Integrated Flow-Cells for Adjustable Sheath Flows

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In this paper two integrated flow-cells are presented that can generate novel sheath flows. The flow-cells allow for dynamic orthogonal control of the sample flow dimensions. In addition to this, the sample flow can be freely positioned inside the channel. The flow-cells are attractive, because they are very simple to fabricate and are compatible with the integration of sensors. Experiments have been carried out demonstrating that the sample flow dimensions can be controlled over a wide range; also the results show good agreement with finite element simulation results.

Introduction

The flow-cells presented here allow dynamic orthogonal control of the sample flow dimensions. Also the sample flow can be freely positioned inside the flow-channel so that the sample flow touches or nearly touches one side of the channel; this assures a good contact with any integrated sensor interface. Finally, another attractive feature of the flow-cells presented here is that they are very simple to fabricate, consisting of a two layer structure and requiring only two etch-steps to fabricate.

The flow-cells presented in this paper distinguish themselves from the flow-cells known in the literature [1] – [9] by their versatility. Both layered sheath flows and coaxial sheath flows can be realized within the same device. What is even more important, due to a number of orthogonal control mechanisms both the dimensions and the position of the sample flow can accurately be controlled. As a consequence the flow-cells can create an optimal sample flow for each specific application. And because they can be fabricated by adding a few post-processing steps to a standard IC-process, many known sensors can be integrated into the device.

Some examples of applications are: an integrated Coulter counter [10], sensors for particle shape analysis [11] and sensors for cell analysis and (bio)chemical analysis.

Flow-Cell 1: Control of Sample Flow Dimensions

Flow-cell 1 has been developed to allow dynamic control of the dimensions of the sample flow (see Fig. 1). In this flow-cell a non-coaxial sheath flow is formed by vertically injecting a sample liquid into a channel through which sheath liquid is flowing. By hydrodynamic focusing a smooth flow of sample liquid is formed that still touches the bottom of the channel. A focusing section brings the channel width down from 625 µm to a width of 160 µm. The application of such a focusing section allows the use of fairly large inlets which are convenient in handling the liquid connections to the chip. The less critical alignment of the inlets and the lower pressure drop over the wider sections are additional advantages. The non-coaxial type of sheath flow that is formed with this flow-cell is suitable for sensors that require contact with the sample liquid such as impedance sensors. The dimensions of the sample flow can dynamically be adapted by two orthogonal control mechanisms.

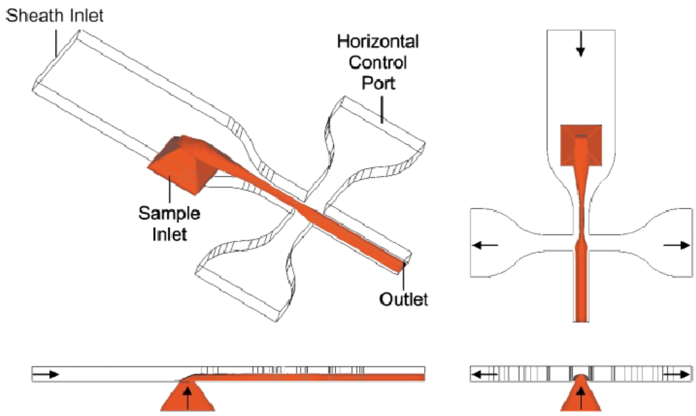

Fig. 1: Model of flow-cell 1, this flow-cell creates a non-coaxial sheath flow and allows control of the sample flow dimensions; here the control ports are used to widen the sample flow.

The vertical dimensions of the sample flow are controlled by the relative flow rate at which the sample liquid is injected in relation to the flow rate of the sheath flow. At higher relative flow rates of the sample liquid, it penetrates further into the sheath liquid thereby increasing the sample flow height. Lowering the relative flow rate of the sample liquid will result in a sample flow with less height.

The horizontal dimensions of the sample flow are controlled by two horizontal control ports that are located on the sides of the flow-channel, downstream of the sample inlet (see Fig. 1). By adding or removing sheath liquid through these control ports at an equal rate the already present sheath flow is horizontally compressed or expanded respectively which leads to a narrow or wider sample flow. Notice that the height of the sample flow is not affected by this control mechanism.

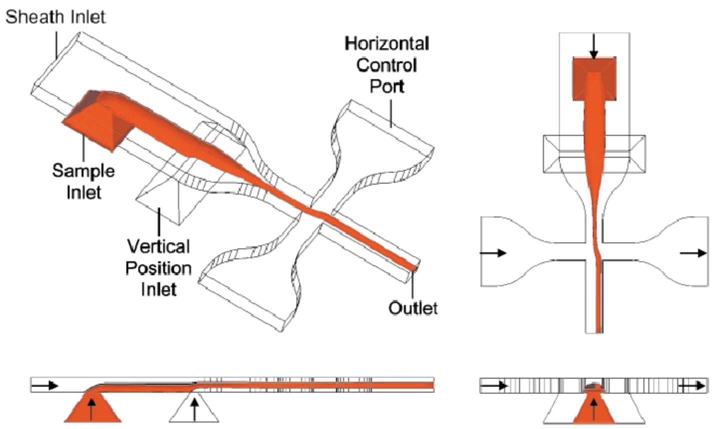

Fig. 2: Model of flow-cell 2, the additional vertical position inlet of this flow-cell also allows positioning of the sample flow in the channel; here the control ports are used to position the sample flow vertically in the centre of the channel with a horizontal shift.

Flow-Cell 2: Additional Control of Sample Flow Position

Flow-cell 2 looks quite similar to flow-cell 1, but there is one main difference. Flow-cell 2 has an additional inlet, located in between the focusing section and the sample inlet (see Fig. 2). This additional inlet gives flow-cell 2 the added functionality to freely position the sample flow anywhere inside the flow channel. Two control mechanisms are required to achieve this.

The vertical position of the sample flow is controlled by the additional vertical control inlet. When sheath liquid is added through this inlet the entire sheath flow in the channel is lifted up from the channel bottom. As a result a coaxial sheath flow is formed that no longer has any contact with the channel bottom. The more liquid is added through this inlet the higher the sample flow is positioned. This vertical position control inlet has a narrow shape (625 µm × 350 µm) to create a flow profile through this inlet that is as uniform as possible. This means that the shape of the sample flow is hardly influenced by the vertical position control, except for some vertical compression.

The same horizontal control ports that are used to control the width of the sample flow can also be used to control its position. In this type of operation the direction of flow through both inlets is now opposite. By adding sheath liquid through one of the control ports and removing it from the other inlet at the same flow rate the sample flow is shifted in the horizontal plane. Apart from the additional inlet the configuration of the inlets of flow-cell 2 is similar to that of flow-cell 1, therefore the sample dimension control mechanisms described for that flow-cell work for flow-cell 2 as well. The coaxial flow that can be achieved with this flow-cell is very suitable for sensors that do not require any contact with the sample liquid and especially those sensors in which the interface might get polluted such as optical sensors.

Fabrication of the Flow-Cells

Both types of flow-cells can be fabricated using the same, relatively simple process. In a glass wafer by isotropic etching the channel is defined with a depth of 100 µm and a minimum width of 160 µm. In a silicon wafer by isotropic etching through-holes are defined that form the liquid inlets of the device. The glass wafer and the silicon wafer are then anodically bonded together to form the complete devices. A photograph of a flow-cell chip is depicted in Fig. 3.

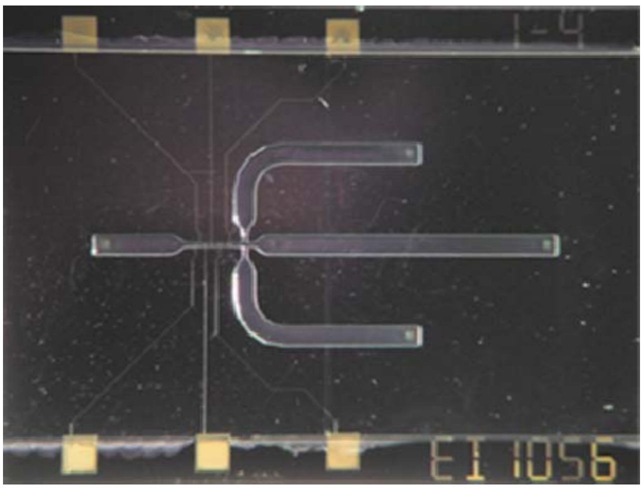

Fig. 3: The flow-cell chip with dimensions of 2 cm by 1.5 cm (the electrical contacts are not used in the experiments).

There are a number of reasons to make the devices like this. Firstly, the dimensions of the sample inlet need to be accurate and etching of silicon can be easier controlled than glass etching. Secondly, with the liquid inlets in the silicon part the glass side of the device is still available for optical inspection during operation. Finally, since the channel was etched in the glass wafer the surface of the silicon wafer is still smooth and suitable for future integration of sensors to form a complete integrated analysis system.

Experimental Verification

Sample Diffusion

First a reference experiment was carried out to determine the influence of diffusion and to see how well it can be modeled. In this experiment the ratios of the flow rate of the sample liquid, the flow rate through the control ports and the flow rate of the sheath-liquid were kept constant at 1:5:10. During the experiment the total flow rate was varied from 1 to 50 µl min^{-1}. The intensity of the dye was measured in the wider section following the narrow section (see Fig. 4), since in this location the visible area is not blocked so much by the rounded corners of the isotropic etching of the channel.

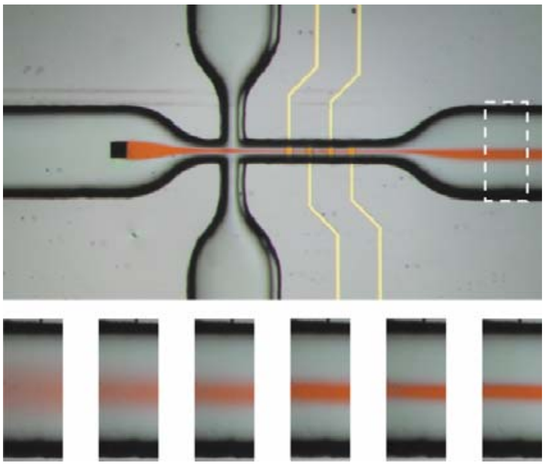

Fig. 4: Illustrative results from the diffusion experiment.

There is a very good agreement between experimental and simulation results. This means that the finite element model represents the real flow-cell very well and that this model can be used for the further experiments. The influence of diffusion is realistically taken into account in the experiments, and for a flow rate higher than 10 µl min^{-1} the influence of diffusion is small, so measurements can be carried out at this flow rate.

Vertical Control of Sample Flow Dimensions

In the first control experiment the vertical dimensions of the sample flow were controlled. Since for this measurement the width control of the sample was not necessary, a device without horizontal control ports was used similar to flow-cell 1. During the experiment the flow rate of the sheath liquid was kept constant at 10 µl min^{-1} and six different flow rates for the sample liquid were applied in a range from 0.05 to 2 µl min^{-1}, which correspond to relative sample flow rates of 0.5% to 20% of the sheath flow rate. Again the intensity of the dye was measured in the wide section of the channel, downstream of the narrow section. Some illustrative results are depicted in Fig. 5.

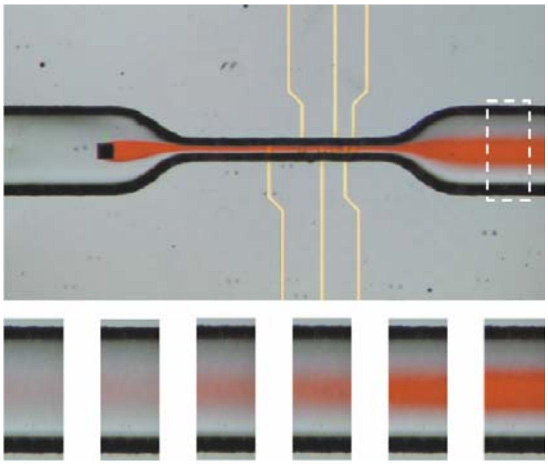

Fig. 5: Illustrative results from the sample height control experiment.

In Fig. 5 it can be seen that the width of the sample is constant for relative flow rates of the sample flow up to 10%; at the highest flow rate the sample flow becomes slightly wider. The results show that the height of the sample can be controlled over a wide range. For the relative flow rates used in the experiment the height of the sample flow can be controlled from 3 to 60 µm in a channel with a depth of 100 µm.

Horizontal Control of Sample Flow Dimensions

In the second control experiment the horizontal dimensions of the sample flow were controlled. During this experiment the sheath liquid and sample liquid flow rates were kept constant at 10 µl min^{-1} and 1 µl min^{-1} respectively. The flow rate through each control port was varied from –3 to +25 µl min^{-1}. The dye was measured at the same location as in the previous experiments; here it was even more important to have a visible area that is maximally wide. Some illustrative results are depicted in Fig. 6.

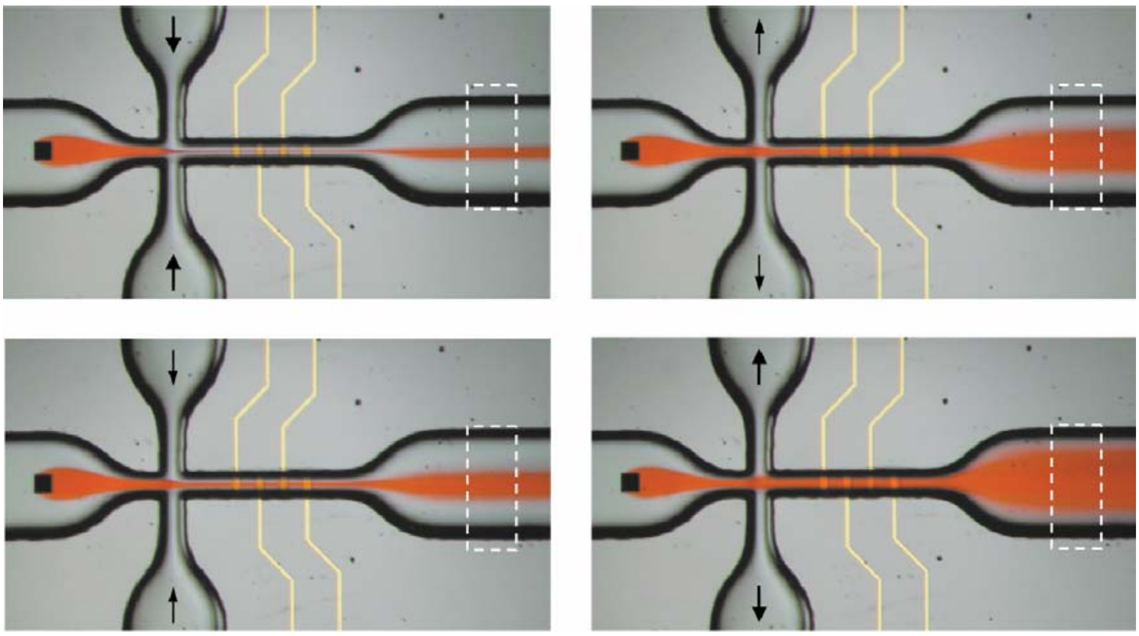

Fig. 6: Illustrative results from the sample width control experiment.

Sample flow splitting and switching

The flow-cell used in the experiment turned out to be a very flexible device. Besides the horizontal and vertical control of the sample also other useful functions can be realized. The first example is sample splitting. For this application only one control port is used. Through this inlet 50% of the total flow of liquid is removed. This results in an equal splitting of the sample (see Fig. 7). By removing more or less liquid through the control port an unequal splitting of the sample is also possible of course.

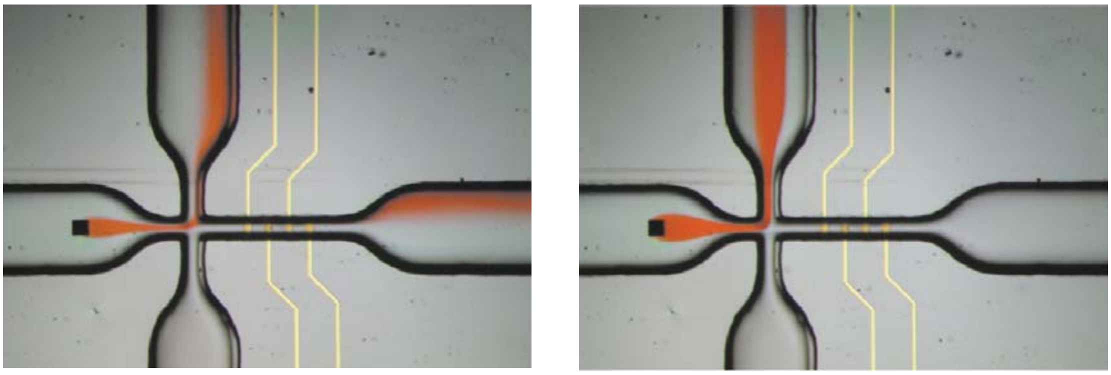

Fig. 7: The flow-cell applied for sample splitting (left) and flow-switching (right).

A second example of the flexibility of the flow-cell is sample switching. Here again only one control port needs to be active. This time the liquid is removed through the control port at a flow rate that equals the flow rate of the total flow of liquid. As a result the complete sheath flow including the sample liquid is switched (see Fig. 7). When a coaxial sheath flow is used such as can be generated with flow-cell 2 this is even possible without the sample liquid touching any wall of the channel.

Conclusions

Two new flow-cells have been developed that are very versatile. The flow-cells can generate both non-coaxial and coaxial sheath flows. Using an orthogonal control mechanism the flow-cells allow dynamic control of the sample flow dimensions. With one additional vertical position inlet the sample flow can also be freely positioned inside the channel. The processing of the flow-cells is very simple, and can be easily combined with the integration of sensors to form a complete integrated analysis system.

Experiments were carried out with one of the flow-cells and compared with finite element simulations performed with the Netflow-module of the finite element package Coventorware. Detailed models of up to 100 000 elements with a well designed grid were required to obtain a high-enough accuracy. Besides the geometry of the model and the flow rates also the diffusion constant of the dye was included in the simulations. A comparison of experimental results and simulation results shows that the complicated flow behavior of the device can be modeled very accurately. Also the influence of diffusion is realistically taken into account. The results on the horizontal and vertical control of the sample flow dimensions show that both mechanisms work well and that they can be predicted from simulation results. The control ports make the flow-cells very versatile so that they can also be used for other applications such as sample splitting and flow switching.

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References

[1] M. Tidare, H. Roos and U. Lindberg, Hydrodynamic Addressing; A Flow Cell for Improved Signal Quality in Bioanalytical Systems, , in Proc. of Transducers '01, Munich, Germany, June 10–14, 2001, pp. 1154–1157.

[2] O. Hofmann, P. Niedermann and A. Manz, Modular Approach to Fabrication of Three-Dimensional Microchannel Systems in PDMS – Application to Sheath Flow Microchips, Lab Chip, 2001, **1**(2), 108–114.

[3] U. D. Larsen, G. Blankenstein and J. Branebjerg, Microchip Coulter particle counter, , in Proc. of Transducers '97, Chicago, June 16–19, 1997, pp. 1319–1322.

[4] K. Roberts, M. Parameswaran, M. Moore and R. S. Muller, A Silicon Microfabricated Aperture for Counting Cells using the Aperture Impedance Technique, , Proc. of 1999 IEEE Canadian Conference on Electrical and Computer Engineering, Edmonton, Alberta, Canada, May 9–12, 1999, pp. 1668–1673.

[5] G. Lee, B. Hwei and G. Huang, Microfluidic Chips with MxN Continuous Sample Introduction Function Using Hydrodynamic Flow Switching, , in Proc. of Transducers '01, Munich, Germany, June 10–14, 2001, pp. 1158–1161.

[6] R. Miyake, H. Ohki, I. Yamazaki and R. Yabe, A Development of Micro Sheath Flow Chamber, in Proc. of MEMS '91, 1991, pp. 265–270.

[7] K. Tashiro, T. Sekiguchi, S. Shoji, T. Funatsu, W. Masumoto and H. Sato, Design and Simulation of Particles and Biomolecules Handling Micro Flow Cells with Three Dimensional Sheath Flow, , in Proc. of µTAS 2000, Enschede, The Netherlands, May 14–18, 2000, pp. 209–212.

[8] A. Wolff, U. D. Larsen, P. Friis and P. Telleman, Chip-Integrated Microfluidic System for Cell Sorting and Cell Culturing, , in Proc. of Eurosensors XIV, Copenhagen, Denmark, August 27–30, 2000, pp. 235–238.

[9] D. Huh, Y. Tung, H. Wei, J. B. Grotberg, S. J. Skerlos, K. Kurabayashi and S. Takayama, Use of Air-Liquid Two-Phase Flow in Hydrophobic Microfluidic Channels for Disposable Flow Cytometers, Biomed. Microdev., 2002, **4**(2), 121–149.

[10] J. H. Nieuwenhuis, J. Bastemeijer, P. M. Sarro and M. J. Vellekoop, Integrated Coulter counter with non-coaxial sheath-flow and dynamic aperture control, , in Proc. of Eurosensors XVI, Prague, Czech Republic, September 15–18, 2002, pp. 1194–1197.

[11] J. H. Nieuwenhuis, J. Bastemeijer, A. Bossche and M. J. Vellekoop, Dynamic Particle-Shape Measurements Using a Near-Field Optical Sensor, in Proc. of 1st IEEE Sensors Conference, June 12–14, 2002, Orlando, Florida, USA.