as high magnetization, can also be combined with base polymers using similar processing to yield, e.g., magnetic NCPs (M-NCPs). Other researchers have employed soft magnetic materials, such as iron or nickel, to realize active functional polymers for actuation mechanisms[28,29]. We have realized similar materials based on, e.g., 30-50nm diameter Ni[30] or micron-sized iron particles[31], and micropatterned them together with non-functional polymers using our hybrid processes. Such soft magnetic polymers are not themselves magnetic, but are attracted to magnetic fields. In addition to these softly magnetic materials, we have also developed M-NCPs based on hard magnetic microparticles, which instead result in micro permanent magnets after a post-fabrication magnetization step under fields in excess of 1 Tesla. While other researchers embed permanent magnetic posts or magnets in PDMS to yield similar structures and results[32], our polymer permanent magnets have a much more compatible fabrication method, using the same soft lithography processing as the rest of the structure. We are currently developing arrays of magnetic microvalves based on such M-NCP diaphragms[33] and flaps. Each microvalve is designed to be individually controlled by separate magnetic fields which can be individually addressed[24].

3. TECHNOLOGIES FOR COMBINING DISPARATE COMPONENTS

Microinstrumentation can be very complex, requiring the interfacing of many different passive and active components such as micro channels, valves, pumps, filters, and chemical reaction chambers, as well as detection systems and other sensors operating on electrical, mechanical, or optical principles (please see Figure 1). These devices must be interconnected together in order to perform complex functions, and may be connected to off chip devices for sample and reagent introduction and waste removal, actuator control and sensor readout. Often components are individually optimized before this integration is attempted, resulting in the need to combine disparate components that may be fabricated using disparate materials and fabrications methods such as those discussed in the previous section.

In general, interconnect requirements fall into the following categories: mechanical, optical, microfluidic, and electronic. Interconnect further falls into two categories based upon what is being connected: component-to-component or chip-to-chip (CTC); and world-to-chip (WTC). Mechanical interconnect usually refers simply to the method with which devices are physically attached to each other. In the SFU µiL, we have generally accomplished this at the same time as microfluidic and/or electronic interconnect as discussed below. We have not focused on optical interconnect, except to ensure that optically read devices such as cell research platforms and surface plasmon resonance (SPR) sensors maintain optical transparency. However, several excellent reviews exist for micro-optical interconnect schemes, which may be combined with electronic and/or microfluidic interconnect[34].

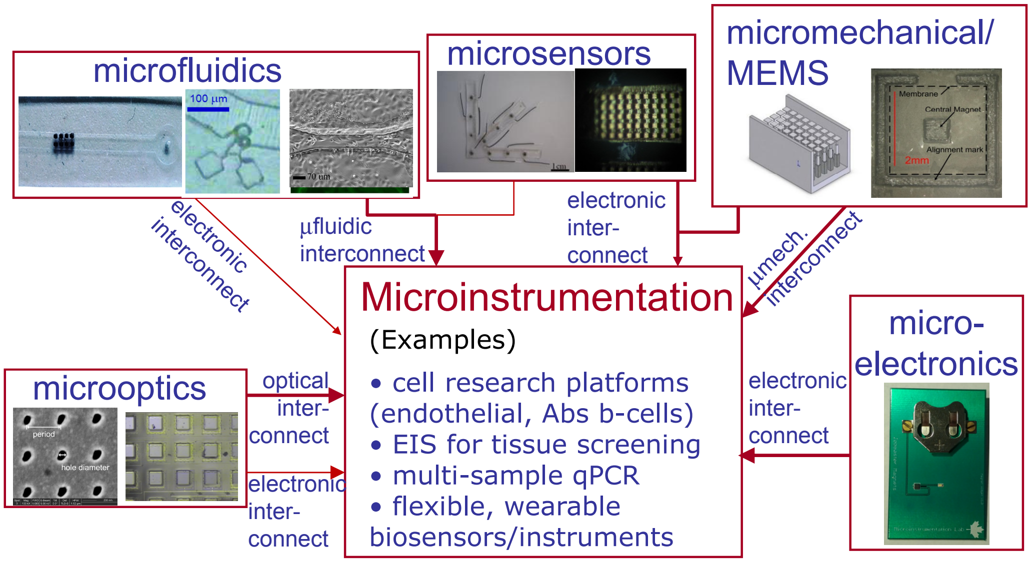

Figure 1. Microinstrumentation can be composed of a number of different subcomponents, often involving disparate materials, which must then be interconnected using various interconnect types and schemes.

Microfluidic CTC interconnect can be accomplished several ways, including: integration of all devices into a single fabrication process flow[35]; embedding of multiple devices in a (usually polymer) package[36]; devices, chips, or substrates stacked in multi-layers[37]; discrete devices modularly packaged using a circuit board or multi-chip-module (MCM) approach[38]; or chip-to-chip direct connect using tubes, ribbon cables, and other specially designed interconnect structures[39]. For many components and systems, a combination of different types of integrated and/or modular approaches may result in the most easily packaged and best performing devices. For example, a hand-held instrument developed by Sandia National Laboratories features both system-to-system modular and stacked modules[40]. Other researchers combine integrated and modular techniques, and it is common for industry to employ cartridges and one or more other methods. Similarly, many methods of WTC interconnect have been investigated, including: simple wells for fluid sample introduction[41]; adhesively bonded tubes or other permanently sealed macro-micro interfaces[42]; and tubes that are not permanently sealed but can be attached mechanically; and socket-type approaches for multiple WTC interconnects[43]. In addition, specialized WTC interconnects are emerging for applications that include high pressure and nanofluidic applications. A more detailed review of both CTC and WTC microfluidic interconnects is given in[44].

One methodology that is being increasingly investigated relies upon modular interconnect using interface structures integrated into the components' process flow, that may then interconnect together even if the components themselves are fabricated in highly disparate materials. Such "plug-and-play" modular schemes have many advantages, including that the individual components can be optimized separately and combined, provided the interconnect structures can be easily introduced into their respective process flows. At the SFU µiL, we have developed a range of "peg-in-hole" micromachined structures and other physical alignment keys that enable microchannel-containing modules in silicon, glass, and polymers to be assembled together in a fluid-tight and potentially electronically interconnected fashion. As these materials are also easily integrated with other materials that we use in our lab, e.g., silicon, glass, and functional NCPs, these structures allow us to produce a variety of instruments assembled from components fabricated in disparate materials. Although not employed for all microinstruments in our lab, we employ this design-for-assembly systematic approach where we can in component and system development.

For the peg-in-hole type interconnects, we have found that the best interconnects (easy to assemble, yet with a high disassembly pull-out force) result from pairing a moderately rigid cylinder (e.g., fabricated in SU-8) with a more compliant (e.g., PDMS) hole, indicating a reliable method to reversibly interconnect microfluidic chips in these different materials. Our interconnects have been leak tested to 6.9 kPa (PDMS interconnect) and 200 kPa (SU-8 interconnect)[45]. While single interconnects can be used, peg-in-hole interconnects work best when used in arrays, as this increases the mechanical strength of the substrate-to-substrate bond. We have employed our interconnects to attach free-standing polymer components together and pass fluid between them, as well as pass fluid on and off chip using similar structures as WTC interconnect[39]. We have also combined disparate materials such as PDMS and SU-8 to demonstrate hybrid interconnects with peg-in-hole structure. These peg-in-hole interconnects have been introduced into the process flows for a variety of components, including microneedles with integrated fluidic interconnect[46] and free-standing polymer transmission surface plasmon resonance (SPR) sensors with integrated fluidic interconnect[47]. We have also employed magnetic nanocomposite polymer structures to aid in assembly of peg-in-hole type interconnects[31].

In addition to peg-in-hole type interconnects, we have also developed other physical alignment keys to attach components. In one example, a lid type structure containing WTC microfluidic ports was fabricated in PDMS and used to seal SU-8 microchannels containing biological cells[48]. The lid is fabricated in PDMS and is pressed to fit onto the SU-8 microchannel and attached using specially designed structures (ridges, grooves, and holes). The PDMS enclosure is assembled onto the SU-8 microchannel via 1 mm high ridges and holes, as well as shorter 300 µm ridges and grooves. By having the ridges and holes in the PDMS, and grooves and ridges in the SU-8, the enclosure is securely aligned and assembled onto the microchannel. Assembly can be easily accomplished manually, in the presence of both fluid and biological cells in the SU-8 microchannel. Other fin-type physical alignment keys can be used to help assembled multiple modules into a jig and provide alignment between levels.

Electronic interconnect methods are often adapted directly from those used for electronic devices, and can be accomplished at the same time as microfluidic interconnect. Many different methods exist, and a full review is beyond the scope of this paper. In the SFU µiL, we have employed our unique hybrid NCP/polymer processing to realize highly flexible electronic circuit boards[23] as well as peg-in-hole type electrical interconnects using C-NCPs. We have also found that we can easily connect wires to C-NCP structures via either embedding of wires directly into the structure[26], or through conductive adhesives.

4. ADDITIONAL EXAMPLE COMPONENTS AND SYSTEMS

This section presents a few additional example components and systems specific to collaborations associated with the µiL that demonstrate how NCP/polymer compatibility, as well as generic structures and packaging approaches, can aid in microinstrument development.

A variety of flexible devices and systems using SU-8 and/or silicone materials for metal-on-polymer or NCP/polymer devices and systems have been demonstrated. In collaboration with SFU Engineering and SFU Chemistry, we have investigated thin film metal on polymers as electroenzymatic sensor microelectrodes, in particular flexible glucose sensors for implantation in contact lenses using both SU-8[49] and PDMS[50] as highly flexible stand-alone substrates, and found them to be promising sensors in terms of sensitivity and drift, especially when pillar-type electrode surfaces are employed to increase the active electrode surface area and sensitivity.

We have developed a number of devices and systems based on hybrid combinations of nanocomposite polymers (NCPs) and undoped polymers. One NCP/polymer application that we have investigated employs C-NCPs as a microfluidic circuit board[23]. A typical resistance value for an 1 mm long 50 wt-% Ag-PDMS electrode with a height of 30 µm and width of 100 µm is 25 Ω (at DC and room temperature, with no additional additives). While a long way away from pure metals (a pure silver block of the same size would be about 5.3 mΩ), the conductivity may be sufficient for short lengths of microelectronic routing or for microelectrodes for specialized applications where flexibility is of paramount importance above conductivity levels.

Nonpolarizable Ag/AgCl electrodes can be realized by chloridizing the outer surface of a C-NCP composed of 60 wt-% 80 nm Ag nanoparticles in PDMS[26]. While we have demonstrated these electrodes for tissue impedance measurements together with collaborators in SFU Engineering Science and BC Cancer Agency, these electrodes also have potential applications in biochemical sensors for flexible microfluidic LOC and µTAS such as may be useful for wearable biomedical monitors. We have also produced Ag/graphene electrodes, which are highly conductive and stable, and show that differences in tissue phantom impedance can be measured using these electrodes, despite their being polarizable and unable to measure exact tissue impedance.

In another collaborative project with SFU physicists, immunologists, and University of Victoria optical engineers and chemists, we have used a stacking approach to develop a microinstrument for capturing single anti-body secreting (Abs) cells in arrays of microwells. These arrays of captured cells can then be monitored via arrays of surface plasmon resonance biosensors mounted on glass substrates, with the sensor and well modules stacked in a jig using physical alignment keys[9]. While only small shifts in transmission peak have thus been observed, with ongoing specificity issues still being addressed, we have been able to capture arrays of cells, and subsequently assemble the instrument using the jig and alignment keys, and take multiple measurements using the apparatus.

5. DISCUSSION AND FUTURE OUTLOOK

The development of bio-microinstrumentation can be a very difficult puzzle of multiple requirements, including the need to combine otherwise disparate materials, development of new materials to overcome compatibility issues, and development of new component interconnects schemes that can stay ahead of the ever-changing materials and component fabrication landscapes. In general, combinations of disparate materials are facilitated if materials are chosen that: 1) are easily interfaced together for reasons of good adhesion and/or easy integration using batch processing; and 2) possess characteristics that yield long-term compatibility and robustness of interface, e.g., are mechanically similar and/or have an excellent chemical or physical bond. Combinations of disparate components are enabled by either: 1) integrating process flow as much as possible; or 2) including interconnect or other physical alignment structures in the component or module process flow, so that methods to attach them already exist when they are completed.

Using passive and active materials that are fundamentally similar avoids many materials compatibility issues such as those between metals and polymers, as we have discovered through our investigations into combinations of polymers and NCPs. There is still a lot to be done in this area. We note, for example, that we have thus far primarily employed the two most popular materials among academics, the uv-light-patternable photopolymer SU-8 and the highly compliant elastomer polydimethylsiloxane (PDMS), mainly because they have a long history of prototyping ease and are familiar materials, rather than because of any particular physical or chemical benefits of these materials. We are currently investigating many other thermosets and select thermoplastics as the basis for NCPs, as well as our interconnect structures, as such materials are becoming industry standards[1]. Also, while silicon chips have been combined previously with, e.g., glass chips in a PDMS package[36], we are currently attempting to combine multiple silicon electronic devices with polymer microfluidic boards using C-NCP electronic routing.

No widely accepted interconnect or materials standards currently exist, and it is not certain that such standards would even benefit the microinstrumentation field in its present form. However, what often works for one device or instrument in one's lab can also work for others. From a prototyping standpoint, having standardized component interconnect certainly has its advantages, and incorporating interconnect structures and physical alignment keys into component development avoids having to "glue together" components later in an ad-hoc fashion. Several researcher groups are working on their own standardization schemes. Researchers have developed microfluidic assembly blocks with a goal toward making user-definable systems based on generic building block structures that include WTC tubing ports, passive channels in generic geometries, chambers, connectors, culture beds for biological cells, and valves[51]. Others[52] have also tried to develop modular, customizable microfluidics. Rather than modules laid side-by-side and stacked on a glass or other substrate materials, they have taken a more microfluidic circuit board or MCM approach. A "plug-n-play" microfluidics based on a modular microfluidic circuit board approach with chip-to-chip interconnect via basic H-shaped microchannel inserts with miniaturized luer fittings fabricated via stereolithography, which are a version of tube-type chip-to-chip fitting but with added geometry for better attachment due to the stereolithography methods, has been proposed[53]. In addition to standardization needs for conventional microfluidic systems, electrowetting-based droplet microfluidic systems[54,55], and systems featuring large scale integration[56] both seek interconnect paradigms. Microinstrument interconnect is an exciting field that progresses and expands every year, expanding from a few references that could be cited by the author in articles in the late 1990's, to hundreds of references for the field of microfluidic interconnect alone[44]. Widely recognized as a bottleneck to commercial acceptance of microfluidics and MEMS, microinstrument interconnect will likely continue to expand in importance as systems become increasingly closer to realization and methods of interconnecting them easily and quickly becomes a selling feature.

6. ACKNOWLEDGEMENTS

The author would like to thank NSERC and CFI for funding; CMC Microsystems for software tools and fluidic testing equipment; Drs. Parameswaran, Kaminska, Gates, Leznoff, Shannon, Li, Kavangh, and Scott research groups for collaborations, many of which are referenced in this article; J. Herchenroeder & D. Miller (Magnequench) for collaboration and donating hard magnetic nanoparticles; K. Kohli & R. Rameseshan (BC Cancer & Fraser Valley Cancer Centres) for collaborative work; current and former uiL students, especially: Dr. Ajit Khosla, Mona Rahbar, Jasbir Patel, Dae-han Chung, Ang Li, Sam Seyfollahi, Sean Romanuik, Dan Hilbich, Connie Drewbrook, Seema Jaffer, Stephanie Westwood, Takaya Ueda, and Matthew Giassa who did much of the uiL work referenced in this article.

REFERENCES

[1] H. Becker, C. Gartner, "Polymer microfabrication technologies for microfluidic systems", *Anal Bioanal Chem* 390(1):89-111 (2008).

[2] B.L. Gray, "Microfluidics on compliant substrates: recent developments in foldable and bendable devices and system packaging", *Proc. SPIE 8344:Nanosensors, Biosensors, and Info-Tech Sensors and Systems 2012*, 834419 (April 26, 2012); doi:10.1117/12.915784, 9 pages.

[3] G.M. Whitesides, "The origins and the future of microfluidics", *Nature*, 442:368-373, (2006).

[4] S Coyle, et.al., "BIOTEX—Biosensing Textiles for Personalised Healthcare Management", IEEE Trans Inf Tech Biomed 14(2):364-370 (2010).

[5] D. Ziegler, T. Suzuki, S. Takeuchi , "Fabrication of Flexible Neural Probes With Built-In Microfluidic Channels by Thermal Bonding of Parylene", *J Microelectromechanical Systems*, 15:6 (2006) 1477-1482.

[6] Scholles, L. Kroker, U. Vogei, J. Kruger, R. Walczak, J. Ruano-Lopez "LABONFOIL: investigations regarding microfluidic skin patches for drug detection using flexible OLEDs", *SPIE Proc* v75930C-1, (2011) 11pp.

[7] T. Ueda, B.L. Gray, Y. Chen, P. Li, "PDMS lid for sealing microchannels after cell culturing", *Micromechanics and Microengineering Europe (MME)*, Aachen, Sept 2008, 4 pp.

[8] C. Khan Malek, L. Roberta, R. Saluta, "Femtosecond laser machining and lamination for large-area flexible organic microfluidic chips*", Euro Phys J Appl Phys* 46 :12503 (2009).

[9] S.F. Romanuik, S.M. Grist, B.L. Gray, D. Hohertz, K.L. Kavanagh, N. Gulzar, J.K. Scott, R. Nirwan, C. Hui, A.G. Brolo, R. Gordon, "Detecting Antibodies Secreted by Trapped Cells Using Extraordinary Optical Transmission", *IEEE Sensors Journal* 11(11): 2732 – 2739.

[10] C. Iliescu, H. Taylor, M. Avram, J. Miao, S. Franssila, "A practical guide for the fabrication of microfluidic devices using glass and silicon", *Biomicrofluidics* 6, 016505 (2012); http://dx.doi.org/10.1063/1.3689939 (16 pages).

[11] I.T. Young, R. Moerman, L.R. Van den Doel, V. Iordanov, A. Kroon, H.R.C. Dietrich, G.W.K. Van Dedem, A. Bossche, B.L. Gray, L. Sarro, P.W. Verbeek, L.J. Van Vliet, "Monitoring enzymatic reactions in nanolitre wells", *Journal of Microscopy* 212:3 (Dec 2003), pp 254-263.

[12] N-T Nguyen, X. Huang, "Miniature valveless pumps based on printed circuit board technique", *Sensors and Actuators A: Physical* , Volume 88, Issue 2, 15 February 2001, Pages 104–111.

[13] D.J. Beebe, J.S. Moore, J.M. Bauer, Q. Yu, R.H. Liu, C. Devadoss, B-H Jo, "Functional hydrogel structures for autonomous flow control inside microfuidic channels", *Nature* vol 404 (6 April 2000), pp. 588-590.

[14] T.F. Didar, A.M. Foudeh, M. Tabrizian, "Patterning Multiplex Protein Microarrays in a Single Microfluidic Channel", *Anal. Chem*., 2012, 84 (2), pp 1012–1018.

[15] A. Wu, L. Wang, E. Jensen, R. Mathies,B. Boser, "Modular integration of electronics and microfluidic systems using flexible printed circuit boards", *Lab on a Chip* 10 (2010) 519-521.

[16] T. Ueda, S. Jaffer, S. Westwood, B.L. Gray, "Design of Electrical Interconnect for SU-8 Microfluidic Systems", *20th Annual Canadian Conference on Electrical and Computer Engineering*, April (2007) 5-7.

[17] J.N. Patel, B. Kaminska, B.L. Gray, B.D. Gates, "A sacrificial SU-8 mask for direct metallization on PDMS", *Journal of Micromechanics and Microengineering*, 19 115014 (10 pages), (2009).

[18]J. N.Patel, B. Kaminska, B.L. Gray, B. D. Gates, "PDMS as a sacrificial substrate for SU-8 based biomedical and microfluidic applications", *J. Micromechanics & Microengineering*, 18:9 (Sept. 2008) 095028, 11 pages.

[19 R Verplancke, F Bossuyt, D Cuypers, J Vanfleteren "Thin-film stretchable electronics technology based on meandering interconnections: fabrication and mechanical performance", *Journal of Micromechanics and Microengineering*, v 22 n1 (2012) 015002.
[20] J.R. Windmiller, J. Wang, "Wearable Electrochemical Sensors and Biosensors: A Review", *Electroanalysis* doi: 10.1002/elan.201200349 (2012).
[21] A. Li, A. Khosla, J. Lee, B. L.Gray, PHC Li, "Fabrication and testing of hydrogel-based microvalves for flow control in flexible lab-on-a-chip systems", *SPIE Proceedings8251, Microfluidics, BioMEMS, and Medical Microsystems X,* 82510Z (February 9, 2012); doi:10.1117/12.910239 (12 pp).
[22] B.L. Gray, A. Khosla, "Microfabrication and applications of nanoparticle doped conductive polymers", in: *Nanoelectronics*, K. Iniewski (editor), McGraw Hill, pp 227-262 (2010).
[23] A. Khosla, B. L Gray, "Properties of conductive micromoldable thermosetting polymer for electronic routing in highly flexible microfluidic systems" *SPIE Proc vol 7593*, Jan 2010, 6 pp.
[24] M. Rahbar, S.Seyfollahi, A. Khosla, B. L. Gray, L. Shannon, "Fabrication of electromagnetically actuated actuators in polymer based microfluidic devices", *220th ECS Meeting*, Boston, Oct 2011.
[25] Stauffer, Aharony, *Introduction to percolation theory*, 2nd ed., Philadelphia, Taylor & Francis, 1994.
[26] D. Chung, A. Khosla, S. Seyfollahi, B. L. Gray, A. Parameswaran, K. Kohli, R. Ramaseshan, "Embedded Process for Flexible Conductive Electrodes for Applications in Tissue Electrical Impedance Scanning (EIS)", *IEEE Sensors Conf.*, Dublin, Oct 2011, 4 pp.
[27] A. Li, A. Khosla, C. Drewbrook, B. L.Gray, "Fabrication and testing of thermally-responsive hydrogel-based actuators using polymer heater elements for flexible microvalves", *SPIE Proceedings* 79290G, 9 pages (2011).
[28] F. Fahrnia, M.W.J. Prins, L.J. van IJzendoorn, "Magnetization and actuation of polymeric microstructures with magnetic nanoparticles for application in microfluidics", *Journal of Magnetism and Magnetic Materials* v321 n12 (2009):1843-1850.
[29] F. Pirmoradi, J. K. Jackson, H. M. Burt, M. Chiao, "A magnetically controlled MEMS device for drug delivery: design, fabrication, and testing", *Lab Chip* 11 (2011), 3072-3080.
[30] A. Khosla, J.L. Korand, M. Haiducu, B.L. Gray, D.B. Leznoff, M. Parameswaran, "Preparation of nickel doped multi-functional micro-patternable polydimethylsiloxane nanocomposite polymer with characterization of its magnetic, electrical and mechanical properties for soft MEMS/Lab on a chip applications", *Nanotech 2010*, Anaheim, June 2010, v 1, pp. 872-876.
[31] S. Jaffer, B.L. Gray, D.G. Sahota, M.H. Sjoerdsma, "Mechanical assembly and magnetic actuation of polydimethylsiloxane-iron composite interconnects for microfluidic systems", *Proc SPIE* vol. 6886, Jan 2008, 12 pp.
[32] C. Yamahata, F. Lacharme, M. A.M. Gijs, "Glass valveless micropump using electromagnetic actuation", *Microelectronic Engineering* v78-79 (March 2005):132-137.
[33] D. D. Hilbich, A. Khosla, B. L. Gray, L. Shannon, "Bidirectional magnetic nanocomposite polymer microactuators for uTAS", *SPIE Proceedings* 79290H, 11 pages (2011).
[34] T. Tekin, "Review of Packaging of Optoelectronic, Photonic, and MEMS Components", *IEEE Journal of Selected Topics in Quantum Electronics* v17 n3 (2011): 704-719.
[35] J.D. Zahn, A.A. Deshmukh, A.P. Papavasiliou, A.P. Pisano, D. Liepmann, "An integrated device for the continuous sampling and analysis of biological fluids", *Proceedings of 2001 ASME International Mechanical Engineering Congress and Exposition*, New York, 6 pp. (Nov 2001).
[36] P. Krulevitch, W. Benett, J. Hamilton, M. Maghribi, K. Rose, "Polymer-based packaging platform for hybrid microfluidic systems", *Biomedical Microdevices* 4(4):301-308 (2002).
[37] A. Han, M. Graff , O. Wang, A.B. Frazier, "An approach to multi-layer microfluidic systems with integrated electrical, optical, and mechanical functionality", *IEEE Sensors Journal*, 5(1):82-89 (2005).
[38] B.L. Gray, S.D. Collins, R.L. Smith, "Interlocking mechanical and fluidic interconnections for microfluidic circuit boards", *Sensors and Actuators A* 112:18-24 (2004).
[39] S. Westwood, S. Jaffer, B.L. Gray, "Enclosed SU-8 and PDMS microchannels with integrated interconnects for chip-to-chip and world-to-chip connections", *Journal of Micromechanics and Microengineering*, 18:6 064014, 9 pp., (June 2008).
[40] R.F. Renzi, J. Stamps, B.A. Horn, S. Ferko, V.A. VanderNoot, J.A>A> West, R. Crocker, B. Wiedenman, D. Yee, J.A. Fruetel, "Hand-held microanalytical instrument for chip-based electrophoretic separations of proteins", *Analytical Chemistry*, 77:435-441 (2005).

[41] T.D. Boone, Z.H. Fan, H.H. Hooper, A.J. Ricco, H. Tan, S.J. Williams, "Plastic advances microfluidic devices", *Analytical Chemistry*, 74: 78A-86A (2002).
[42] B.L. Gray, D. Jaeggi, N.J. Mourlas, B.P. van Drieënhuizen, K.R. Williams, N.I. Maluf, G.T.A. Kovacs, "Novel interconnection technologies for integrated microfluidic systems", *Sensors and Actuators A* 77(1):57-65 (1999).
[43] D. Sabourin, D. Snakenborg, M. Dufva, "Interconnection blocks: a method for providing reusable, rapid, multiple, aligned and planar microfluidic interconnections", *Journal of Micromechanics and Microengineering*, 19: 035021, 9 pages (2009).
[44] B.L. Gray, "Fluidic interconnects for microfluidics: chip-to-chip and world-to-chip", in: *Microfluidics & Nanofluidics Handbook (V2)*, S.K. Mitra, ed., CRC Press/Taylor Francis, 2011.
[45] S. Jaffer, B.L. Gray, "Polymer mechanically interlocking structures as interconnect for microfluidic systems", *Journal of Micromechanics and Microengineering*, 18 035043, 10 pp., (March 2008).
[46] O. Lui, B.L. Gray, "Microneedle array with interconnects for transdermal drug deleivery", *29th Canadian Medical and Biological Engineering Conference*, June 2006, 4 pages.
[47] S. M. Westwood, B. L. Gray, S. Grist, K. Huffman, S. Jaffer, and K. L. Kavanagh, "SU-8 Polymer Enclosed Microchannels with Interconnect and Nanohole Arrays as an Optical Detection Device for Biospecies", *IEEE 30th Annual Engineering in Medicine and Biology Conference*, Vancouver, August 2008, 4 pages.
[48] T. Ueda, B.L. Gray, Y. Chen, P. Li, "Flexible enclosure for fluidic sealing of microcomponents", *Proceedings of SPIE* vol. 6886-0P-1, January 2008, 9 pages.
[49] J.N. Patel, B.L. Gray, B. Kaminska, B.D. Gates, "Flexible glucose sensor utilizing multilayer PDMS process", *IEEE 30th Annual Engineering in Medicine and Biology Conference*, Vancouver, August 2008, 4 pages.
[50] J. Patel, B.L. Gray, B. Kaminska, B. Gates, "Flexible polymer sensors for monitoring glucose in tears*" J Diabetes Sci & Tech*, Sept 2011, 5(5): 1036-43.
[51] M. Rhee, M. A. Burns, "Microfluidic assembly blocks", *Lab on a Chip* 8, 1365-1373 (August 2008).
[52] K. Shaikh, K.S. Ryu, Z. Fan, C. Liu, "Fabrication of through-wafer fluid interconnects with low dead volume and integrated back-plane fluid jumpers", *7th International Conference on Miniaturized Chemical and Bioechemical Analysis Systems (Micro-TAS)* , Squaw Valley, 1053-1056 (October 2003).
[53] P.K. Yuen, "SmartBuild – A truly plug-n-play modular microfluidic system", *Lab on a Chip* 8, 1374-1378 (August 2008).
[54] T.T. Kanagasabapathi, K.V.I.S. Kaler, "Surface microfluidics--high-speed DEP liquid actuation on planar substrates and critical factors in reliable actuation", *Journal of Micromechanics and Microengineering*, 17:743-752 (2007).
[55] R.B. Fair, "Digital microfluidics: is a true lab-on-a-chip possible?", *Microfluidics and Nanofluidics*, 3(3):245-281 (2007).
[56] T. Thorsen, S.J. Maerkl, S.R. Quake, "Microfluidic large-scale integration", *Science*, 298:580-584 (2002).