Membrane Deflection-based Fabrication and Design Automation for Integrated Acoustofluidics

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Department of Electrical Engineering

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UNDER MY SUPERVISION BY

Daniel Freitas

ENTITLED

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Automation for Integrated Acoustofluidics

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Membrane Deflection-based Fabrication and Design Automation for Integrated Acoustofluidics

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Abstract

Continuous-flow microfluidic large-scale integration (mLSI) is a developing field first introduced in the early 2000s, that continues to offer promising solutions to many biochemical, biophysical and biomedical problems. In his seminal paper, Thorsen et al. 2002 demonstrated the fabrication of high-density microfluidic systems capable of complex fluidic routing in combinatorial arrays of multiplexors, mixers, and storage assemblies integrated with micromechanical valves. mLSI has been a powerful tool for scientific research by allowing for dramatic reduction in the volume of reagent needed for experimentation and offering highly parallelizable and dynamic process flows. These systems have since been the focus of strong interdisciplinary academic research efforts. Despite the success in scientific applications, the mLSI technologies have not found widespread use in commercial environments. One critical issue preventing mLSI to realize its full potential is the need for specialized fabrication techniques that are scalable and more suitable for the unique requirements of biology.

The work presented here demonstrates an mLSI integrated acoustofluidic platform that offers versatility while maintaining a robust fabrication process. In particular, conductive liquid metal-based acoustic transducers integrated with micromechanical valves to facilitate dynamic switching of the resonant frequency of the device and generated surface acoustic waves (SAWs) is demonstrated. Shortcomings in the fabrication of fluidic channels for mLSI integrated acoustofluidic applications are examined, and solutions to these problems are presented. A novel and scalable soft-lithographic method is introduced, that allows for the fabrication of large valvable channels with tunable height that exceeds practical limitations dictated by previous photolithographic techniques. A thorough characterization of this method and demonstration of its robustness techniques are included here as a promising data to promote further exploration of the technique as a viable commercial solution for the fabrication of many classes of mLSI bio-devices. The testing of a computer-aided design software, Columba, is briefly discussed.

Keywords: IDT, surface acoustic wave, mLSI, acoustofluidics, lithography, fabrication
## List of Abbreviations

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<th>Abbreviation</th>
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<tr>
<td>mLSI</td>
<td>Microfluidic Large Scale Integration</td>
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<tr>
<td>SAW</td>
<td>Surface Acoustic Wave</td>
</tr>
<tr>
<td>IDT</td>
<td>Interdigitated Transducer</td>
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<tr>
<td>LM</td>
<td>Liquid Metal</td>
</tr>
<tr>
<td>EGaIn</td>
<td>Eutectic Gallium-Indium</td>
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<tr>
<td>PDMS</td>
<td>Polydimethylsiloxane</td>
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<tr>
<td>IC</td>
<td>Integrated Circuit</td>
</tr>
<tr>
<td>SSAW</td>
<td>Standing Surface Acoustic Wave</td>
</tr>
<tr>
<td>APTES</td>
<td>3-Aminopropyltriethoxysilane</td>
</tr>
<tr>
<td>GPTES</td>
<td>3-Glycidoxypropyltrimethoxysilane</td>
</tr>
<tr>
<td>LiNBO$_3$</td>
<td>Lithium Niobate</td>
</tr>
<tr>
<td>VNA</td>
<td>Vector Network Analyzer</td>
</tr>
<tr>
<td>PMMA</td>
<td>Poly(methyl methacrylate)</td>
</tr>
<tr>
<td>ELISA</td>
<td>Enzyme-linked Immunosorbent Assay</td>
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<tr>
<td>TMCS</td>
<td>Trimethylchlorosilane</td>
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<tr>
<td>HCl</td>
<td>Hydrochloric Acid</td>
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CHAPTER 1. Introduction

1.1 Background

The work presented here, motivated by several aspects of microfluidic large-scale integration (mLSI), details the exploration of reconfigurable acoustofluidics, scalable soft-molding and design automation to promote wider adoption of mLSI technologies in academic and clinical settings. mLSI was first introduced by Thorsen et al. 2002 [1], with the demonstration of high-density microfluidic chips capable of complex fluidic routing in combinatory arrays of multiplexors, mixers, and storage assemblies integrated with micromechanical valves. mLSI has been shown to be a powerful tool for rethinking most traditional biochemical, biophysical and biological experimentation [2-5]. Microfluidic systems are unique in their dramatic reduction of sample and reagent volumes, highly parallelizable and modular design, and have canonically been hailed as ‘lab-on-a-chip’ solutions to otherwise hardware-intensive, traditional experimental techniques. Even with the large wave of support, however, many of these ‘lab-on-a-chip’ platforms have remained in academic pipelines and largely failed to make meaningful entries into the commercial and clinical realms. While many disagree on the reasons microfluidic technologies have been slow to reach their potential [6-8], at least part of the answer is the inability of bio-devices to generalize as solutions to many complex problems. Device-specific and most of the time complicated fabrication processes that are not amenable to scale, along with the challenges in device design, that currently must be done manually in a computer aided design software (e.g. AutoCAD), make the clinical adoption of mLSI technologies impractical.

Acousto-fluidics is an example of a promising technology that has seen limited adoption due to the complicated fabrication processes and static nature of the devices [9-11]. Acoustic wave
based solutions for bio-particle isolation are attractive for many reasons, but currently rely on the direct patterning of metallic interdigitated transducers (IDTs) onto a piezoelectric substrate. This approach lacks dynamic capability, since once the IDTs have been patterned there is no method to reconfigure their operating resonant frequency. This means that the device can only be used and optimized for a very specific range of particle sizes for manipulation. In the first part of this thesis, an mLSI integrated liquid metal-based acousto-fluidic platform is explored, that is capable of adjusting the resonant frequency of the device after electrode fabrication, significantly extending the dynamic capability.

Additionally, shortcomings in traditional mLSI fabrication methodologies are explored. These shortcomings limit not only acousto-fluidic device fabrication, but also largely restrict mLSI technology from being integrated into many promising application areas for microfluidic adaptation (e.g. high throughput C. elegans studies for in vivo drug trials and large scale phenotypic and genotypic platforms to better aid the development of stem cell and cancer research) [12-16]. A novel fabrication methodology is presented that will widen the potential for researchers to extend the use-cases of mLSI integrated sciences to many corners of academia and industry.

Finally, this thesis concludes with a brief exploration into design automation for microfluidic devices, including examples of fabricated devices designed with software developed in collaboration with the Technical University of Munich and the National Tsing Hua University in Taiwan. These approaches have the potential to increase the throughput of device design in the
same way these design automation technologies have equipped the integrated circuit (IC) fabrication pipeline with the ability for rapid-prototyping of many design iterations.

1.2 Aims/Objectives

The thesis presented here aims to explore the advantages of mLSI integrated technologies with specific focus on mLSI integrated acousto-fluidic devices, and the hindrances in the commercialization of these technologies. Further, this thesis presents solutions to fabrication and device design bottlenecks to spurn wider adoption of mLSI technologies outside of the academic realm. In particular the following issues are discussed in detail:

- mLSI for reconfigurable acousto-fluidic applications.
- Drawbacks and limiting factors in commercial adoption of acousto-fluidic and similar mLSI technologies.
- Scalable fabrication solutions for commercial mLSI workflows.
- Design automation for mLSI device development.

1.3 Thesis Structure

Chapter 2 demonstrates the design, development and implementation of a reconfigurable LM-based acousto-fluidic device. It also includes a discussion on drawbacks and commercial barriers.

Chapter 3 defines and explores a novel and scalable fabrication solution for mLSI. Detailed performance characterization, valvability and robustness studies are also included.
Chapter 4 briefly discusses design automation for mLSI bio-devices. Implementation of bio-chips generated by a first-of-its kind CAD software is illustrated here as well, and drawbacks are explained.

Chapter 5 holds a brief conclusion and statement on future work in mLSI.

1.4 Thesis Contributions

This thesis will address the concerns and limitations in the commercialization of mLSI bio-devices and provide novel fabrication and design solutions to aid clinical adoption. The ideas here will help bring academic implementations of critical biomedical technologies closer to real world applications in patient care, environmental monitoring, biopharmaceutical research, and many other fields. The conclusions drawn from this work will guide future developments in the scalability of mLSI and other microfluidic devices, whose repercussions have the potential for far reaching societal impact.
CHAPTER 2. Reconfigurable IDTs

2.1 Motivation for LM IDT Approach

The separation and manipulation of bio-particles is a critically important tool for many biophysical, biochemical and biomedical applications [17-21]. The importance of large and sub-micron bio-particle separation has been extensively reviewed elsewhere [22-24]. In particular, the sorting and identification of critical biomarkers (e.g. circulating tumor cells), allergens and carcinogens in food and water, and the isolation of traditionally difficult to purify bio-particles (e.g. exosomes). Recent developments have adopted dielectrophoretic [25-26], inertial [27-28], magnetic [29], and acoustic [30-31] based methods to improve separation techniques. In particular, the use of acoustic fields in the form of surface acoustic waves (SAWs) in modern lab-on-a-chip devices has recently led to acoustofluidic technologies that offer new functionalities, like the three-dimensional control of single cells within micro-channels and manipulation of cell-cell interactions using SAWs [32-33]. SAW resonators have been used in the radio and television industries as transmitters due to their high frequency range of operation, and also in common

![Diagram](image)

**Figure 2.1** (a) Schematic of a liquid metal based SAW device with integrated valves. (b) Actuation of valves compresses the electrode channel and breaks the electrical paths. (c) Application of a RF signal to the electrode channel generates SAW propagating on the substrate. (d) A picture of the device.
consumer products as filters (e.g. mobile phones), but their inclusion in microfluidic devices for biological applications is more recent.

The use of SAWs in these devices is attractive for modern applications because they are non-invasive, label-free, energy efficient, allow for the separation of bio-particles based on mechanical properties alone, and can be easily integrated into existing microfluidic designs. SAWs are produced along a piezoelectric substrate by applying spatially modulated radio frequency (RF) (1-20 MHz) electric potential to interdigitated transducers (IDTs). The modulated RF input causes a propagating mechanical stress in the piezoelectric substrate (As shown in Figure 2.1).

The acoustic wavelength produced by the IDTs depends on the electrode finger width and the spacing between electrode fingers. Interference principles can be exploited to create one-dimensional standing surface acoustic waves (SSAWs) across microfluidic channels. In SSAW devices, two identical IDTs located on opposite sides of a microfluidic channel produce two counter-propagating SAWs that induce a standing acoustic wave pattern, and associated acoustic radiation forces are applied. These acoustic radiation forces have a strong dependence on particle size and compressibility (see Eq. 1). Technologies based on these SSAW principles have recently gained attention as a promising and versatile technique for noninvasive manipulation and size based sorting of cells [34-35]. Some other applications include the separation of circulating tumor cells (CTCs), particle focusing, and the efficient and non-invasive mixing of reagents for biological assays [36-38]. However, current SAW technology relies on complex lithographic techniques, and once IDTs have been patterned onto the surface of the device there
is no effective way to adapt their properties in order to change the SAWs they produce. While the range of particle sizes and compressibility’s that can be manipulated by a single device depends heavily on parameters including RF input, fluid density, IDT angle relative to the channel walls and the geometry and design of the device (i.e. the length of IDT active region and the number of segmented channels after this region both contribute to the allowable separation resolution), these all require labor intensive optimization. Even with thorough optimization processes, any change to the particle sizes of interest requires a complete redesign of the device. Thus, the ability to directly reconfigure the device resonant frequency offers an easy-to-use tool for researchers that allows for variable particle sizes to be separated without significant device changes.

\[
F_{\text{rad}} = \frac{2\pi^2 r^3}{\lambda} \Phi(\tilde{K}, \tilde{\rho}) \frac{p_a^2}{\rho_0 c_0^2} \sin\left(\frac{4\pi}{\lambda} y\right); \quad \Phi(\tilde{K}, \tilde{\rho}) = \frac{1}{3} \left[ \frac{5\tilde{\rho} - 2}{2\tilde{\rho} + 1} - \tilde{K} \right]
\]

**Eq. 2.1** The equation that governs dependence of acoustic radiation forces on particle size, particle compressibility, fluid density and IDT operating principles. Where \(r\), \(\lambda\), \(p_a\), \(\rho_0\), \(\rho\), and \(c_0\) represent the particle radius, acoustic wavelength, pressure amplitude, particle density, normalized density (fluid density/particle density), and acoustic wave velocity, respectively. \(\Phi\) is the contrast factor, which is a measure of the particles compressibility w.r.t the fluid compressibility. Here, \(K\) represents a normalized compressibility factor (compressibility of the particle/compressibility of the fluid).

Recent work has demonstrated the ability to replace traditionally patterned metallic interdigitated transducers (IDTs) with liquid metal (LM) alloys [39]. The metallic IDT electrodes that are used for standing surface acoustic wave (SSAW) generation, are replaced with microfluidic channels filled with liquid metal EGaIn (75% Ga, 25% In) where the fluidic channel patterns are created
in the form of desired IDT structure. EGaIn is a liquid at room temperature and can therefore be easily injected into the electrode micro-channels using a pneumatic pump. Due to PDMS gas permeability, micro-channels without flow outlets can be utilized to produce single electrode IDTs, however the structure of liquid IDT channels is typically designed as a serpentine-shaped microchannel with an inlet and outlet to allow for easier and more effective filling. Serpentine IDT channels operate similar to single electrode IDTs [39]. The consequence of this design change is that the acoustic wavelength is now given by 8x the IDT finger width, instead of 4x the IDT finger width in single electrode channel devices (please see Figure 2.3).

2.2 Basics of LM IDT Approach

The LM IDT approach in combination with microfluidics allows acousto-fluidic control of particles in a single layer of PDMS that can be fabricated by simple and low-cost soft-lithography techniques. mLSI is a widely used technology for biological and chemical automation applications [40-44]. Thousands of valves as small as 6 µm in width can be integrated in 6 µm x 6 µm areas [50] on a single microfluidic chip through mLSI, and the control of the chips can be simplified by utilizing multiplexers. The advantages of the small liquid metal volume requirement and automated reconfiguration capability together with the robust fabrication procedure make mLSI a powerful technology for acousto-fluidics. In this work, the development of LM-based acousto-fluidic technologies was furthered by integrating microfluidic large-scale integration (mLSI) with LM IDTs, which allows the electrode finger width to be reconfigured, and thus the wavelength and resonant frequency of the SAW producing device.
The reconfigurability and moldability of this hybrid LM-based SAW platform is experimentally demonstrated by measuring the electrical characteristics S-parameters by a vector network analyzer to demonstrate the ability to achieve variable resonant frequencies on a single device, greatly extending the range of associated acoustic radiation forces. In addition, this hybrid platform has the capability of generating standing SAWs on a piezoelectric substrate, which can theoretically focus micro-sized bioparticles in a fluidic channel to the low acoustic radiation force potential regions, in the same way demonstrated by traditional acoustophoretic devices [10-11]. The device, however, falls short of reconfigurable particle manipulation, and these shortcomings will be thoroughly explored. The versatility of the platform developed here opens possibilities of reconfiguring an electronic filter with a wide frequency tunability and manipulating biological samples such as cells in a three-dimensional region with high flexibility and precision. The following approach utilizes a LM-filled electrode channel to generate SAWs on a piezoelectric substrate, and micromechanical valves to structurally reshape the electrode channel to reconfigure the transducer pattern for modulation of the SAW resonant frequency. This mLSI integrated platform stands to diversify modern acousto-fluidic technologies by realizing a single device to manipulate a range of particle sizes, instead of the traditional one device-to-one particle size approach.

2.3 Design and Fabrication of LM IDTs

Here, traditional multilayer photo-lithography methods are utilized for mold fabrication as described elsewhere [45]. In traditional multilayer photo-lithography, flow and control layers are fabricated independently, creating two silicon master molds, each with unique channel dimensions and geometries patterned with either negative or positive tone photoresist. The flow
layer holds channels that will be used for fluid flow, in this case those that will contain LM. The control layer holds the valve networks that are used on top of the flow channels to reconfigure and re-route fluids. The use of two independent molds is required to ensure there are no fluidic

Figure 2.2 This figure shows a simplified cross-section of half of our finished device (well regions and IDTs shown in (A) and (B) are replicated on the other side as well), helping to illustrate the need for membrane removal and facilitate understanding of channel geometry. (A) Well regions were included to minimize the contact between PDMS and our LiNbO$_3$ substrate, (B) Control channel width was designed to be 75 µm to allow for effective valving while providing extra tolerance during alignment. Flow channel width (noted here as $\alpha$) was either 100 µm, 125 µm or 150 µm, and both flow and control channel height were 10 µm. (C) A large center channel is included for particle flow. IDTs on either side of this channel produce SSAW used for particle manipulation.
interconnections between flow and control features. Channel geometries were selected based on the required operating principles of the liquid metal IDTs (i.e. acoustic frequency and wavelength). The center flow channel, positioned equidistantly between the IDT pair, was fabricated as high as 60 μm (30 μm contribution from the flow layer plus 30 μm contribution from the control layer) to easily allow for the flow of large bioparticles. Well regions at the same height were added behind the IDTs to minimize the amount of PDMS in contact with the LiNbO$_3$ substrate. This is because PDMS-substrate contact has been shown to absorb, and thus diminish, acoustic power. The liquid metal IDT flow channels were fabricated 10 μm high to allow for easy valving. Larger flow channel height would be ideal for increased energy density, and thus increased acoustic power, however photolithographic limitations make the fabrication of rounded channels larger than 10 μm exceedingly difficult to produce. The control layer was fabricated similarly. The control channel height is 10 μm, and the width is 75 μm where valve actuation is required and 25 μm where valve actuation is undesirable (crossover channels [1]). See Figure 2.2 for a simplified cross-sectional illustration showing channel geometries.
The devices presented here were designed to produce two IDT configurations, noted as wide and narrow. The wavelength of IDT generated SAWs depends on electrode finger width (see Figure 2.3), note that increasing acoustic wavelength leads to decreasing acoustic power as illustrated by the wavelength dependence shown in Eq. 1.

Three channel width ($\alpha$) variants were chosen, $\alpha = 100$ µm, $\alpha = 125$ µm, and $\alpha = 150$ µm. The lower bound ($\alpha = 100$ µm) was determined based on practical limitations for tolerance in layer alignment during soft lithography.

Chip fabrication methods used here are based on traditional multilayer soft-lithography, where PDMS casting, curing, cutting and punching were used as described elsewhere [45]. In general, silicon master molds are used to cast the features into PDMS devices. Special considerations, however, had to be made for successful alignment and bonding. The well regions meant to minimize PDMS-substrate contact, as described above, have relatively small membrane thickness (< 10 µm) compared to a large planar area (59 mm$^2$ to 91 mm$^2$ for the 100 µm and 150 µm).
20 µm devices, respectively. Due to these geometries, the membrane lacked structural integrity (red regions in figure 2) and frequent collapses were observed. Collapses led to device failure, so membrane removal had to be considered. A number of methods were tested to remove the well region membrane, with careful excision via scalpel chosen as the simplest and most effective. Similarly, the membrane within the large flow channel was removed in this manner as well because the membrane acted as an obstruction that could interrupt particle fluid dynamics. Furthermore, EGaIn has roughly twice the viscosity of liquid water, and by nature tends to form an oxide layer on the liquid surface when exposed to atmospheric conditions [46-47]. The combination of these effects makes the filling of small fluidic channels with LM exceedingly difficult at typical mLSI pressure inputs. The higher pressure required for effective filling led to delamination of the device from the substrate with traditional plasma bonding [48]. To remedy this problem, APTES/GPTES chemical bonding was used as described elsewhere [49]. This approach forms strong and robust chemical bonds between PDMS and rigid substrates and proved sufficient at pressures as high as 30 psi. Full device fabrication is shown in Figure 2.4.

2.4 Operation and Testing of LM IDTs

The different operational states in the devices discussed here, were designed such that the wider IDT configuration was twice the acoustic wavelength (thus, half the resonant frequency) of the narrow IDT configuration. Important considerations about pneumatic architecture and successful device implementation included (1). the ability for valve actuation to completely cut electrical connection while (2). maintaining a connection between device inlets and outlets. During device operation, all serpentine microchannel IDTs are first filled with liquid metal. With no valve actuation, the device is not operational because of electrical connection between the left and right
halves of the IDTs. Valves are then actuated to cut electrical connection in order to configure different operational states (see figure 2.5).

Figure 2.4 This figure describes the photo- and soft-lithographic methods used for device fabrication. (1) The first layer of flow (left) and control (right) silicon molds are patterned on 4” silicon wafers, both to a height of 10 µm, using SPR-220 and SU-8 photoresist, respectively. (2) A second layer is added, to a height of 30 µm, to both flow (left) and control (right) silicon molds, again with SPR-220 and SU-8, respectively. (3) 20:1 PDMS is spin-coated onto the silicon flow mold at a speed of 3000 rpm, and (4) 5:1 PDMS is poured onto the silicon control mold. (5) After curing, the control layer is peeled, punched and aligned atop the flow layer, and allowed to thermally bond for 1-3 h. (6) After control-flow layer thermal bonding, the two-layer device is removed from the silicon wafer. (7) The remnant membranes in the well regions and center flow channel are carefully excised with a scalpel, and the entire device is chemically bonded (APTES/GPTES) to the LiNbO₃ substrate.
The closed valves effectively cause the resistance to go to infinity creating an open-circuit as shown by Araci et.al [50]. Valve sets 1, 2 and 3 in Figure 5 are used for electrode reconfiguration. Upon actuation of valve set 1, the narrow IDT configuration is selected, whereas upon actuation of valve sets 2 and 3, the wide IDT configuration is selected.

**Figure 2.5** Micromechanical valves integrated LM-IDT device. (a) electrode channel was pre-filled with liquid metal before actuating valves 1, 2 and 3. (b) valve 1 was actuated to generate a narrow configuration in which the periodicity of LM-IDT was 400 mm. (c) valves 2 and 3 were actuate together to generate a wide configuration in which the periodicity became 800 mm. (d-e) experimental demonstration of formation of LM-IDT transducer pattern via valves. Actuation of valve 1 pushed the liquid metal sideways and generated gap regions that act as perfect electrical isolations, as a result the narrow configuration was obtained.

Due to the ability of valve actuation to effectively cut electrical connection (and conversely the release of valve actuation to allow for electrical re-connection), the method here avoids the need to wash and refill the IDT microchannels with liquid metal in different operational states, previously shown as practically difficult [8-9, 51], requiring repeated use of acidic solvents like
HCl to remove the EGaIn oxide layer or potential-driven recapillarity. Note that HCl was used to prepare the device for testing and allow easier initial filling of LM, however once this process is complete it does not need to be repeated during the lifetime of the device.

During testing, liquid metal (SigmaAldrich), was flowed into the electrode channel by applying pneumatic pressure. External electrical connectors (Pogo connectors, Digi-key) were inserted into the reservoirs of the electrode IDT channels, providing external electrical connection. Prior to the operation of on-off micromechanical valves, an evaluation of the electrical characteristics of the LM-IDT device was carried out for the purposes of design optimization of the electrode channel, and to ensure proper electrical connection.

A vector network analyzer was used to characterize the LM-IDT through the measurement of the scattering parameter (S11). A reflection dip appearing at the SAW resonant frequency is shown by the blue curve in Figure 2.6b, and the top inset in this figure displays the impedance of LM-IDT in a smith chart. The reflection dip near 13 MHz indicates the source electrical energy was delivered to the LM-IDT and efficiently converted into mechanical SAWs propagating along the piezoelectric substrate. The S11 value -5 dB reflects an inefficient energy delivery to the LM-IDT due to impedance mismatch between the VNA and LM-IDT, and only about 70% of the electrical energy was transferred to the LM-IDT. Note the conversion efficiency is inherently determined by the electromechanical coupling coefficient of the LiNbO3 substrate. Although adjusting electrode overlap and number of electrode pairs can improve the impedance of LM-IDT and the energy delivery efficiency, this is a time-consuming optimization
process that requires iteratively changing the design until satisfactory results are achieved. This potentially becomes very inconvenient when the operational frequency needs to be changed. Rather than optimizing the impedance of LM-IDT, a tunable impedance matching network was used to adjust its impedance to that of the VNA, which maximized electrical energy delivery from VNA to LM-IDT. A circuit diagram of the matching network is depicted in Figure 2.6c, where a tunable inductor is connected in shunt with two tunable capacitors. After applying the matching network, as shown by the bottom inset in Figure 2.6b, the impedance of the LM-IDT at the frequency of the reflection dip, was tuned to 50 Ω. This impedance matching increased the energy delivery efficiency from original 70% to nearly 100%, as shown by -30 dB attenuation at the dip of the red curve.

S-parameters were measured now with different LM-IDT operational states. A device was selected with a channel width of 100 µm and configured as previously described with valves set
1 or valves sets 2 and 3 to allow for both narrow and wide configurations, respectively. As shown in Figure 2.7, different reflection dips were observed at different resonant frequencies, implying that different propagating SAWs were achieved at each LM-IDT configuration.

### 2.5 Drawbacks

The previously discussed relationship between frequency and LM-IDT structure periodicity reveals that the modulation of SAW resonant frequency can be achieved by altering the periodicity of the LM-IDT pattern. However, traditional SAW device structure is capable of only a single periodicity, requiring a new device and fabrication process to adapt to different experimental conditions, thereby continual modulation of the periodicity on the same device becomes impractical. Here, to overcome this limitation, two electrode configurations that could be obtained by programmable actuation of three micromechanical valves in different combinations, is presented as illustrated by Figure 5 (b-c).

As shown in Movie 1, dye solution was used to ensure the valves were placed at the right
locations and two configurations could be obtained. Prior to actuating any valves, the electrode channel and reservoirs were prefilled with liquid metal by pressure pumping, as shown in the Movie 2. When valve set 1 is actuated, liquid metal electrical connection is cut. As a result, a narrow electrode configuration was generated, which resembles a typical metallic double electrode IDT, as shown by Figure 5 (d-e). In addition, as presented by Movie 3, releasing valve actuation allows for the LM electrical connection to be re-established. These reveal that this valve actuation process is reversible and the alteration of electrode pattern can be dynamically modulated. Similarly, when valve sets 2 and 3 were actuated, part of the IDT electrodes were electrically isolated from the external electrical circuit, generating a wide electrode configuration. The impedances of the LM-IDT in both configurations were matched appropriately before characterizing their S11 parameters by VNA. As demonstrated, the reflection dips appeared at different resonant frequencies for these two configurations, implying propagating SAW at different wavelengths were generated on the piezoelectric substrate. This reversible reconfiguration process allowed us to dynamically modulate the resonant frequency of the device by switching valve set actuation. Modulating the SAW parameters in a programmable fashion like this makes it possible to deploy these LM-IDT devices as tunable acoustic filters. Due to the scalability of mLSI integrated devices, these filters may be fabricated to operate in a wide frequency range, efficiently utilizing the frequency spectrum.

Although the device shows effective frequency selective behavior, and works well as an on-chip reconfigurable RF load, it suffers from a critical drawback, that also plagues the adoption of other mLSI technologies in commercial settings. Ultimately, through testing the ability of the LM-IDT generated acoustic forces to manipulate 30 µm polystyrene beads, it was determined
that the device lacked the required energy density to produce meaningful surface acoustic waves for particle manipulation. The two parameters effecting the channel’s cross-sectional area that determines energy density are the feature width and height. Feature width could not be increased past 150 \(\mu\text{m}\) without a large decrease in SAW frequency, so the only way to increase the energy density of the IDTs is to increase the channel height. Modern lithographic techniques, however, limit the height of valuable channels, due to the need for a phenomenon called reflow. Once channel height exceeds 30 \(\mu\text{m}\) it becomes exceedingly difficult to produce rounded channels required for perfect valving at widths < 150 \(\mu\text{m}\) without expensive and incredibly precise equipment, and once the height exceeds 50 \(\mu\text{m}\), it becomes impractical to attempt rounding the channels with reflow at all [71]. As the second part of this work, a novel soft-lithographic method is presented that allows us to reliably produce leak free valving on chips with much greater feature heights, and in a much simpler and cost-effective manner, than allowed by previous methodologies.
CHAPTER 3. Deflection-based Molding

3.1 Need for Deflection-based Molding

Microfluidic large-scale integration (mLSI) relies on traditional soft- and photo-lithographic techniques for the fabrication of micro-devices, thoroughly described elsewhere [52-55]. As application areas in mLSI have expanded, the need for unique device features and channel geometries has led to adaptations of these techniques that include gray-scale photolithography [56-57], the use of 3D printing and direct-write technologies for mold and chip fabrication [58-61], micro-milling [62-63], surface treatment for the control of hydrophobicity and adhesion [64-66] and substrate functionalization for biological assays [67-68]. These techniques, however, are not without limitation. The integration of micromechanical valves for control of fluid flow is a necessary tool for mLSI devices [69-70]. Current methodology, however, makes it exceedingly impractical to integrate these valves for features with larger aspect ratio and channel heights. This limitation is one of the critical factors in preventing mLSI technologies from being widely adopted for research and clinical use, and is evidenced by the aforementioned study of mLSI integrated acousto-fluidics. Many potential application areas for mLSI bio-chip design require the manipulation and flow of mammalian cells, beads and other large particles. Secondly, the reliance on master molds, either fabricated on silicon wafers with traditional photolithography or via direct-writing processes like 3D printing [58-61] or micro-milling [62-63], limit the throughput of device development by requiring a unique master mold for each design iteration (i.e. one mold cannot currently be used to produce biochip designs with different channel dimensions). Here, this work presents a novel and scalable soft-lithographic method, that addresses the valvability of micro-channels with larger height and aspect ratio and provides a way to manufacture dynamic molds with tunable feature heights. This method is shown to be a
powerful addition for mLSI fabrication methodologies by allowing mLSI to be adopted for device-designs requiring the flow of large bio-particles, and increasing the throughput of device development and rapid-prototyping of device designs. The technique is shown to be scalable, robust, and capable of fabricating biochips on different substrate surfaces.

Rounded channels are required for valves to form a perfect seal (Figure 3.1). To create rounded channels, traditional lithographic methods rely on a phenomenon called reflow. During reflow, positive tone photoresist (SPR-220 or AZ-50 XT) is exposed to an extended hard-bake time at high temperature, and the surface of the photoresist stretches and undergoes a physical transformation from a rectangular to a parabolic cross-section. The problem however, is that this technique fails to work with larger channel dimensions (Figure 3.1).

Thus, when creating features greater in height, perfect valving is not possible. The valvability of reflow-produced channels has been extensively characterized elsewhere [71]. Fordyce et al. show the fabrication of valvable channels for features as high as 70 µm, but this is only possible with low aspect ratio structures (channel width of 250 µm). When high aspect ratio is required (>0.5), this limitation is closer to 50 µm. Previous attempts to fabricate large rounded structures have been made, using novel materials like polyolefins [72] to create molds, using the surface tension of uncured PDMS in an open channel [73], PMMA micro-machining [74] and backside diffused-light exposure lithography [75]. These methods, while capable of producing rounded channel architecture are in most cases very labor-intensive, require expensive and specialized equipment, have static or difficult to control dimensions, and ultimately lack scalability. Of particular interest are soft-molding modes of round channel fabrication [76-78], most recently
demonstrated by Hongbin et al. [79] Here, a dynamic approach uses thin membrane deflection to imprint rounded channel structures into partially cured PDMS. The channel deflection has been analytically modeled to allow for precise control over channel height, and is relatively simple to implement. This method for round channel fabrication is both cost-effective and tunable, but does however suffer from a few critical drawbacks. (1) Using the deflection-based technique described by Hongbin et al., it is practically impossible to reproducibly fabricate very thin flow layers (<100 µm) that are required in many microfluidic applications with valves. In a typical mLSI device the flow channels are bonded to a rigid substrate like glass. In order to valve these channels, the height of the bulk flow layer (not to be confused with channel height) needs to be relatively small. It may help to think about trying to stop the flow of water in a garden hose by stepping on it, if the rubber walls of the hose were 1 m thick. Due to this constraint, this method is incapable of fabricating a valvable flow layer in contact with a rigid

![Figure 3.1](image)

**Figure 3.1** This figure illustrates the physical limitations on reflow produced rounded channels. (A) When features are fabricated with traditional mLSI channel heights (<50 µm), the reflow phenomenon causes positive tone resist to undergo a physical transformation, creating rounded channels. (B) When the feature heights are have large aspect ratio, feature width is difficult to control and will widen as the channel rounds, making these high aspect ratio structures impractical to produce. (C) When creating low aspect ratio structures, a different problem occurs. Because reflow is difficult to control, low aspect ratio structures typically garner these inconsistent and assymetric patterns where the edges tend to bulge up and the bulk photoresist in the center thins.
substrate (e.g. glass, LiNbO3). While Hongbin et al. demonstrate devices bonded to glass, the thickness of the devices prevents valvability. This is critical for mLSI applications that require direct sample contact with a functionalized surface (e.g. ELISA assays) or with a specialized substrate (e.g. acousto-fluidics). (2) This method lacks scalability. The approach described by Hongbin et al. would require one pressure input per individual channel on the device. This works for single device, isolated fabrication, but due to linear scaling, the fabrication of a 50 – 100 channel device or multiple devices at once, becomes impractical without considerable hardware. To address these concerns, this thesis further develops the fabrication technique so that devices can be made directly in contact with a substrate, at very small layer heights capable of being properly valved, more in line with the demands of traditional mLSI bio-devices. Also, this work has modified the fabrication process to demonstrate greatly improved dynamic range of produced channel heights, and scalability by fabricating many individual, disconnected channels with a single pressure input. Thorough analyses of valvability and robustness are also presented.

3.2 Basics of Deflection-based Molding

To accomplish this, a deflection-based elastic mold was created that leverages upward valve actuation to imprint the desired channels into wet PDMS while it cures. Note that instead of using partially cured PDMS as demonstrated by Hongbin et al. this work instead uses uncured, wet PDMS. Using wet PDMS has some disadvantages, like the inability to degas the bio-chip and a decrease in mold-membrane stability at high pressures, but as will be demonstrated, proper procedural design allows the method to be robust, amenable to scale and offers an increase in dynamic range. By controlling experimental parameters, including the membrane thickness and Young’s modulus, the actuation pressure and channel width, the ability to reliably produce
rounded channels with a much-improved dynamic range of tunable channel height is shown. The device fabrication (illustrated in Figure 3.2) requires that a thin spin coated PDMS membrane be bonded to a control layer, such that actuation of this layer causes a corresponding deflection of

**Figure 3.2 (TOP)** This illustrates the fabrication process for the creation of an elastomeric mold. (1) Follows traditional soft-lithographic technique, where a PDMS layer is made from a silicon master-mold with the desired feature configuration. Once the layer has cured (60 min @ 80 °C), the chip is cut and punched as is typical in traditional mLSI biochip fabrication. (2) The control layer is placed feature-side down onto a thin membrane, spin-coated on a bare, clean silicon wafer. This membrane will deflect in response to pressure applied from the control layer, creating raised features in the pattern of the desired channels. (3) Once the control layer-membrane complex has thermally bonded, it is removed from the silicon wafer and treated with plasma for 30 sec followed by TMCS for 20 min. This chemical treatment will prevent PDMS from bonding to the membrane. (4) A border region is made from thick PDMS, and is reversibly bonded by curing for 5-10 min @ 80 °C. (MIDDLE) To produce chips, (1) wet PDMS is poured into the border region and (2) pressure is applied to the desired channels. This will transfer the pattern from the PDMS elastomeric mold to the new PDMS layer. Pressure must be applied continuously while the new chip cures (3 hours @ 60 °C). When the chip has fully cured, (3) the entire border region is removed. The vacancy is now occupied by the desired biochip, which may then be (4) punched and bonded to substrate. Cross sections of the device were taken to characterize the height of the channel, which is dependent on the referenced (BOTTOM) equation. Patterned channel height can be controlled by modulating (i.) the thickness of the thin membrane, adjusted by increasing or decreasing the spin speed, (ii.) the young modulus of the thin membrane, which can be controlled by changing the PDMS A:B ratio, (iii.) the pressure applied and (iv.) the width of the channel being pressurized.
the membrane. Height and aspect ratio characterization, robustness, valvability of channels far surpassing previous height and aspect ratio limitations and scalability are all demonstrated. The proposed method can be adapted to direct channel-on-substrate fabrication. This technique will undoubtedly be useful for biological applications that require valvable channels for analyses and experimentation with mammalian cells or otherwise large bioparticles, and also for efforts in scaling mLSI biochips by allowing for more versatile rapid-prototyping from a single silicon master mold.

### 3.3 Mold Fabrication and Operation

The fabrication of the described elastomeric molds (process illustrated in Figure 3.2), begins with patterning the desired feature architecture onto a silicon wafer with traditional photolithography. PDMS (5:1) molds are then cast using the silicon master mold (the control layer) and a thin PDMS membrane is spin coated onto a bare, clean silicon wafer. It is important that the wafer used for spin coating our membrane is clean, to avoid impurities. The thickness and young’s modulus of this membrane in part determines the dynamic range of the deflected height, controlled by the spin speed and the elastomer to curing agent (A:B) ratio, respectively. For the purposes of this work a young’s modulus of 0.1 MPa, approximated with a 30:1 (A:B) ratio [80] was used for all experiments, and spin speeds of both 4000 and 6000 rpm (for 1 minute) were examined, giving measured membrane heights of ~15 µm and ~10 µm, respectively. It should be noted that Hongbin et al. report a membrane thickness of 20 µm with a spin speed of 1000 rpm. We are not sure how this was achieved, as spinning at 1000 rpm should produce a thickness closer to 75 µm [81]. The control layer is cured for 60 min at 80 °C, and the thin membrane is cured for 45 min at 80 °C. The control layer (first cut & punched as in typical
soft lithography) is then thermally bonded to the thin PDMS membrane, by curing at 80 °C for 1-3 hours. Once bonded, the two-layer mold is treated with 30 sec plasma followed by 20 min TMCS. This process is common in many microfluidic applications and coats the surface of the mold with silane, to prevent additional PDMS from bonding to it. Finally, a border region is created from thick, fully cured PDMS (5:1), and reversibly bonded to the top of our two-layer mold by curing for 10 min at 80 °C. Note that the border region is used to constrict the area where wet PDMS is poured to only regions of interest on our mold. Note also that any feature on the elastic mold that is covered by the bulk PDMS border region, will not produce deflected channels. Also note that features on the mold with larger areas tend to be at greater risk of membrane-failure. This makes sense because the large area will experience more force. Because pressure will be applied directly beneath the punch holes in the control layer during mold operation, which are much larger (1 mm x 1 mm) than the channels, and thus are at greater risk of membrane failure, it is important to ensure the border region covers the areas where punch holes are made.

The operational parameters for our elastomeric mold are illustrated in Figure 3.2. First, pressure is applied to the control layer to cause a corresponding membrane deflection. Pressure inputs range from 3-15 psi for molds with a membrane spun at 6000 rpm and from 3-20 psi for molds with a membrane spun at 4000 rpm. The range of pressure inputs is smaller for thinner membrane molds because of the increased chance of failure at high pressures. While pressure is applied, wet PDMS (10:1) is poured into the border region and is allowed to cure at 60 °C for 3 hours. It is important that pressure remains constant throughout the entirety of the curing process to avoid uneven and inconsistent channel heights. Since the PDMS is poured while pressure is
applied at 60 °C, the device will not be able to be degassed, as is typical with traditional soft
lithography, so extra care needs to be given to ensure no bubbles form while pouring. Once
cured, the entire border region (now with the new chip and desired features patterned in the
center), is removed from the mold. It is important that the border region is removed gently to
avoid tearing the mold membrane. This can then be cut into cross sections to characterize the
channel dimensions, or punched and bonded to a substrate to create an operational device.
Alternatively, molds similar to those that were used for chip fabrication can now be used as
pneumatic valves to programmably open and close the channels in the flow layer. To use the
chips in this manner, instead of bonding the devices to a glass substrate, they can instead be
plasma bonded to another PDMS layer. This creates a two layer PDMS-PDMS device, with
integrated micromechanical valves.

3.4 **Mold Performance Characterization**

Once the biochips had been fabricated using the elastomeric mold, the channel dimensions were
characterized via cross-sectional imaging, and functionality was examined by flowing known
size polystyrene beads through two layer devices to demonstrate effective valve operation.

To characterize the channel dimensions and dynamic range of the proposed technique, cross
sections were taken of finished devices, imaged on an Olympus IX 71 microscope with a Lumera
Infinity 2 camera, and measured using ImageJ and MATLAB. Channel heights were measured at
spin speeds of 4000 and 6000 rpm, for channel widths between 100 µm and 400 µm, with
pressure inputs between 3 and 20 psi (4000 rpm) and 3 and 15 psi (6000 rpm). The young’s
modulus was kept constant at 0.1 MPa across all experiments. The results were plotted and also
compared to analytically calculated expectations (Figure 3.3). As can be seen, the channel heights follow the expected results more closely at lower pressure inputs, and experience larger error in aspect ratio as pressure increases. This is likely because as the aspect ratio approaches 0.5, the increase in height cannot be effectively predicted using the analytical expression in Figure 3.2. Geometrically this makes sense, because an aspect ratio of 0.5 means that the channel cross-section forms a perfect half circular structure, and any further increase would require that the channel deform outward, a process that’s not favorable for the PDMS membrane, and requires more stress than analytically expected. Even with a lower dynamic range than analytically expected, this work still demonstrates a large improvement upon previous methods.

Figure 3.3 (TOP) The results of our deflection height characterization for a membrane spin speed of 4000 rpm (left) and 6000 rpm (middle), a young’s modulus of 1 MPa (approximated with a 30:1 PDMS ratio), across channel widths ranging from 100-400 µm. Pressure inputs ranged from 3-20 psi for 4000 rpm spin speed and 3-15 psi for 6000 rpm spin speed. A smaller pressure range was used for the higher spin speed because thinner membrane is more fragile and experiences failure at 20 psi. Membrane thickness was measured for both spin speeds at found to be ~ 15 µm and ~ 10 µm, respectively. The previous upper limit for valvable channels using traditional lithography methods is marked on the graphs with a star. The dynamic range of individual channel widths at different spin speeds (a-h) are 17 µm, 40 µm, 71 µm, 96 µm, 16 µm, 46 µm, 45 µm, and 117 µm, respectively. Analytically calculated expected heights were compared with experimentally measured heights (right), for a channel width of 200 µm and spin speeds of 4000 rpm and 6000 rpm. (BOTTOM) Experimental images from our cross-sectional characterization. In particular, 300 µm channel width at a membrane spin speed of 4000 rpm for pressures of 5, 10, 15 and 20 psi (from left to right).
and also far surpasses the height and aspect ratio limitations that are afforded by reflow photolithography. Our improvement in dynamic range upon previously reported deflection-based results most likely comes from the use of uncured, wet PDMS, and thinner mold membranes compared to previous methodologies.

The channel widths were determined from an average calculated in MATLAB by examining the intersection of linear and circular Hough Transforms. An artifact of this technique, not seen in traditional soft- and photo- lithographic methods, occurs at the edges of the channel. As can be seen in the experimental images in Figure 3.3, the channel does not meet the base at an expected angle, and instead has raised ‘tails.’ This is consistent with previously reported results [67] and this is likely derived from the deformation of the mold under pressure. This has no impact on the channels ability to be valved properly, but does cause minor bonding problems that need to be taken into account. For a spin speed of 4000 rpm, by modulating the pressure input and channel widths, a dynamic range of 243 µm in deflected channel height is achieved (15 µm height with a pressure of 3 PSI and channel width of 100 µm and 258 µm height with a pressure of 20 PSI and channel width of 400 µm). With a spin speed of 6000 rpm a dynamic range of 251 µm in deflected channel height is achieved (19 µm height with a pressure of 3 psi and channel with of 100 µm and 260 µm height with a pressure of 15 PSI and channel width of 400 µm). The dynamic range of individual channel widths can be found in Figure 3.3.

To determine the functionality of our channels, their viability to control the flow of large polystyrene beads was tested to examine the potential for use with large bio-particles, an application area for mLSI that would benefit greatly from the ability to use valves. All
polystyrene beads used here were diluted to 0.1 g/mL with 0.05% TBS Tween 20 buffer and isopropyl alcohol to ensure an even distribution of beads flowing through the channels. 30 μm beads were tested first, to ensure our channels had the ability to meet particle sizes typical of channels fabricated with current methods. Once this was confirmed, we tested the channels ability to control 100 μm beads to show the ability of this fabrication method to surpass current standards, and open up the prospect of mLSI valve networks for applications that require bioparticles, or otherwise large samples. All bead experiments were tested on chips produced by molds with membranes spun at 4000 rpm, with pressure inputs of 10 psi and with channel widths of 250 μm, 300 μm and 350 μm. As illustrated, 100 μm beads could easily flow through channels greater than 250 μm in width, and while 250 μm wide channels work for low bead concentrations, they clogged easily when bead aggregation was observed. This makes sense given the previously illustrated channel height characterization, these channels have a height of 110 μm. Figure 3.4 illustrates polystyrene bead flow and valve actuation with different flow channel and control valve sizes. Note that imperfect valving is observed when a valve is actuated on top of a polystyrene bead (Figure 3.4 (c)). This makes sense as the inelastic beads would act as an imperfection on the channel surface and inhibit perfect valving. This effect results in sieve-like valve behavior, and while this allows for buffer flow beneath the valve, large samples will still remain trapped. Movies 4-6 all demonstrate active fluid control by actuation of micromechanical valves. The complete stop of bead flow when trapped between two actuated valves also provides evidence to perfect, leak-free sealing. The ability to control the flow of large particles in this manner proves to be very promising for microfluidic applications that require large particle sizes, e.g. mammalian cells, spheroids.
Figure 3.4 This illustrates the manipulation of 100 µm polystyrene beads in different sized fluidic channels with integrated micromechanical valves. (TOP) shows beads flowing in (LEFT) 250 µm and (RIGHT) 350 µm flow channels respectively. Valve widths are 300 µm and 350 µm. Polystyrene beads were diluted 0.1 g/mL with 0.05% TBS Tween20 buffer and isopropyl alcohol to an appropriate density to ensure an even distribution of beads flowing through the channels. Arrow denotes the direction of flow, circles indicate open valves, and circles with “X’s” indicate closed valves. For a 250 µm wide flow channel, 100 µm beads were prone to clogging which resulted in accumulation of beads within the flow channel. However, with 350 µm wide channels, beads were able to flow easily under pressure. Actuation of the valves successfully stopped fluid flow and could be used to manipulate beads. (BOTTOM) When the valve closed on top of a polystyrene bead, the bead created a disturbance on the surface of the channel and imperfect valving was observed. This image shows that the flow of buffer solution was not halted when the valves were actuated and instead a sieve-affect was demonstrated.
3.5 Robustness

One concern this thesis wanted to address was the robustness of the technique. To do so, the same elastomeric mold was used to fabricate a set of 10 devices consecutively, and the channel dimensions were characterized after each trial. The aspect ratio across these 10 devices was plotted to comment on the reproducibility (Figure 3.5). First, the average aspect ratio of each channel width was taken, across all 10 trials, and then the aspect ratio of each channel width for each trial was normalized as a fraction of the average aspect ratio for that channel width achieved across the 10 trials. These fractions were plotted against trial number, and the standard deviation was used to produce our relative error. As you can see, the normalized aspect ratio is increasing with trial number, however it stabilizes and begins to flatten out after 5 trials between normalized values of 1 and 1.1. This increase is most likely due to the plastic deformation of the membrane from removal of the border region/chip after curing. Plastic deformation was discussed by Bartlett et al. [81] The decrease in change over trial number highlights the possibility of priming the elastomeric molds before use by cycling them 5-7 times so that the bio-devices that are fabricated fall within a narrower, more predictable range of aspect ratios. Even with priming,
however, the method does not have high enough precision to be used for more sensitive applications, where control of channel dimensions needs to be in the 10 µm regime. Another potential solution to the instability of the aspect ratio is to repeat TMCS treatment between trials [67]. This would reduce the plastic deformation caused by the fabricated device sticking to the mold membrane.

3.6 Direct-on-substrate Fabrication

To address concerns with previously described deflection molding methods, a fabrication process (illustrated in Figure 3.6) is presented for making bio-devices with very thin flow layers, in contact with a substrate.

The two-layer mold is fabricated as previously described. Once the mold has been plasma/TMCS treated to prevent further PDMS bonding, instead of cutting a border region, spacers were created by spinning PDMS to the desired layer height (e.g. 50 µm). The thin PDMS spacers are placed on the corners of the mold surface, as well as over the punch holes and any features not desired in the final device. Once the spacers are placed on the mold we plasma treat again for 30 sec to increase the bonding strength between the substrate and the spacer surface. Then, a small amount of pressure is applied to avoid collapsing the membrane (3-5 psi) and PDMS (10:1) is poured onto the surface of the mold. A plasma treated glass substrate was then placed onto the wet PDMS, and weights were added to ensure the glass substrate maintained contact with the 50 µm spacers. Air pressure was then increased to ensure the membrane deflected into the glass substrate, flattening against the surface. It is important that the pressurized channels are filled with water. Operation of the mold with just air will destroy the device by forcing bubbles into the wet PDMS. Using air will also result in inconsistent channel heights.
Figure 3.6 (TOP) This image illustrates the fabrication method used for directly patterning channels onto a glass substrate with our previously described elastomeric mold, such that the channel makes contact with the substrate surface. The mold is plasma/TMCS treated to prevent bonding with wet PDMS, and 50 µm PDMS spacers are added to control the thickness of the fabricated layer, and the whole device is plasma treated again. A small amount of pressure is applied initially to ensure the membrane does not burst (3-5 psi), and wet PDMS (10:1) is poured directly onto the surface. A glass slide is plasma treated to increase PDMS-substrate bonding and placed directly onto the wet PDMS surface. Weights are added to allow the glass substrate to remain in contact with our PDMS spacers, and the pressure is increased (10 psi) so that the channels inflate to press against the surface of the glass substrate creating a flattened region. The PDMS is allowed to cure for 2h, at which point the elastomeric mold is separated from the glass slide, which will now have our patterned features bonded to the surface. (BOTTOM) This shows experimental results for our previously described fabrication method for directly patterning features onto a glass substrate, using our elastomeric mold. (A) 250 µm (B) 300 µm (C) 350 µm and (D) 400 µm wide channels were fabricated onto glass and PDMS substrates. PDMS was used (top) to allow for easier cross-sectional imaging. As you can see the flattened region increases as our channel width increases (as expected because of the larger deflection) and corresponds to a widened contact region when imaged from the top-down (bottom). The implications of this method are (i). the ability to create thinner flow layers, (ii). to allow the flow layer to remain in contact with the substrate (as is required by many mLSI application areas), and (iii) to allow our fabrication technique to be used with both push-up and push-down pneumatic valves.
This was allowed to cure for 3 hours at 60 °C, and then the entire substrate was removed, now with the thin layer of PDMS bonded to the surface. For characterization, bulk PDMS was used instead of a glass substrate, for easier cross-sectional imaging. As you can see in Figure 3.6, channels created include a flattened region in contact with the substrate, with the width of the contact region increasing with increasing channel width, as expected due to the larger deflection. This implies, that with this method, since the layer height will be fixed to the thickness of the PDMS spacers, increasing the deflection can be used to modulate the width of the channel-substrate contact region. These chips were also fabricated on glass slides, so that top down imaging could reveal the change in texture, indicating direct contact with glass. The ability to fabricate chips in this way is necessary to the applicability of this technique to be adopted for a wide range of mLSI applications. In the previously described work with reconfigurable acousto-fluidics, the limited channel height for valvability led to issues with energy density, and the device was unable to produce strong enough acoustic waves to guide particle manipulation. By using this technique, this work proposes that researchers can now fabricate much larger channels capable of being valved, while maintaining contact with a piezoelectric substrate, allowing for a high enough energy density to produce strong acoustic waves for particle manipulation.

3.7 Device Valvability

The most important function of the technique is the ability to valve very large channels. Leak-free valvability of both PDMS-PDMS devices and the direct-on-substrate devices was tested. For a schematic of valve-actuation for both PDMS-PDMS devices and direct-on-substrate devices see Figure 3.7.
As previously described, two layer PDMS-PDMS devices can be made by plasma bonding the flow layer fabricated by deflection molding to a traditional control layer. A 300 µm flow channel was filled with red-dye and examined at five different valve locations (ranging from 150 µm to 350 µm in width, in 50 µm increments). A constant pressure of 25 psi was applied to the control channels and the pressure driving the fluid flow was increased from 3 psi to 20 psi in 1 psi increments. Images were taken at every pressure point. The images were analyzed using ImageJ, and absorbance values were calculated.
taken at each flow-control intersection, at each pressure increment. These values were normalized with respect to the absorbance of a fully open valve and the absorbance of a completely closed valve. The known channel height when completely open was then used to calculate the beer’s law constant, cε [82]. This constant was used to analytically calculate the channel height (path length) as the channel was valved. These channel heights were converted to valve closure, as a percentage, and plotted against the pressure differential in the channel (Figure 3.8). The resulting trend is expected, with the lower valve widths being incapable of valving the large channel, and actuation pressure (pressure differential required to close the valve) decreasing for larger and larger valve widths. Ultimately, you can see that three out of five valve-flow cross sections achieved 100% valve closure at reasonable actuation pressure (10 psi, 13 psi and 15 psi for valve sizes of 350 µm, 300 µm and 250 µm respectively). The 200 µm valve was close to achieving perfect valving, with 98% closure at 22 psi, and it is clear that the 150 µm wide valve was completely insufficient to close the 300 µm channel, with a maximum value of 51% closure.

While these data show promising channel valvability, this work needed to further experiment in order to ensure that the seal was complete, and that no leaking was observed. A 300 µm channel was closed with a 300 µm valve with a control pressure of 25 psi. Red dye was flowed into one side of the channel, and clear buffer was flowed into the other side, with a constant flow pressure of 5 psi. This was left for 24 hours, with images taken every 30 minutes. ImageJ was used to measure the absorbance of each side at each time point, and the contrast between the two channels was measured. As you can see there is no decrease in contrast over time, meaning that the valve forms a leak-free seal. The insets show the valved channel at t = 1 hour and t = 21 hours.
µm wide flow channel was closed with a 300 µm wide valve at a control pressure of 25 psi. Red dye was flowed into one side of the channel and a clear buffer was flowed into the opposite side. The flow pressure was maintained constant at 5 psi on both sides. This was left for a period of 24 hours, with images being taken every 30 minutes. The data was processed in ImageJ for absorbance to plot the change in contrast between the two channels over time (Figure 3.9). It was found that after 24 hours there was no decrease in contrast, evidence that the valves were forming perfect, leak-free seals. Additionally, after the period of 24 hours, pressure was increased until the seal broke at a pressure differential of 14 psi, which is consistent with the results in Figure 3.8.

A thin flow layer was fabricated directly onto a glass substrate as previously described, and a corresponding control layer was plasma bonded to the surface. To show leak-free valvability with the channel-on-substrate fabricated devices, and to comment on the potential to be adopted for mLSI acousto-fluidic applications, a 150 µm flow channel was filled with a liquid metal (LM), and a pressure differential was incremented from 0 psi to 30 psi, with a 250 µm valve. Note that the flow channel was treated with HCl prior to filling with LM to prevent the formation of an oxide layer on the LM surface. At each pressure
increment resistivity was measured, and the time required for the device to reach equilibrium resistance was recorded. For all actuation pressures of 16 PSI and greater we observed a large increase in resistance, confirming leak-free valvability (Figure 3.10). Note that a 150 µm flow channel was used to comment on the applicability of this technique to be used for mLSI acousto-fluidic devices. As was discussed in our exploration of these devices, the correlation between SAW frequency and acoustic power, makes channels wider than 150 µm insufficient for particle manipulation.

As can be seen, while the time to reach resistive equilibrium varies, effective separation of LM is still observed at several pressure differentials. The image insets in the graph show the channel at discrete pressure points, and it is clear that the LM electrical connection is cut upon increasing valve pressure, and that electrical re-connection is achieved by decreasing the pressure differential back to 0. The hysteresis shape of the graph is typical of valve resistivity studies [51]. This result evidences the ability to apply the described fabrication method to mLSI integrated acousto-fluidic applications, like the one explored previously. This device was also fabricated and filled with red dye to

Figure 3.11 This figure illustrates the valvability of our channels fabricated directly on a glass substrate using methods previously described. The pressure differential in the image above was set at 20 psi. (A) is a wide angle view showing flow channels from 150-350 µm in width and control channels from 100-350 µm in width. (B) is an image of the entire chip, and (C) and (D) show images before and after valve actuation, respectively.
provide a visualization of the process with more traditional fluid dynamics (Figure 3.11).

### 3.8 Scalability

The ability of the proposed method to scale well is another important concern for further adoption of deflection-based fabrication in mLSI application areas. There are two principle aspects of our device explored here to demonstrate scalability.

First, the ability of this technique to produce a single, large microfluidic device is shown. A simple passive microfluidic serpentine mixer was created with three inlets and five outlets. The mixer was fabricated as previously described with a mold membrane spun at 4000 rpm and pressure input of 10 psi. The mixer channel width is 300 µm. The device is shown in Figure 19. Here, it can be noticed that the device design narrows at the T-junctions on the mixer. Since the regions where channels merge have a larger area than the individual channels, a much greater deflection when fabricated without this modification was observed. While the device could still

![Figure 3.12](image.png)

**Figure 3.12** This shows our valve controlled gradient generator produced with our deflection molding technique. Both 3 inlet x 6 outlet (MIDDLE), before valve actuation and 2 inlet x 5 outlet (RIGHT) after valve actuation are shown. These chips were fabricated to demonstrate scalability and were made on a 4” wafer sized mold. (LEFT) Image of the whole chip during testing.
be fabricated in this manner, it led to a notable increase in risk of membrane failure. The device was bonded to a control layer that contained a valve to switch between the three inlet-five outlet configuration and a smaller, two inlet-four outlet configuration. The flow and control layers were aligned and plasma bonded together, and red, blue and green dye were flowed into the mixer inlets. Effective switching between device configurations was demonstrated (see Figure 3.12). Movie 7 also shows this process.

**Figure 3.13** This figure illustrates our ability to produce isolated feature with a single pressure input, as opposed to being restricted to 1 pressure input per device feature. To accomplish this you can place the border region such that it covers any features that you do not want patterned into the final device. (A) The border region is cut and placed as desired, (B) the mold is pressurized and wet PDMS is poured into the vacant regions of the bulk PDMS border, (C) after curing the entire border region is removed, and only the desired features are patterned into the device. (D) Individual punches can now be made on isolated features, and the device may be bonded to substrate or PDMS. This simple example is easily scalable to many 10s or even 100s of isolated device features, and the ability to use the border region to select for only features of interest allows researchers to design modular molds to rapidly prototype many different bio-chip layouts.
Perhaps the more important aspect of scalability is the fabrication of multiple isolated channels with a single pressure inlet. In order for this method to be practical in large scale environments, reducing the required hardware is a critical concern. Mold designs were developed with as many as twelve individual channels that shared a single, common center channel. Normally, if this channel was pressurized with previously described deflection-based techniques, you would obtain a single device, with twelve channels connected along the center. However, by cutting and placing the border region such that it covered the shared channel, the ability to produce twelve isolated channels from a single pressure input is demonstrated (see Figure 3.13 for description). This simple demonstration can be easily scaled to microfluidic devices with many 10s, or theoretically even 100s of isolated features, and the ability to select which features are patterned into the final device allows for researchers to create highly modular molds that are capable of producing many different chip designs.

### 3.9 Discussion and Future Outlook

Here, this work has presented a cost-effective, simple, scalable and robust deflection-based fabrication solution to address the issue of round-channel patterning, that offers new routes to mLSI integration for promising areas of traditional science. Thorough characterization of deflected channel height was demonstrated, showing a large increase in dynamic range over previous attempted deflection-based methods, modulated with membrane spin speed, channel width and input pressure. Methods to integrate micromechanical valves were offered, and functionality of devices fabricated in this manner by controlling the flow of large polystyrene beads was illustrated. Most importantly, this basic method was adapted to allow direct patterning of thin-layer channels onto substrates in a way that allows the researcher to both (1) maintain
flow channel-substrate contact for applications requiring functionalized glass surfaces or specialized substrates, and (2) integrate pneumatic valves. Leak-free valvability of both PDMS-PDMS and PDMS-substrate devices was demonstrated by (1) using absorbance measurements at discrete pressure differentials to analytically determine path length (translated to channel height and valve closure, as a %) with the application of beer’s law, (2) analysis of contrast changes between clear buffer and red-dyed flow channels separated by an actuated valve over a period of 24 hours and (3) measuring resistivity across a flow channel filled with LM at incrementally increasing control pressures. Finally, the scalability of the proposed method was examined, and this work successfully demonstrated an ability to both (1) fabricate large devices and (2) fabricate isolated features with only a single pressure input.

Further development of this deflection-based fabrication method will allow adoption of mLSI technologies by many new and promising application areas. Specifically, academic and industrial applications requiring high throughput mammalian cell or large bioparticle analyses [83], the use of spheroids for microfluidic co-culture systems [84-86], mLSI integrated acousto-fluidic applications [87-88], centrifugal fluidics or other microfluidic approaches that require rapid-prototyping of device features with different geometries [89-90], creation of cylindrical channels to mimic micro vessels for organ-on-a-chip bio-devices used for in-silico alternatives to drug trials [91-92], and applications requiring complex channel architectures for precise control of fluid dynamics in large channels like inertial or hydrodynamic fluidic separation methodologies [93-95]. Microfluidics has offered many unique solutions to complex biological and chemical problems, but many of these devices have remained research projects because of their sophisticated design and difficult to scale fabrication, and their specific single-application use
cases [96-98]. The cost-effective, robust and scalable deflection-based technique that has been presented here is a critical step forward in microfluidic commercialization. The methods discussed stand to potentially be integrated into the design and implementation processes for many application areas we are not yet aware of, and the hope is for researchers to adapt this method to aid wider adoption of mLSI bio-devices.
CHAPTER 4. Design Automation for mLSI

4.1 Overview of Need for Design Automation

One of the predominant issues with the tractability of mLSI bio-devices at scale, comes from the difficulty of manual design processes that are required for biochip implementation. Microfluidics as a field, still relies on manual design methodologies that require researchers to spend arduous amounts of time drawing biochip schematics in CAD software. While this is not an insurmountable problem, aside from being a time sink, human designers will never be able to optimize biochip feature spacing in the same way that automated processes are able to optimize IC chip layouts. This is less of a concern for bench-top applications where the chip designs are not very large and researchers can often devote many hours to the perfection of a few critical features. It is, however, a major bottleneck in commercializing microfluidic devices. Commercial settings demand many iterations of very large integrated microfluidic chips, and often times have many restrictions on channel dimensions to minimize operational overhead.

In recent years, design automation research for mLSI has evolved rapidly, aiming to replace the laborious manual design with an automated CAD software. However, many previous attempts to automate mLSI design fall short by over-simplifying both channel architecture and layer-interaction. While previous design automation techniques may handle simple channel designs well, many realistic mLSI bio-chip applications require more sophisticated understanding of complex fluidic routing and valve networks. As part of this work, bio-chips generated with a module model library, Columba, for mLSI design automation, created by our collaborators at the Technical University in Munich and Tsing Hua University in Taiwan, were fabricated and implemented. Columba can be programmed with a plain-text command, and will both output the
proposed multi-layer device architecture and fluidic routing designs, as well as spatially optimize the device layout given researcher specific design rules. Columba is validated here by fabricating output designs and demonstrating their functionality. Columba is the first design automation tool that can seamlessly synchronize with a manufacturing work-flow. Here, this thesis will briefly illustrate results obtained using Columba, for further understanding of the software please see Reference [99].

4.2 Examples, Drawbacks and Improvements Needed

The goal of Columba was to provide an easy to use method for automated mLSI design. As such, the software includes many base-level microfluidic components that can be called and placed by plain-text user commands. Some of these components include fluidic inlets and outlets, on-chip rotary mixers, reaction chambers, both control and flow layers, and multiplexors for complicated

Figure 4.1 These are example designs and fabricated devices entirely generated by Columba. As you can imagine creating these schematics by hand would be incredibly tedious and the end result would most likely lack the symmetry and spatial optimization provided by an automated system.
pneumatic control routing. The user tells Columba which components it will need and the software produces AutoCAD compatible outputs that can be directly used for mask printing. See **Figure 4.1** for sample designs produced for fabrication and testing.

The chips fabricated from Columba designs are still within the scope of human efforts, but manually creating these schematics would be time consuming and error-prone. The result of manual design would likely be much less symmetric and lack spatial optimization. With Columba, this process is reduced to short written commands, which greatly reduce the time required for chip design and thus improve the throughput of rapidly prototyping micro-devices. See **Figure 4.2** for an example workflow.

**Figure 4.2** This figures shows an example of the Columa automated mLSI design tool workflow. **(LEFT)** The user designed rules and parameters for a complex fluidic device using a large multiplexor to control the manipulation of flow into 5 mixers and 4 reaction chambers. **(MIDDLE)** The AutoCAD compatible output that can be directly used for mask printing. **(LEFT)** A fabricated device where the blue fluid represents the multiplexor, the green fluid represents the control layer and the red fluid is showing the flow layer.
Although automated solutions like Columba are still relatively new in the mLSI space, they already show promise for future commercial endeavors. As microfluidics continues to provide unique solutions for environmental, health-care and research related problems, the demand for commercialization is expected to increase. Having sophisticated design automation toolsets will ease the transition into large-scale implementation efforts, and Columba is an early example towards this direction. In the fabrication and testing of Columba-generated bio-chips challenges that make bench-top and commercial implementation difficult with current versions of the software were observed. While Columba did produce the intended features in a spatially optimized manner, much more efficiently than human alternatives, it was recognized that some design attributes increased the device complexity or in some cases were insufficient for the intended fluidic operations. Several situations were observed where the valve multiplexing component was insufficient at allowing proper valve selection for required tasks (Figure 4.3).

For example, in the chip depicted a researcher may want to leave the rotary mixer open while sealing the reaction chamber, such that fluid may be loaded into the mixer from the inlets without contaminating the reaction chamber. There are only two possible configurations that allow both the mixer to be open and the reaction chamber to be closed, and it is then impossible to load fluid from inlet three into the mixer. Secondly, a researcher may want to seal both sides of the reaction chamber for cell culture studies. There is only one such configuration that allows both reaction chamber valves to be sealed, and it requires that every other channel on the chip is also sealed, which makes fluidic multitasking impossible. Lastly, researchers may want to seal the back of the reaction chamber and mixer, while leaving the front of the reaction chamber open to allow fluid or cell culture loading. There are only two configurations to allow for this scenario, and limit the options to either (1) loading fluid from just inlet two or (2) loading fluid from both
Figure 4.3 This illustrates inefficiencies with bio-chip designs produced by Columba. (A) Full chip schematic with an inset that focuses on the upper left-hand corner of the device. This area contains 10 multiplexer horizontal channels (numbered), a segment of the integrated valves (green) and three fluidic inlets. The fluidic inlets can take one of two paths in this illustration, (1) to a rotary mixer or (2) to a reaction chamber. Note that constant pressure is applied to the control layer (green) and whether or not the valves seal different channels is determined by the multiplexor. If a multiplexor is actuated over a wide valve location it seals the valve itself, preventing it from closing flow channels. (B) Example multiplexor configurations to perform specific functions. Note here that if all of the multiplexors are open (green circle) then all of the on chip valves will be closed, and likewise if every multiplexor is closed (red cross) then none of the on chip valves will be closed and fluid will be able to flow freely into any path. The multiplexor configurations shown represent (FROM LEFT-TO-RIGHT) (1) Sealing both sides of the reaction chamber, (2) allowing the mixer path to remain open while sealing the reaction chamber and (3) sealing the back of the reaction chamber and the mixer path, while allowing the front of the reaction chamber to remain open. In each case there are only 1 or 2 possible configurations to achieve the relatively straightforward scenarios, and none of them allow the researcher to adapt to different experiments. The lack of versatility in the device makes large scale adoption at the current stage difficult.
inlet 2 and inlet 3 at the same time. These are only a few examples of inefficiencies encountered during implementation, and they provide insight into the work still to be done before design automation can be integrated into existing mLSI workflows. Even though the implementation insufficiencies make large scale adoption difficult in its current form, the design automation software seen here is only a building block for further development that may help mLSI make clinical and commercial inroads. For that to happen the engineering of design automation software will need to interface better with the biological sciences.
CHAPTER 5. Conclusion and Future Work

5.1 Conclusion

This thesis has explored mLSI integrated technologies, with particular attention paid to mLSI integrated acousto-fluidics. Commercial barriers, namely fabrication and device design bottlenecks, were discussed as applied to acousto-fluidics, and parallels were drawn to many categories of mLSI integrated workflows. A novel fabrication solution was presented and thoroughly characterized. It was shown that this method is tractable at scale, robust, and capable of producing very large, valuable channels in contact with rigid substrates, not previously possible. Additionally, design automation for mLSI was explored, and examples of device implementation using a first-of-its-kind CAD software was illustrated. The drawbacks were considered, and needed improvements were outlined. The results presented here contain original commentary on the needed technological developments to promote clinical adoption of critical mLSI integrated bio-devices, and will hopefully act as a guide for future research.

5.2 Future Work

The ideas presented here pose solutions to some of the common problems preventing mLSI technologies from gaining wider adoption, but more importantly highlight areas where improvement and further method development are needed. The potential for mLSI bio-devices to impact next generation solutions to biological and biochemical problems has been well documented, but the implementation of these mLSI bio-devices has remained largely in academic circles. As was discussed here, further consideration needs to be given to the design
and fabrication of microfluidic technologies in order to promote their tractability at scale. While this work has demonstrated novel fabrication and design automation methodologies to streamline device development, the hope is for researchers to adapt these methods, test their limitations and expand on the processes discussed in this thesis.

Future developments in mLSI fabrication need to focus on robust solutions capable of generalizing to devices for different applications, with different complicated fluidic architectures. The majority of traditional microfluidic research spends too much time focusing on application-specific modes of fabrication which are often too complicated to be applied in commercial settings. Fabrication approaches need to instead focus on being reconfigurable and modular, a process that will be aided by continued work on design automation. For ‘lab-on-a-chip’ technologies to impact large scale problems researchers need to be equipped with tools that reduce the effort required in manual design and fabrication optimization, so they can focus on the applications themselves. A truly reconfigurable and robust fabrication method supported by design automation capabilities similar to those that have promoted scalability in the IC industry, will be required for the industrialization of mLSI bio-devices.
References


