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# Microfluidics in silicon/polymer technology as a cost-efficient alternative to silicon/glass

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**Abstract**
We investigate TMMF photopolymer as a cost-efficient alternative to glass for the leak-tight sealing of high-density silicon microchannels. TMMF enables low temperature sealing and access to structures underneath via lamination and standard UV-lithography instead of costly glass machining and anodic bonding. TMMF is highly transparent and has a low autofluorescence for wavelengths larger than 400 nm. As the photopolymer is too thin for implementing bulky world-to-chip interfaces, we propose adhesive bonding of cyclic olefin copolymer (COC) modules. All materials were tested according ISO 10993-5 and showed no cytotoxic effects on the proliferation of L929 cells. To quantify the cost efficiency of the proposed techniques, we used an established silicon/Pyrex nanoliter dispenser as a reference and replaced structured Pyrex wafers by TMMF laminates and COC modules. Thus, consumable costs, manpower and machine time related to sealing of the microchannels and implementing the world-to-chip interface could be significantly reduced. Leak tightness was proved by applying a pressure of 0.2 MPa for 5 h without delamination or crosstalk between neighboring microchannels located only 100 $\mu$m apart. In contrast to anodic bonding, the proposed techniques are tolerant to surface inhomogeneities. They enable manufacturing of silicon/polymer microfluidics at lower costs and without compromising the performance compared to corresponding silicon/glass devices.

(Some figures in this article are in colour only in the electronic version)

## 1. Introduction

Since the last decade, microfluidics has become a huge field of research with more than 2000 publications per year [1, 2]. However, this research is mainly limited to proof-of-concept demonstrations, and only a few of the developed prototypes have been transformed into commercial devices [3, 4]. Recently, the high manufacturing costs have been recognized as an important contributing factor for this discrepancy and even as one of the most important stumbling blocks for the commercial success of microfluidic devices [5, 6]. In order to reduce costs, huge efforts have been spent on replacing silicon-based devices by all-polymer solutions. Prominent examples of materials and technologies are SU-8 lithography [7–9], casting of PDMS [10, 11], injection molding [12, 13] and thermoforming of polymers [14, 15].

However, cost alone is not the only factor in material selection and silicon remains the material of choice when high chemical resistance, mechanical strength, temperature stability, high aspect ratio or high accuracy on large footprints (no shrinkage) are indispensable. Besides, silicon benefits

 

from established MEMS processes for integrating on-chip functionalities, manufacturing uniform through holes, e.g. dispensing nozzles and interconnecting vias, as well as obtaining tailored surface properties. As a consequence, silicon is still widely used in both academic research, e.g. for pumps [16], pipettes [17, 18], dispensers [19], reactors [20], viscosimeters [21] or cell counters [22] and in microfluidic foundries, e.g. LioniX, Micralyne or Micronit [23]. In order to create a working device out of the microstructured silicon substrate, it is necessary to seal the microchannels and provide access to fluidic inlets and outlets (world-to-chip interface). The most common method for sealing silicon microchannels and implementing world-to-chip interfaces is anodic bonding to borosilicate glasses, e.g. Pyrex® 7740, Borofloat® 33 or Schott 8329 [24]. Processing of glass substrates, however, is usually performed by costly techniques such as electrochemical discharge machining, ultrasonic machining, wet etching or sandblasting and is followed by aligned wafer-level anodic bonding and separation of the silicon/glass stack into individual dice, often with a total thickness of a few millimeters. These steps, often regarded as microfluidic packaging [25–28], account for a very significant part of the manufacturing costs and may cause higher costs than the silicon micromachining itself. Therefore, even when the microfluidic network is fabricated in silicon, significant reduction of costs can be achieved by replacing glass and anodic bonding with polymers and alternative sealing/bonding procedures, respectively. In this paper, we present two cost-efficient approaches for the packaging of silicon microfluidic chips in order to provide

- leak-tight sealing of the microchannels and precise access to fluidic structures underneath via lamination of TMMF followed by standard UV lithography, and
- world-to-chip interfacing via bonding of the silicon microfluidics to thick, structured cyclic olefin copolymer modules (COC, a thermoplastic material) using a pressure sensitive adhesive.

## 2. A comparative study

To evaluate the benefits of the proposed processes regarding costs and performance, we used the commercially available 24-channel TopSpot printhead as a reference. The TopSpot technology was introduced in 2000 [29] and is used for the highly parallel printing of biological samples such as oligonucleotides [30], proteins [31] and living cells [32]. A TopSpot printhead consists of a silicon chip with a thickness of 380 $\mu$m sandwiched between two Pyrex layers via anodic bonding. The chip has a footprint of 36 mm × 20 mm and holds 24 microchannels with a cross-section of 80 $\mu$m × 80 $\mu$m and 24 nozzles with a diameter of 50 $\mu$m, all fabricated by DRIE. The top Pyrex layer provides the world-to-chip interface by reservoirs with a diameter of 2 mm at the end of each channel (fluidic inlet). The required reservoir volume of 6 $\mu$L defines a minimum thickness of this layer of 2 mm. The bottom Pyrex layer with a thickness of 150 $\mu$m is used to seal the microchannels and has an opening in order to enable dispensing out of the nozzles (fluidic outlet). Neighboring channels are located only 100 $\mu$m from each other, which makes high demands on the sealing process.

Micromachining of silicon is indispensable for obtaining the required quality of the nozzle array. Pyrex wafers, however, are usually employed because silicon/Pyrex anodic bonding is a robust and established process, even if not cost efficient. Our goal was to develop a more efficient solution adapted to common microfluidic demands. Therefore, we have investigated the possibility of replacing Pyrex by polymers. Due to the following aspects, the TopSpot printhead can serve as a good reference: (i) the requirements on the sealing of the microchannels inside a TopSpot printhead are very similar to those of many other devices: leak tightness, no clogging or distortion of the channel cross-section, accurate access to fluidic microstructures underneath and access for visual inspection, e.g. transparency; (ii) the integration of large on-chip wells, as provided by the Pyrex reservoirs in a TopSpot printhead, is the most frequently used technique for implementing world-to-chip interfaces [33].

## 3. Selective sealing of silicon microchannels

Recently, dry film photopolymers have moved away from their original purpose of providing sacrificial layers for the fabrication of printed circuit boards and were used for fabricating electroplating moulds [34, 35], stamp cavities [36] and replication tools [37, 38], for wafer bonding [39, 40] and sensor packaging [41], as an etch mask for silicon-DRIE [42] and as a permanent material for microfluidic applications [43–46]. So far, the most frequently used permanent films are Riston (DuPont) and Ordyl SY (Elga Europe). Recently, dry films with improved chemical and thermal resistance and superior properties in terms of aspect ratio and resolution have been introduced to the market. For the purpose of our study, we used the negative tone photopolymer TMMF. TMMF is designed to be applied via hot roll lamination and is available in the following thicknesses: 14 $\mu$m, 35 $\mu$m, 45 $\mu$m and 55 $\mu$m. For the purpose of our study, TMMF with a thickness of 55 $\mu$m was used. By multilamination, a total thickness which is a multiple of the used film thickness can be achieved [47]. However, lamination and patterning of more than four layers, corresponding of a maximum thickness of 220 $\mu$m, proved to be challenging. TMMF provides a resolution down to 5 $\mu$m and an aspect ratio up to 6 [48].

Prior to applying the dry film, the silicon substrates should be clean and dry. However, no special surface treatment (e.g. oxygen plasma, annealing, etc) is required. The resist layer is protected by two polyester (PET) layers, one on each side. To seal the channels, one of the PET layers was peeled off and the film was applied onto the substrate using a Riston HRL rubber roller (DuPont). Since patterning of the lid is performed after lamination, no alignment is required when applying it onto the pre-structured substrate. Cross-linking of the dry film was initiated using i-line exposure with an exposure dose of 150 mJ cm$^{-2}$. A printed shadow mask (8000 dpi resolution, soft contact mode) was used to prevent cross-linking of the resist over fluidic inlets and outlets. This is required in order to enable selective removal of the

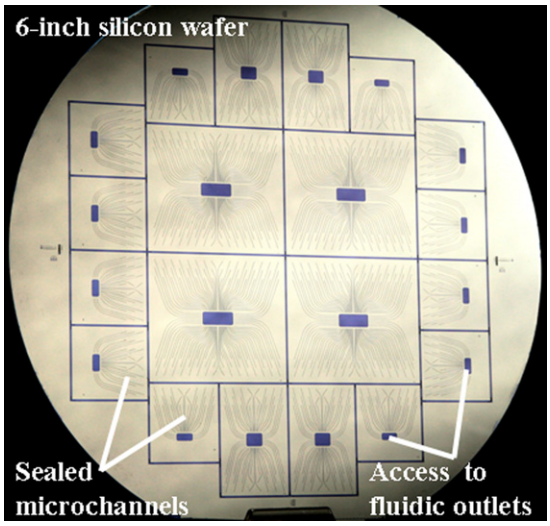


**Figure 1.** Silicon wafer with sealed microfluidic channels and an access to fluidic outlets provided by lamination and UV lithography of TMMF photopolymer.

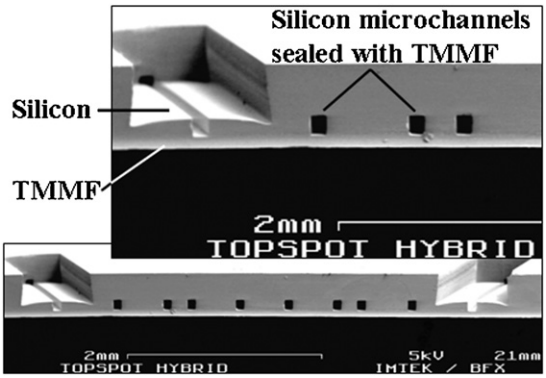


**Figure 2.** Cross-section of silicon microchannels after sealing with TMMF.

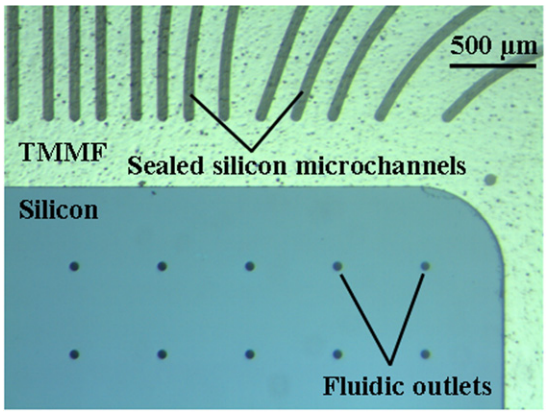


**Figure 3.** Selective removal of the lid was achieved with high accuracy and without leaving any residuals on the silicon surface.

lid and provide access to these areas. After exposure, the second protective layer was peeled off and polymerization of the photoresist was completed using a two-step hotplate post exposure bake (PEB) at 90 °C and 150 °C for 10 min and 45 min respectively. Following PEB, the hotplate was switched off and the substrates were allowed to slowly cool down to room temperature. Removal of the unexposed lid was performed by immersion of the wafer in propylene-glycol-methyl-ether-acetate (PGMEA, SU-8 developer) for 7 min followed by spin drying to expel the dissolved film out of the channels and repeated immersion in PGMEA for additional 3 min. Finally, the silicon/TMMF assembly was immersed in isopropyl alcohol and rinsed with deionized water. After these steps, the silicon microchannels are sealed and precise access to inlets or outlets is provided by lithography (figure 1).

The most critical parameter for the sealing process proved to be the temperature of the rollers during lamination: too high temperatures cause sagging of the lid and may even lead to a channel blockage, whereas too low temperatures do not provide sufficient bond strength to the substrate. For our study, best results were achieved with a roller temperature of 60 °C, lamination speed of 1 m $min^{-1}$ and pressure of 0.1 MPa (measured via Pressurex® pressure sensor film, Fuji). These parameters provided sufficient bond strength and, as shown in figure 2, negligible sagging of the lid. After development, the unexposed areas of the lid could be removed without leaving any residuals on the silicon surface (figure 3).

### *3.1. Leak tightness of the silicon/TMMF stack*

To characterize the quality of the sealing, we performed a leakage test under the following conditions: a TopSpot printhead with TMMF sealing instead of Pyrex was used and 5% (v/v) RBS cleaning solution (Carl Roth GmbH, Germany) and deionized water were alternatingly pushed through the nozzles and microchannels at an overpressure of 0.2 MPa for 5 h. During the test, the printhead was dipped in an ultrasonic bath and heated at 80 °C. This load corresponds to 50 washing procedures as used for the standard silicon/Pyrex printheads. The test did not show any delamination or other obvious damage of the lid even for those regions where the width of the TMMF bond area between neighboring microchannels was only 100 $\mu$m.

A key requirement for any multichannel device is to prevent crosstalk. For TopSpot printheads, this requirement is even more challenging due the extremely small distance between neighboring microchannels. Thus, subsequent to the pressure test, the quality of the sealing was further analyzed by filling the reservoirs in a checker-board pattern using 100 nM Rhodamine B in a buffer solution and pure water, followed by printing the layout onto epoxy coated glass slides (Corning) using an E-Vision microarrayer (BioFluidix, Germany). Following, the printhead was cleaned and the pattern was inverted, so that every reservoir that had previously been filled with the labeled solution was filled with pure water and vice versa. The test was completed by analyzing the fluorescence image of the droplets deposited onto the slide using a LaVision BioAnalyzer from BioTec (lowest detection limit around 6.87E+04 molecules per $\mu m^2$ at 2 s exposure time). The image did not show any crosstalk and proved the high quality of the sealing (figure 4).

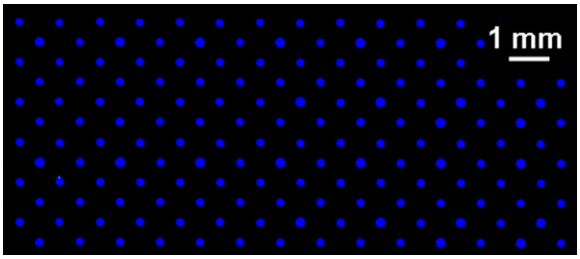


**Figure 4.** Fluorescence image of droplets deposited onto a microarray slide. Leak tightness between neighboring microchannels was proved by spotting a checker–board pattern using 100 nM Rhodamine B in a buffer solution and deionized water.

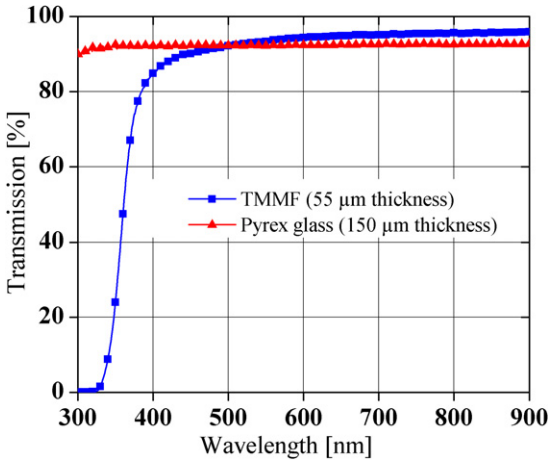


**Figure 5.** Transmission spectra of TMMF (55 $\mu$m thickness) and Pyrex (150 $\mu$m thickness) taken at normal incidence.

### *3.2. Optical properties of the lid*

Pyrex substrates are well known for their high optical clarity. Thus, the optical properties of TMMF are important in order to decide if TMMF is suitable to replace Pyrex for a given application.

*3.2.1. Transparency.* TMMF is transparent and enables easy optical inspection of buried microchannels. The cut-off wavelength (50% transmission) of TMMF was measured to be around 365 nm. In the wavelength range of 400–900 nm, the transmission of cured TMMF with a thickness of 55 $\mu$m is comparable to that of the used Pyrex reference (figure 5). The measurements were taken at normal incidence using a Unicam UV 300 spectrometer.

*3.2.2. Autofluorescence.* Autofluorescence of the cover lid may cause a high background signal and affect the detection of fluorescently labeled targets. Thus, even when not relevant for the present application, the autofluorescence of TMMF was analyzed using a PerkinElmer luminescence spectrometer FL55. For prominent dyes such as Cy3, Rhodamine, TAMRA, yellow fluorescent protein (YFP), green fluorescent protein (GFP), FITC, fluorescein and cyan fluorescent protein (CFP), the TMMF cover with a thickness of 55 $\mu$m delivers roughly the same low autofluorescence as commonly used Pyrex

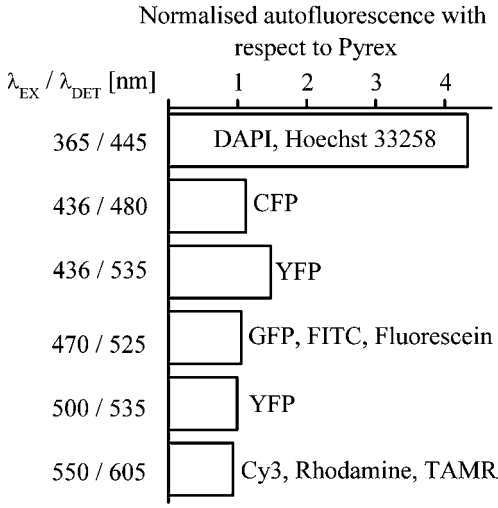


**Figure 6.** Autofluorescence of a TMMF cover (55 $\mu$m thickness) normalized with respect to the values obtained for a Pyrex reference (150 $\mu$m thickness) at the same excitation/emission wavelength pairs.

sealing wafers with a thickness of 150 $\mu$m (figure 6). Only the autofluorescence at the excitation/emission wavelength combination of 365/445 nm, corresponding to, e.g., DAPI or Hoechst 33258, was roughly four times higher for TMMF.

## 4. Implementing world-to-chip interfaces

TMMF is available only in the sub-100 $\mu$m thickness range which is too thin to support bulky on-chip reservoirs or other world-to-chip interfaces. In order to meet these additional interface requirements, we have investigated the bonding of bulky COC modules to the silicon chip. COC (grade 5013, TOPAS advanced polymers) was chosen due to its superior optical properties and higher chemical resistance compared to other widely used thermoplastics such as PMMA and PC. Besides, it meets USP Class VI and ISO 10993 biocompatibility requirements and withstands all common sterilization methods [49]. The modules can be easily manufactured in a cost-efficient way by milling or injection molding. Two methods were tested for bonding the structured COC modules to a silicon microfluidic network.

The first method was based on using a two-component epoxy adhesive (Epo-Tek 375, Polytec-PT). An adhesive layer with a thickness of about 20 $\mu$m was transferred onto the COC as described in [50]. Since COC is slightly hydrophobic (static contact angle for water: 95°), bonding was impossible without a proper surface pre-treatment. Thus, surface wetting and bond strength were improved by activation in oxygen plasma for 4 min at 200 W. Bonding two materials with a large difference in their coefficients of thermal expansion (0.6E-04 $K^{-1}$ for COC versus 0.3E-07 $K^{-1}$ for silicon) needs an intermediate layer that reduces thermal stress. This requirement implies either high elasticity or large thickness of the intermediate adhesive layer. After curing, Epo-Tek 375 at a thickness of 20 $\mu$m became too rigid to compensate the thermal mismatch and cracks appeared on the COC surface when the assembly

was heated up to the washing temperature of 80 °C. Increasing the thickness, however, was not possible due to the risk of channel clogging by spontaneous transport of adhesive from the bonding interface into the channels via capillary forces during the curing process.

The second bonding technique was based on applying a flexible pressure sensitive tape (3M 9965). The tape has a thickness of 51 $\mu$m and is coated on each side with 18 $\mu$m thick acrylate adhesive. The tape was first laser cut to obtain the required size and open access holes to the corresponding reservoirs. Generally, bonding of the COC modules to the microfluidics can be performed either before or after wafer dicing. In the present study, in order to avoid dicing of a stack with a large thickness, the wafer was first diced and the chips were bonded one by one to the COC modules. Bonding was initiated by applying a slight pressure by hand. It does not need any curing and can be visually detected by a color change at the bonding interface. The used pressure sensitive tape proved to be adequate to compensate the thermal mismatch between COC and silicon without any cracks after 50 heating cycles to 80 °C. 3M 9965 does not require surface treatment prior to bonding and significantly simplifies the aligning process as it can be accomplished while the components are in contact and with no risk of clogging.

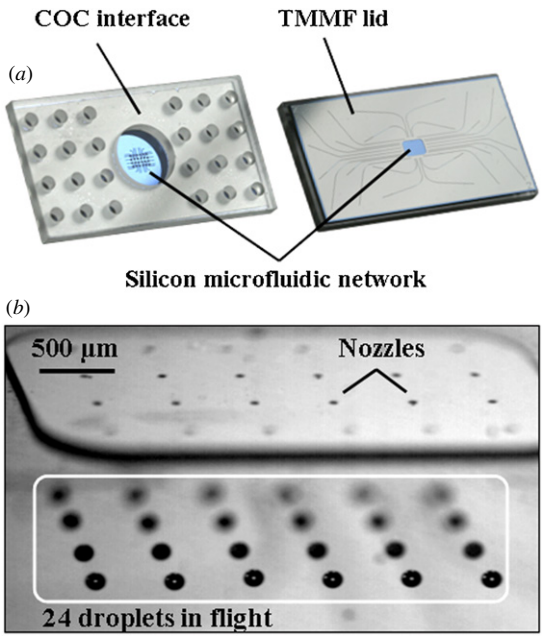


**Figure 7.** Reservoir side (*a*) and nozzle side (*b*) of the silicon/polymer 24-channel printhead. Accurate dispensing was verified by stroboscopic observation of the droplets in flight (*c*). Droplet size appears smaller than that in figure 4 due to wetting effects on the slide.

## 5. Biocompatibility of the used polymers

The biocompatibility of any material is characterized by parameters such as degree of cellular toxicity, degree of protein and DNA denaturation, adsorption, absorption, etc. It is not feasible to measure all parameters for the wide variety of physically diverse media handled in microfluidics. Therefore, the cellular toxicity of the used polymers was analyzed as a first indication of biocompatibility. An elution test method according to ISO 10993-5 was applied to determine the cellular toxicity of hard-baked TMMF and 3M 9965. A DMEM cell culture medium containing extractables from the test materials was applied to a monolayer of L929 cells (mouse fibroblasts) replacing the medium that had nourished the cells until that point. The cells were incubated for 24 h at 37 °C. Finally, the amount of LDH (lactate dehydrogenase, indicator of relative cell viability) in the test medium was compared to the LDH amount in the control media. Organo-tin polyvinylchloride (PVC, a known cytotoxic material) and Thermanox™ Coverslips (Nunc) were used as positive and negative control material, respectively. The analysis showed no cytotoxic effects on the cell proliferation, which was confirmed in a second detailed study with a focus on TMMF [51].

## 6. Performance and cost-efficiency: Si/polymer versus Si/Pyrex

A silicon/polymer TopSpot printhead was manufactured using TMMF and COC for sealing and interfacing, respectively (figures 7(*a*) and (*b*)). The dispensing performance of the printhead was controlled by stroboscopic observation. Obviously—since only peripheral components were replaced by polymers—the performance of the printhead, characterized by the homogeneity of droplet formation and speed during flight, remained the same compared to the established silicon/Pyrex equivalent (figure 7(*c*)).

To provide a clear cost analysis, individual processing steps were grouped into four processing blocks: (1) silicon micromachining, (2) selective sealing of silicon microchannels, (3) implementing world-to-chip interfaces, and (4) surface modification and test. While processing blocks (1) and (4) remain the same, processing blocks (2) and (3) are based on either silicon/glass or silicon/polymer techniques. To quantify the savings arising from using the silicon/polymer technique, consumable costs (measured in euros) as well as manpower and machine time (measured in hours) were analyzed for a typical manufacturing batch of 60 printheads (10 wafers, 6 printheads per wafer). In this analysis, consumable costs refer to raw material costs for Pyrex, COC and TMMF plus processing of the Pyrex substrates and COC modules, which was done by an external company. Material costs for Pyrex and COC are based on an order quantity of 10 substrates and 60 modules, respectively. Material costs for TMMF are based on the minimum order quantity and the corresponding proportional costs required for 10 wafers. TMMF processing was separately considered as manpower and machine time. Such analysis is generic enough to enable easy conversion into cost schemes of other organizations. The results are summarized in figure 8. The comparison is based on a production yield of 100%, which was proved after fabricating more than 150 printheads.

In the case of processing block (2) representing the selective sealing of silicon microchannels, consumable costs,

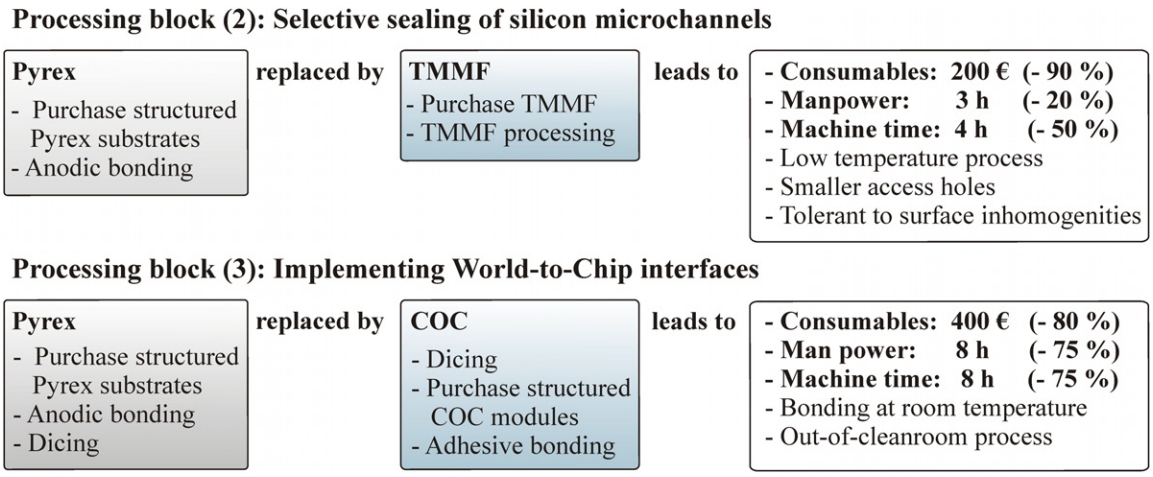


**Figure 8.** Comparison of the main cost drivers for the silicon/glass and silicon/polymer techniques based on a typical manufacturing batch of 60 printheads.

manpower and machine time were reduced by 90% and respectively 20% and 50% by applying TMMF instead of Pyrex. The main factor contributing to this cost advantage are the significantly lower costs for purchasing TMMF compared to structured Pyrex wafers of 150 $\mu$m thickness. Furthermore, TMMF lamination requires less machine time than anodic bonding. Further advantages related to TMMF are: (i) easy formation of access holes with smaller size and higher accuracy, (ii) bonding at lower process temperatures and (iii) higher tolerance to surface inhomogeneities when compared to silicon/glass anodic bonding.

In the case of processing block (3) representing the implementation of world-to-chip interfaces, consumable costs, manpower and machine time were reduced by 80% and respectively 75% and 75% by using COC instead of Pyrex. Several factors contribute to the cost effectiveness of COC: (i) lower costs for purchasing structured COC modules compared to structured Pyrex wafers and (ii) less manpower and machine time required for dicing a single silicon wafer with a thickness of 0.38 mm compared to dicing a Pyrex/Si/Pyrex triple stack with a total thickness of 2.53 mm. Further advantages are processing at room temperature and out-of-cleanroom environment as well as the high tolerance to surface inhomogeneities.

## 7. Conclusions

Numerous devices such as pumps, dispensers, cell counters, etc even nowadays are fabricated in silicon/glass technology. In our study, we investigated the efficiencies of two silicon/polymer processing alternatives. These are applicable for many silicon/glass devices where anodic bonding of silicon microfluidics to structured glass wafers is motivated by the superior quality of leak-tight sealing and/or easy implementing of world-to-chip interfaces. We show that the material combinations silicon/TMMF and silicon/COC enable sealing and respectively interfacing at much lower costs and without compromising any other feature provided by the standard silicon/glass approach. Additional advantages provided by the silicon/polymer alternatives are lower bonding temperatures as well as higher tolerances to process conditions and surface inhomogeneities. We believe that the presented silicon/polymer processing will significantly enhance the commercialization of silicon-based microfluidic devices.

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