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# A highly parallel picoliter dispenser with an integrated, novel capillary channel structure

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**Abstract**

We present a cross-contamination free highly-parallel picoliter dispenser based on direct liquid displacement. Such dispensers are essential for the (mass) fabrication of microarrays [J. Ducrée, H. Gruhler, N. Hey, M. Mueller, S. Békési, M. Freygang, H. Sandmaier, R. Zengerle, TopSpot—a new method for the fabrication of microarrays, Tech. Digest, The Thirteenth IEEE Annual International Conference on Micro Electro Mechanical Systems, Mizyazaki, Japan, 23–27 January 2000, pp. 317–322] and are able to dispense up to 384 different reagents at a pitch of 500 μm simultaneously [A. Kuoni, M. Boillat, N.F. de Rooij, A highly parallel piezoelectric printing device for microarray technology, Tech. Digest, The 17th International Conference on Micro Electro Mechanical Systems, Maastricht, The Netherlands, 25–29 January 2004, pp. 466–469]. In contrast to an earlier design [Sens. Actuators A 103 (2003) 88] we investigated different nozzle diameters and a novel capillary channel design. We present a systematic study concerning the relation between nozzle diameter and ejected droplet volume. The change from 35 to 60 μm in nozzle diameter resulted in a doubling of dispensed volume for most used elastomers and irrespective of actuation parameters. Minimum and maximum dispensed volumes have been determined to be 125 and 1700 pl. Those results are based on a new design, which also includes passive microstructures for droplet homogeneity as well as modified microchannels for improved priming and prevention of cross-contamination. Based on this, the coefficient of variation (CV) of droplet velocity could be reduced from 50% down to less than 5%. The CV of droplet volume is clearly below the measurement error (8%).


*Keywords:* Picoliter dispenser; Non-contact printing; Microchannel; Microfluidics; Microarrays; Biochips

## 1. Introduction

Microarrays have become essential analysis tools in the permanently growing biotechnology sector [4,5]. They enable a fast and highly-parallel analysis of target molecules in an unknown sample. A microarray consists of hundreds, up to thousands of small "probe molecule"-spots, arranged in a regular order. As a general rule, every probe is sensitive towards one particular target molecule. Therefore one of the main requirements is the prevention of cross-contamination between the probe molecules.

Several microarray production approaches exist [6]. A high throughput microarray production implies a fast method for dispensing a multitude of different probes. A printhead with 96 channels at a pitch of 500 μm, firing simultaneously by pneumatic actuation was already presented [7]. Based on this TopSpot-technology a fully automated production line with an up to now unmatched throughput was built. The almost fixed droplet volume and its high dependence on the liquid viscosity are main limitations of the pneumatic actuation principle [8,9].

A much more flexible actuation principle based on direct liquid displacement was developed to overcome these limitations. This method allows a tunable droplet range from 100 to 700 pl for DI water at standard operating conditions using nozzles with 50 μm in diameter [3]. The wide and easy tunability of droplet volume and dynamics is the main advantage compared to other highly parallel pico- or nanoliter dispensers [1,2,8,10]. Some problems were encountered which should be solved by an improvement of the picoliter dispenser system. Cross-contamination should be reliably excluded, the tuneable droplet volume range should be extended and the homogeneity

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of droplet volume and speed in one array should be improved.

A TopSpot printhead and the used direct liquid displacement principle are shown in Fig. 1. Core of the Topspot printheads is a micromachined silicon layer, sandwiched between two pyrex layers. The reagents are filled into the reservoirs formed by the upper glass layer. Capillary channels draw the reagents to the center print window, into the nozzles. The nozzle inlets are covered by an elastomer material. A piezo-stack actuator moves a hard plastic piston, which is placed onto the elastomer causing a displacement of the elastomer into the nozzle inlets. Droplet dynamics and volume can be tuned by speed and amplitude of the piezo movement [3]. Wetting of the nozzle area respectively a leakage of the nozzles during actuation is prohibited by a hydrophobic coating. A solution based process described by Breisch et al. [11] was used to apply the coating to the nozzle area.

A central point of the operation is the order of elastomer placement and printhead filling. The reagents can be filled into the printhead before or after the elastomer is placed into the print window. A high risk of cross-contamination between the reagents is present, if the elastomer is placed after the printhead is filled (Fig. 2a).

The risk of cross-contamination can be excluded by placing the elastomer first. This seals the capillary channels from each other before they are filled with the reagents. This approach was not practicable with the prior design because the nozzles, which are the air exits, got filled with liquid before

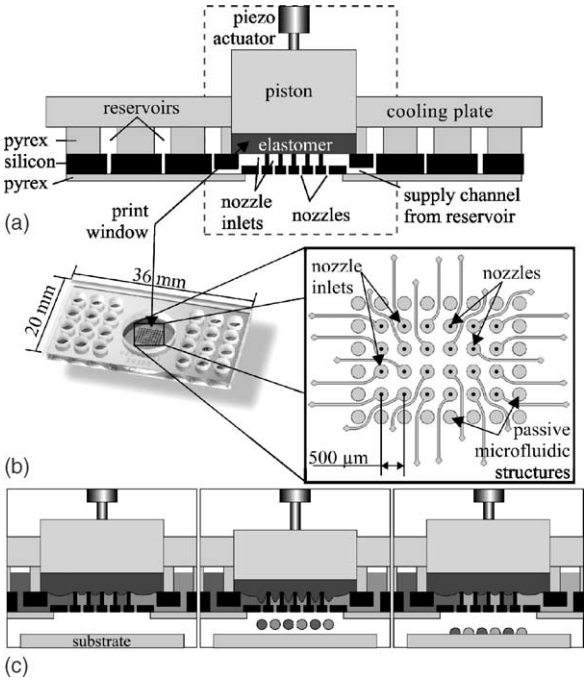


Fig. 1. The TopSpot picoliter dispenser: (a) cross-section of printhead with an inserted elastomer and piston, (b) 24 channel printhead and its print window, and (c) actuation: left: printhead filling and elastomer placement; middle: printing based on direct liquid displacement; right: nozzle refilling.

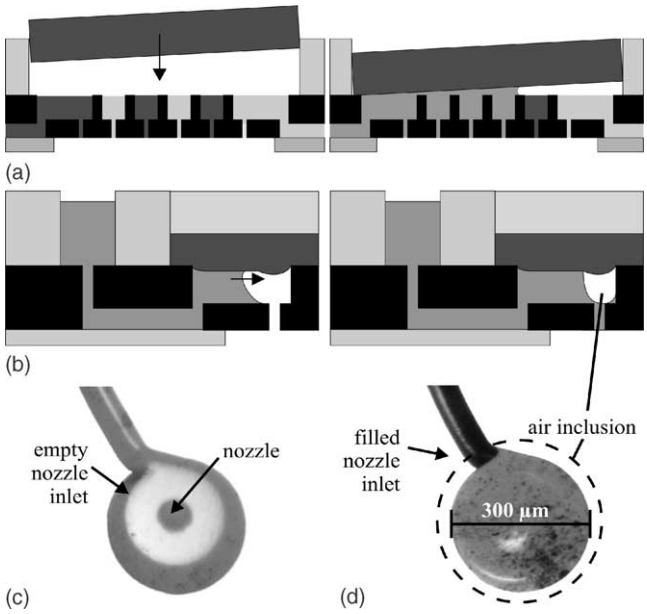


Fig. 2. Filling of printhead and elastomer placement: (a) filling of printhead first: high risk of cross-contamination, (b) elastomer placement first: a trapped air bubble leads to a malfunction of the direct liquid displacement, (c) photographs of an empty nozzle inlet, and (d) a filled nozzle inlet with the trapped air bubble. The nozzle inlets are covered by a clear elastomer to enable an optical control.

all air was displaced out of the capillary channels (Fig. 2b). The result was a trapped air bubble, which nearly filled out the entire nozzle inlet. Photographs of a nozzle inlet before and after filling are shown in Fig. 2c and d. Now we present a new, two-level capillary channel design which overcomes that problem. Additional passive microstructures and adaptations of capillary channel lengths were integrated in a new printhead design to improve droplet homogeneity.

## 2. Experimental

### 2.1. Printhead fabrication

The basic fabrication process was already described in [7]. All microfluidic structures are etched into silicon by four DRIE (ASE standard process) steps. The processed 380 μm thick silicon layer is sandwiched between two anodically bonded pyrex layers, which are structured by ultrasonic drilling. The upper, 2 mm thick pyrex layer forms the reservoirs and the print window. The 150 μm thick bottom pyrex layer seals the capillary channels. Fig. 3 shows a cross-section of the printhead with all the geometries. Five fundamental microfluidic structures have to be etched into the silicon layer:

1. Capillary channels on bottom and top side.
2. Nozzles on bottom side.
3. Nozzle inlets on top side.

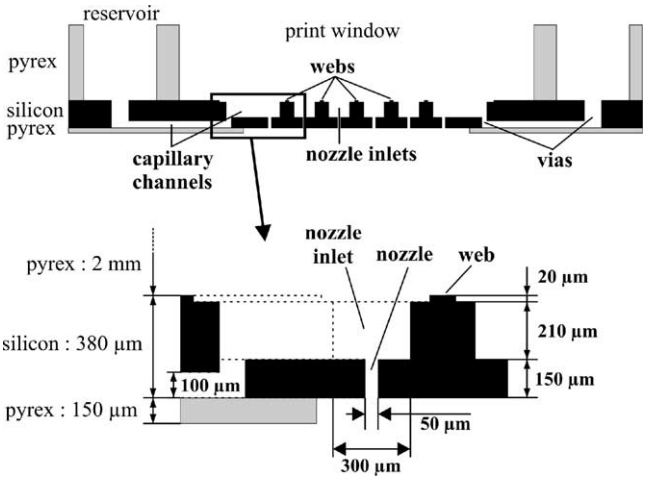


Fig. 3. Cross-section and geometries of the fabricated printheads.

4. Webs around nozzle inlets to enable novel two-level capillary channel structure.
5. Vias from bottom to top side to connect reservoirs, capillary channels and nozzle inlets.

The process flow is depicted in Fig. 4.

### 2.2. Printhead preparation

Before actuation can take place, the printhead has to be filled and an elastomer has to be inserted into the print window. The elastomer can be placed before or after the printhead is filled. Both approaches were evaluated.

A transparent elastomer was used to enable the optical verification of the filling procedure. To achieve a sensitive cross-contamination check fluorescent dyes were used as print medium. DI-water alternating with 15 µM Dyomics® DY-550 solved in a 10% glycerol solution were filled into the printhead.

First experiments were performed with an elastomer placement after the printhead was filled. In the past, special shaped elastomers were used for a controlled elastomer lowering [3]. In contrast to that, a bearing area for the elastomer was integrated in the new improved design. This enables the usage of unshaped elastomer plates, which can be fabricated in a much easier and more reproducible way. Due to the bearing area the elastomer can be placed without causing cross-contamination. A controlled vertical movement of the piston allows a lowering of the elastomer without a slope. This minimizes the risk of cross-contamination during the elastomer placement. Fig. 5a–c illustrates this principle.

Printheads with a hydrophobic coating in the print window and without were used. The hydrophobic coating was applied by placing the printhead for 1 h at room temperature in an HMDS atmosphere. To avoid a hydrophobic coating in the capillary channels, nozzle inlets and nozzles, these structures (see Fig. 5d) were filled with DI water before the coating process began.

Further experiments were performed to evaluate the second approach, where the elastomer is placed before the reagents are filled into the printhead. Therefore, a new, two-level capillary channel design was developed to overcome the problems of trapped air bubbles. Fig. 6 shows the working principle of the new, two-level capillary channel structure. The lower level is self-filled by capillary forces first, followed by the upper level which is filled in reverse direction.

The two filling steps of upper and lower level were decoupled for a better control and observation of the filling

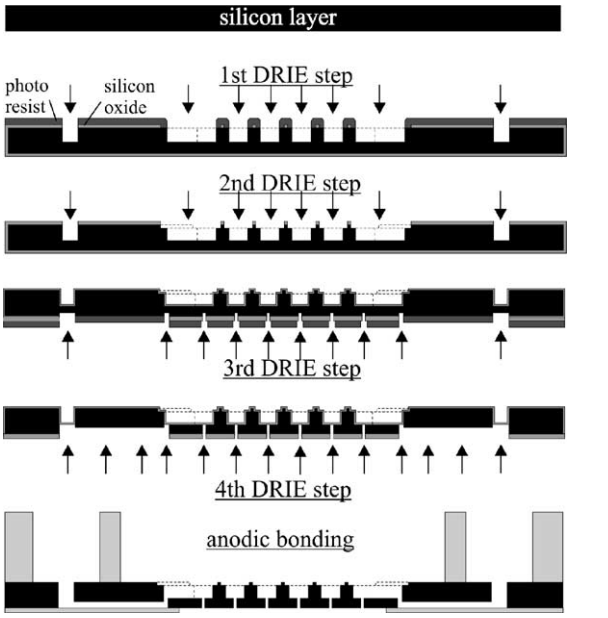


Fig. 4. Process flow for manufacturing the TopSpot printheads. Silicon oxide and photo resist were used as mask layers.

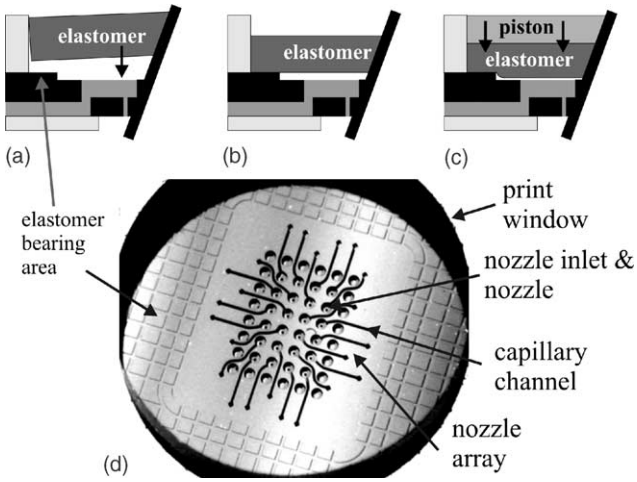


Fig. 5. Added elastomer bearing area to enable elastomer placement without slope: (a) placement of elastomer, (b) elastomer placed in printhead. Elastomer is supported by the bearing area and it does not get in contact with reagents in nozzle inlets in this stage. (c) Lowering of elastomer without slope by controlled movement of piston, (d) photograph of print window with nozzle area and elastomer bearing area.

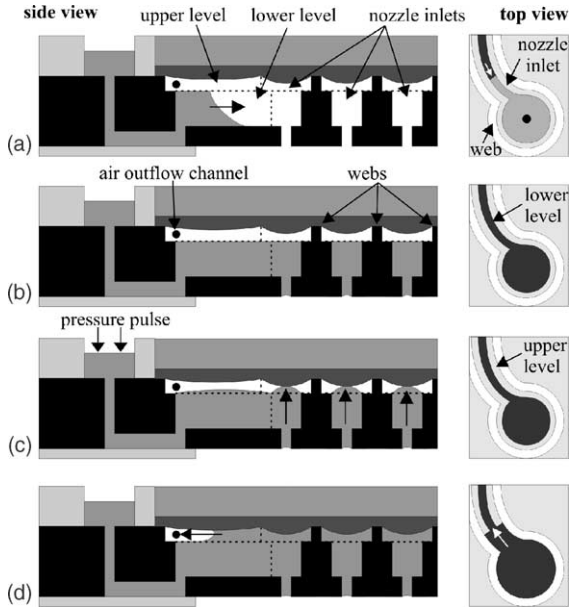


Fig. 6. Working principle of the new two-level capillary channel design: (a and b) self-filling of lower level, (c) the displaced upper level causes the liquid to stop after self-filling of the lower level. A small pressure pulse onto the corresponding reservoir initiates the filling of the upper level. (d) Filling of upper level in reverse direction, displacing air out of the printhead through a passive air outflow channel.

process. The upper level and the decoupling of the two filling steps were realized by adding a small web around the nozzle inlet. Due to a small step between web and nozzle inlet, the liquid can not be drawn into the upper level by itself. This causes the liquid to stop, after the lower level is self-filled. The second filling step of the upper capillary channel level is manually initiated by a small pressure pulse onto the corresponding reservoir (Fig. 6c). The larger diameter of the nozzle inlet compared to the width of the inlet channel makes sure that here the liquid is pushed out highest. This means, that the liquid gets at first in contact with the elastomer at the center of the nozzle inlet. After contact between liquid and elastomer the capillary forces can act again and the liquid is drawn in reverse direction through the upper level (Fig. 6d). This way, the air is displaced away from the nozzle inlet, out of the printhead through the passive air outflow channels. An SEM photograph of the new design is shown in Fig. 7.

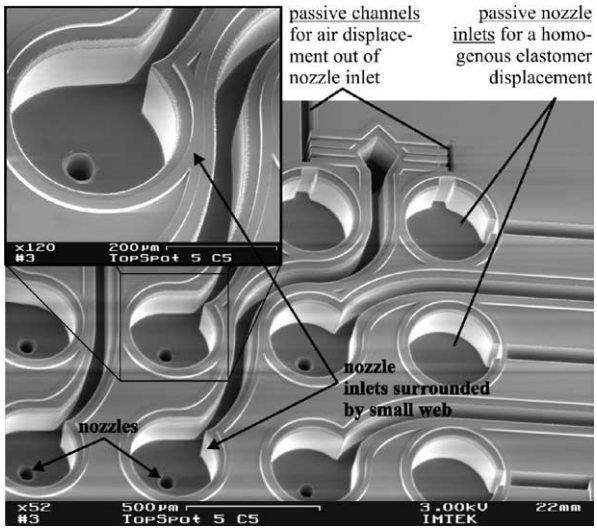


Fig. 7. SEM photograph of the new printhead design.

### 2.3. Printing

Droplet flight was observed with a stroboscopic camera (Visit Video Stroboskop MOCRON-RT). Only one row of six nozzles was observed to enable a concise observation of droplet homogeneity. The droplet diameters were measured by analyzing the camera recordings with an image analysis software. Considering lighting gradients and motion blur of the flying droplets we assume a resulting measurement error of 8% for the droplet volume.

The droplet volume can be tuned by piezo stack amplitude and droplet speed is adjusted by actuators velocity [3]. Droplet speed has to be adjusted for a stable operation. Stable operation means that exactly one droplet is ejected from each nozzle. If the piezo speed is too low, the droplets do not tear off and if it is too high, satellite droplets appear. Nozzle diameters of 35, 40, 45, 50, 55 and 60 μm were evaluated. Piezo stroke and speed were measured with a laser vibrometer (Polytec Fiber Interferometer OFV 512).

Additionally the influence of elastomer hardness was determined. Sylgard® 184 (PDMS) and Sylgard® 186 silicone elastomers (Dow Corning®) were used. Their hardness was varied by different mixing ratios of the elastomer base and "Dow Corning® 200 Fluid 50 cS". Table 1 lists all used elastomers.

Table 1
Different mixing ratios of used elastomer types

| Elastomer | Elastomer base | | 200® Fluid 50 cS (wt.%) | Hardness (ShA) |
|---|---|---|---|---|
| | Sylgard® 184 (PDMS) (wt.%) | Sylgard® 186 (wt.%) | | |
| 1 | 100 | 0 | 0 | 50 |
| 2 | 0 | 100 | 0 | 33 |
| 3 | 0 | 80 | 20 | 18 |
| 4 | 0 | 60 | 40 | 8 |

Dow Corning® Sylgard® 186 elastomer base was mixed with "Dow Corning® Fluid 50 cS" to reduce the hardness.

## 3. Results and discussion

### 3.1. Cross-contamination

Problems were encountered when the elastomer was placed into the print window after the printhead was filled. Already the optical control showed a cross-contamination between the reagents when an uncoated printhead was used. This observation was confirmed by the results of the fluorescence reader, shown in Fig. 8a. Each one of 10 printhead preparations led to a cross-contamination during elastomer placement. We could avoid in some cases cross-contamination by using the hydrophobic coated printheads. Cross-contamination could be detected again, when the elastomer was placed with a too large slope or if the hydrophobic coating degenerated. Three of ten preparations of the hydrophobic coated printheads led to a cross-contamination. Since the reliable exclusion of cross-contamination is a fundamental requirement for printing microarrays, the test series was stopped after 10 experiments. Concluding, cross-contamination could be avoided but not reliably excluded (Fig. 8b) when the elastomer was placed after printhead filling. To exclude cross-contamination reliably it is necessary to place the elastomer before the printhead is filled. The new two-level capillary channel design, shown in Fig. 6, made it for the first time possible to fill the nozzle inlets reliably without generating an air inclusion. Fig. 9 shows three nozzle inlets at different filling stages.

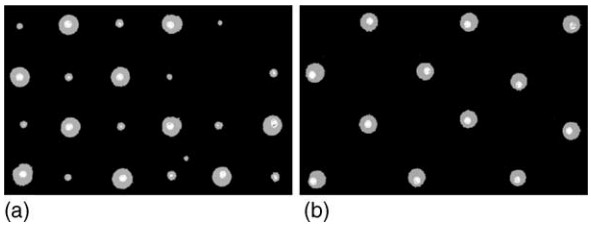


Fig. 8. Cross-contamination check. Water alternating with 15 μM Dyomics® DY 550 solved in 10% glycerol solution was filled into a 24 channel printhead. Then the elastomer was inserted: (a) a mixing between the reagents was observed if a printhead without a hydrophobic coating was used and (b) if a hydrophobic coated printhead is used, cross-contamination can be prevented.

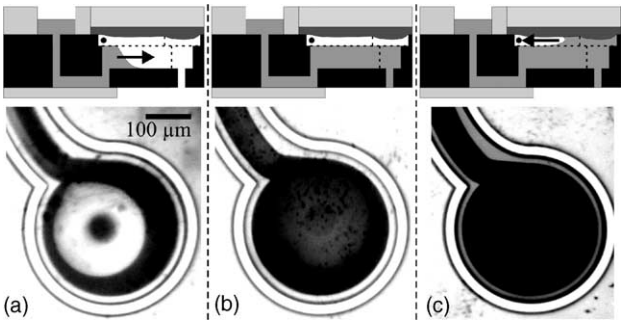


Fig. 9. Optical control of the new capillary channel filling method. Three photographs of a nozzle inlet show different steps of the filling process. The inlet was covered by a transparent elastomer: (a) empty nozzle inlet, (b) the lower level of the nozzle inlet got self-filled and the liquid stopped, and (c) after a short pressure pulse onto the corresponding reservoir (cf. Fig. 5) the upper level is self-filled in reverse direction. The air is displaced out of the printhead through the passive channel structures shown in Fig. 7.

### 3.2. Printing performance

Prior printhead designs led to different characteristic patterns of ejected droplet rows. The responsible mechanisms were already described [3]. In consequence a passive nozzle inlet row was added and the incoming channel length were adapted in the new improved design (Fig. 10a). The result was a reduction of the CV of droplet speed from 50% down to less than 5% at stable operation (Fig. 10b). At the

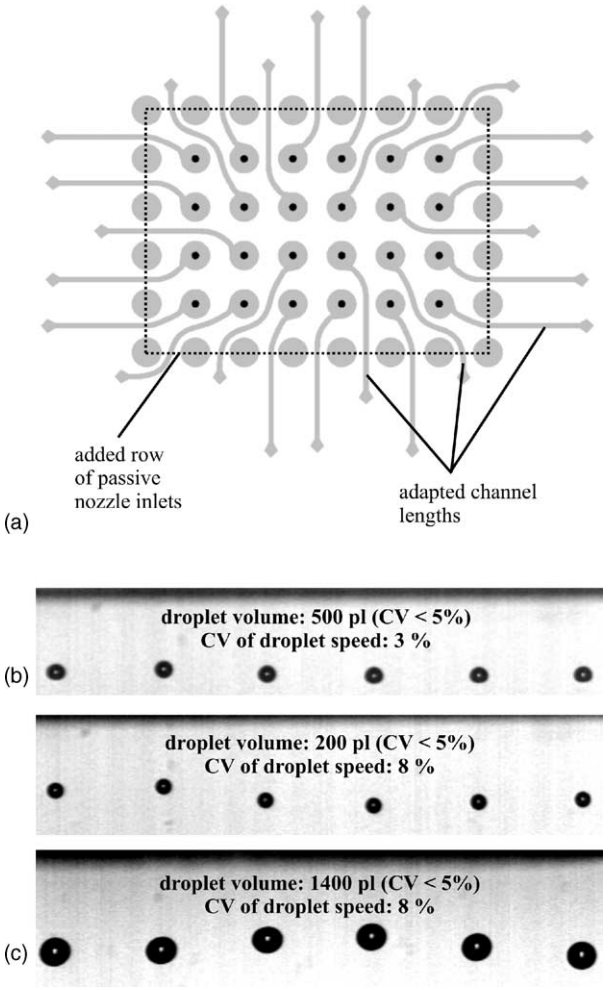


Fig. 10. New improved printhead design and resulting droplet homogeneity: (a) improved printhead design. A row of passive nozzle inlets was added and the channel lengths were adapted due to conclusions of prior publications [3]. (b) Six droplets ejected by one nozzle row. Typical CVs of droplet speed below 5% could be observed at stable operation. (c) The droplet volume can be tuned in a range from 200 to 1400 pl, using nozzle diameters of 50 μm. Even at these extremes of ejectable droplet volumes the CV of droplet speed did not exceed 8%.

extremes of ejectable droplet volume range CV was slightly higher (8%, cf. Fig. 10c).

The volume deviation was below the measurement error of 8% even at a CV of droplet speed of 50% [3]. The experiments with the new printhead design showed again volume deviations clearly below the measurement error. The relative droplet volume deviation of one specific nozzle in 50 consecutive ejections was below 1%.

### 3.3. Nozzle diameter and elastomer hardness

A linear relation between nozzle diameter and droplet volume was found, as shown in Fig. 11. The deviation of droplet volumes of five different experiments at constant piezo stroke was maximum 8%. Between the experiments the printhead was cleaned and the elastomer was replaced.

With a piezo stroke of less than 3 μm it was not possible to achieve stable droplet ejection. The used piezo actuator enables a maximum stroke of 9 μm. This led to a working range of 3–9 μm for all experiments.

The experiments with the three silicone elastomers ("elastomers 2–4", cf. Table 1) basing on Sylgard® 186 showed that the droplet volume is doubled at constant piezo stroke by increasing the nozzle diameter from 35 to 60 μm. For example, droplet volume is doubled from 450 to 900 pl using the 33 ShA hard "elastomer 2" or doubled from 850 to 1700 pl by using the softest "elastomer 4" at constant piezo stroke of 9 μm. This also shows that by decreasing the elastomer hardness the ejectable droplet volume range can be increased dramatically.

The doubling of droplet volume was not observed for the Sylgard® 184 based, 50ShA hard "elastomer 1". Here the droplet volume increased from 270 to 400 pl by increasing the nozzle diameter from 35 to 60 μm at a piezo stroke of 9 μm.

Summarized, the maximum ejectable droplet volume of 1700 pl can be dispensed by using the soft "elastomer 4", a nozzle diameter of 60 μm and a piezo stroke of 9 μm. A droplet with a minimum droplet volume of 125 pl can be ejected by printing with the harder "elastomer 1", a nozzle diameter of 35 μm and a piezo stroke of 3 μm.

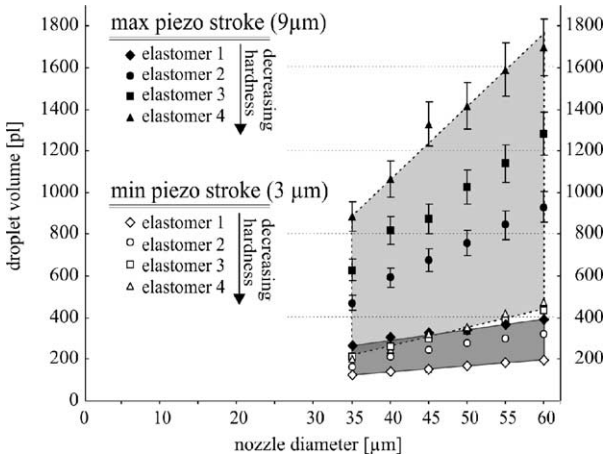


Fig. 11. Measured droplet volumes versus nozzle diameter at given elastomer hardnesses. The elastomers listed in Table 1 were used. The two highlighted areas indicate the tunable droplet volume ranges for two elastomer types, when piezo stroke is varied between minimum (3 μm) and maximum (9 μm) and nozzle diameter is varied between 35 and 60 μm. The light grey area shows the tunable droplet volume range, using the softest elastomer. The dark grey area shows the tuneable range, using the hardest elastomer.

## 4. Conclusion

Droplets with tuneable volumes from 125 to 1700 pl were ejected in stable operation by using elastomers of different hardnesses, nozzle diameters from 35 to 60 μm and a piezo stroke between 3 and 9 μm. The volume range can be enlarged even further by using a piezo with a larger stroke, nozzles with larger diameters or a weaker elastomer. With this, the spotsize of the microarray can easily be adapted to the substrate surface properties.

The droplet volume deviation of six droplets in a row was clearly below the measurement error of 8%. Experiments have to be performed to investigate the (in)dependence of droplet volume on liquid viscosity.

When the elastomer is placed after the printhead is filled, cross-contamination could only be avoided if a hydrophobic coated printhead was used. Still, cross-contamination could not be excluded for all experiments.

Cross-contamination could be excluded reliably by a new two-level capillary channel design which allows an elastomer placement before the printhead is filled. A first test design for proof of principle, which allows a manual initiation of the second filling step. A self-filling of the two-level capillary channel is possible by justifying the ends of upper and lower level of the new capillary channel structure.

The added passive microfluidic structures to the printhead design led to a more homogenous elastomer displacement into the nozzle inlets. Based on this the CV of droplet speed could be reduced from 50% [3] down to less than 5%.

The current development allows the use of the presented technology for a highly flexible microarray production.

## Acknowledgements

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## Biographies

*C.P. Steinert* was born in Germany in 1975. He received his Dipl.-Ing. degree in microsystem technology in 2001 at the University of Freiburg, Germany. Since January 2002, he is working as a R&D engineer on a PhD project in the laboratory for MEMS applications at the Institute for Microsystem Technology (IMTEK). His diploma and current work is in the field of life siences, where he develops a dispensing device for the (mass) production of microarrays.

*I. Goutier* studied microsystem technology at the Universtiy of Freiburg, Germany. He received his Dipl.-Ing. degree in 2003 at the institute for microsystem technology (IMTEK). From March to September 2003, he worked as R&D engineer at the lab for MEMS applications. His research activities were in the field of life sciences with a main focus on microarray fabrication. In October 2003, he started further business studies in Berlin, Germany.

*Oliver Gutmann* received his Dipl. Ing. degree in biotechnology from the Ecole Supérieure de Biotechnologie (ESBS) in Strassbourg (France) in 2001. He made his diploma thesis at Genescan Europe AG (Germany) in 2001 titled “production of protein microarrays using TopSpot”. Afterwards he worked as a R&D engineer at Genescan Europe AG. Since 2002, he is working towards a PhD degree at the Universisty of Freiburg, Institute of Microsystem Technology (IMTEK), Chair for MEMS Applications. Oliver’s research interests include microarrays, microfluidics and microsystem technology.

*Hermann Sandmaier* was born in Ruhstorf, Germany in 1955. He received the MS and PhD degrees in electrical engineering from Munich Technical University in 1982 and 1988, respectively. He was working with the Fraunhofer Institute in Munich from 1982 to 1995, developing microsensors for physical and chemical quantities as well as microfluidic devices. He is currently head of the Institute for ‘Mikro- and Informationstechnik’, a research center of German ‘Hahn-Schickard Gesellschaft’, and a professor at Stuttgart University. His research interest focuses on microsensors, microfluidics, and microelectromechanical systems besides topics in technology, fabrication, and modelling. He received the Schlumberger award in 1989. In 1998, he has organized the MEMS Workshop in Heidelberg. He was an Editorial Board Member of Sensors and Materials, Steering Committee Member of MEMS-Workshop, Program Committee Member of Sensors and Eurosensors as well as European Technical Program chair of Transducers’01 in Munich. Currently, he is an Editorial Board Member of the *Journal of Micromechanics and Microengineering*.

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*Bas de Heij* obtained his MSc degree in the year 1996, from the university of Twente (NL) on work entitled ‘Micromachining in Stainless steel’. For his PhD work he joined the group at the IMT in Neuchâtel (CH) from Prof. De Rooij. His PhD thesis was finished in the year 2000 and is entitled ‘Development of a micromachined vaporiser for inhalation drug therapy’. In that same year he joined the group of Prof. Zengerle. His main interest is the development of methods and equipment for the highly parallel generation of nL and sub-nL droplets.

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