Direct Integration of Micromachined Pipettes in a Flow Channel for Single DNA Molecule Study by Optical Tweezers

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***Abstract*—We have developed a micromachined flow cell consisting of a flow channel integrated with micropipettes. The flow cell is used in combination with an optical trap setup (optical tweezers) to study mechanical and structural properties of λ-DNA molecules. The flow cell was realized using silicon micromachining including the so-called buried channel technology to fabricate the micropipettes, the wet etching of glass to create the flow channel, and the powder blasting of glass to make the fluid connections. The volume of the flow cell is 2 μl. The pipettes have a length of 130 μm, a width of 5–10 μm, a round opening of 1 μm and can be processed with different shapes. Using this flow cell we stretched single molecules (λ-DNA) showing typical force-extension curves also found with conventional techniques. These pipettes can be also used for drug delivery, for injection of small gas bubbles into a liquid flow to monitor the streamlines, and for the mixing of liquids to study diffusion effects. The paper describes the design, the fabrication and testing of the flow cell. [615]**

***Index Terms*—Buried channel technology, KOH, micropipettes, optical tweezers, powder blasting, Pyrex wafer, reactive ion etching (RIE), silicon micromachining, silicon nitride, single DNA molecule.**

I. Introduction

THE traditional techniques of studying molecule properties used in biochemistry are based on measuring a great number of molecules at the same time, therefore only average features are determined. Recent advances in scanning probe and optical techniques opened the way for single molecule detection and manipulation; scanning probe techniques allow the study of single molecules on surfaces, and optical techniques characterize it in complex environments [1].

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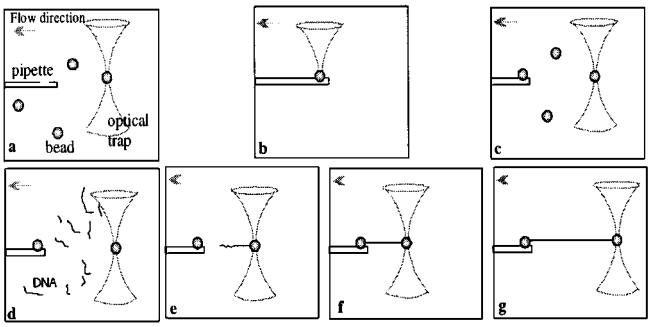


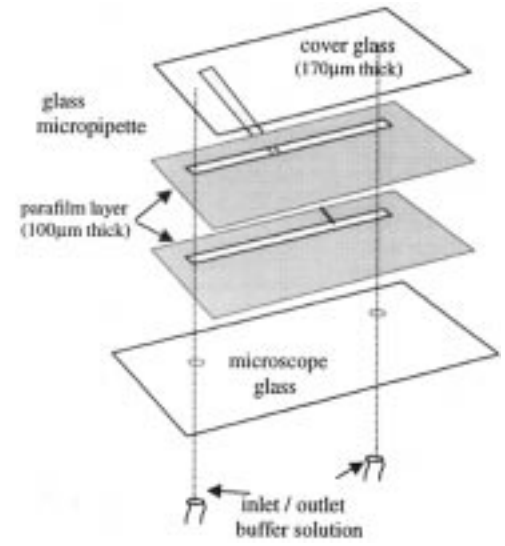
Fig. 1. Sketch of the attachment of a single DNA between two polystyrene beads, one gripped with a glass pipette and one with the optical tweezers.

Improvement of these research methods (e.g., accuracy, easyness of operation) can be done, for example, by using micromechanical technology [2]–[6]. Micromechanical structures can be developed not only aiming at applications (e.g., sequencing) but also for new investigation equipment for fundamental research [7]–[10].

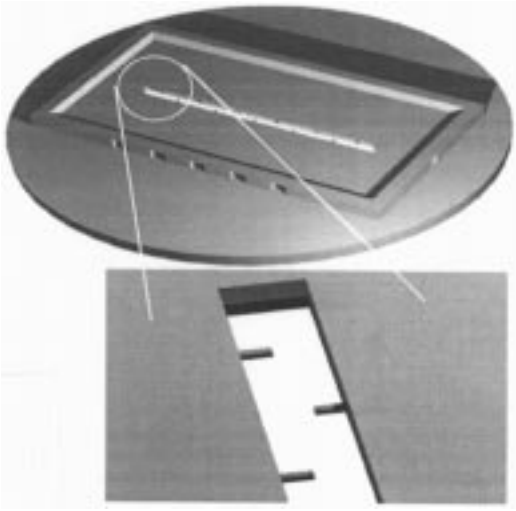
There are various ways to study mechanical and structural properties of single DNA molecules [1], [2]. One of these methods uses an optical trap in conjunction with two polystyrene beads to apply a stretching force on a DNA molecule. Each end of the single DNA molecule is biochemically bound to a bead using streptavidin-biotin. One bead is held by a capillary glass pipette and the other bead by an optical trap, which is used to apply and measure the stretching force on the DNA molecule at a certain elongation [11]–[13].

The assemble of the bead-DNA-bead system before the stretching experiment can start is, briefly, as follows. Through the flow channel a buffer with beads is flown. A bead is captured with the optical tweezers [Fig. 1(a)] and is transferred on top of the pipette [Fig. 1(b)]. A second bead is trapped by the optical tweezers [Fig. 1(c)]. Another buffer with DNA is flown through the channel [Fig. 1(d)] until one molecule sticks to the bead in the optical trap [Fig. 1(e)]. The fluid flow is used to connect the second bead to the DNA molecule [Fig. 1(f)]. After this procedure, the stretching experiment can start [Fig. 1(g)].

Although this technique reveals nicely some typical characteristics, such as the spring constant of the molecule, experiments on an assembly of DNA molecules have to be performed one-by-one. Having many micropipettes in one flow channel, parallel measurements on single molecules may be performed allowing for rapid "statistical" data acquisition.



(a)



(b)

Fig. 2. Sketch of (a) the commonly used flow cell unit and (b) the micromachined flow cell.

This paper describes a way, i.e., silicon micromachining, to integrate many pipettes in the same flow channel to allow for the just mentioned simultaneous measurements. The flow cell consists of a flow channel with integrated micropipettes. Buried Channel Technology [14] is used to make the micropipettes, wet etching of glass to create the flow channel, and the powder blasting [15] of glass to make the fluid connections. The common flow channel is made by hand by gluing two microscope cover glasses together using two parafilm as spacer, in which a glass capillary pipette is integrated [see Fig. 2(a)]. It would be easier having a flow cell with the pipettes already integrated [Fig. 2(b)].

The microfabrication method has the advantages 1) to create a flow cell in which many pipettes are already integrated into a flow channel, 2) that various shapes of the micropipettes can be obtained by using different designs and technological processes, and 3) that reproducible dimensions of the pipettes and channel are obtainable. This makes it possible to choose for each type of experiment the best pipette shape.

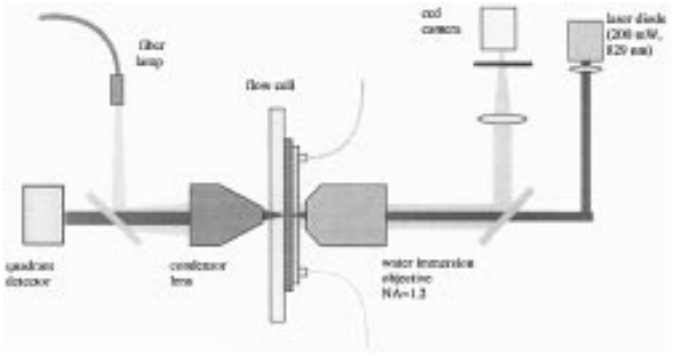


Fig. 3. Sketch of the optical trap setup with flow cell.

Besides DNA measurements, these pipettes can be also used for drug delivery, for injection of small gas bubbles into a liquid flow to monitor the streamlines, and for the mixing of liquids to study diffusion effects.

II. Setup for DNA Handling

The current optical trap setup (Fig. 3) is a homemade microscope system and a flow cell unit that are described in more details in [13]. A laser diode is used for the optical tweezers [16], in which micrometer-sized polystyrene beads can be trapped just behind the focal point of a 100× objective (water immersion, $\mathrm{NA} = 1.2$). When external forces are exerted on the trapped bead, the bead will move out of the centre of the laser beam. The transparent bead acts as a small lens and causes a deflection of the beam proportional to the force [17]. This is measured by a quadrant detector. A maximum force of 70 pN can be exerted on the bead, the optical trap stiffness is about 200 pN/μm, and the precision in determining the DNA molecule length is 5–10 nm [13].

III. Design Rules for the Flow Cell

The constraints resulting from the optical trap setup give the design rules for the flow cell.

1) The flow cell has to be optically transparent. The channel is etched in silicon, and Pyrex is chosen as a cover glass material to allow the light to pass.
2) The thickness of the cover glass must match the objective to create a good optical trap inside the flow channel. In our case, 175 μm.
3) The position of the micropipettes in the flow channel is determined by the maximum depth of the optical trap to the cover glass. In our case at about 80 μm.
4) There is a minimum width for the transparent flow channel. The maximum angle of incidence is about 65° for a beam coming from an objective with $\mathrm{NA} = 1.2$, in water. When the optical trap is at the maximum (80 μm) underneath the cover glass, the cover glass must be optically flat and transparent over a distance of at least $80\ \mu\mathrm{m}/\sin(65) = 340\ \mu$m. The flat cover glass area is chosen to be $500\ \mu\mathrm{m} \times 30$ mm.
5) The micropipette opening is defined by the bead diameter, about 2 μm; for the experiments described here we are using 2.5 μm.

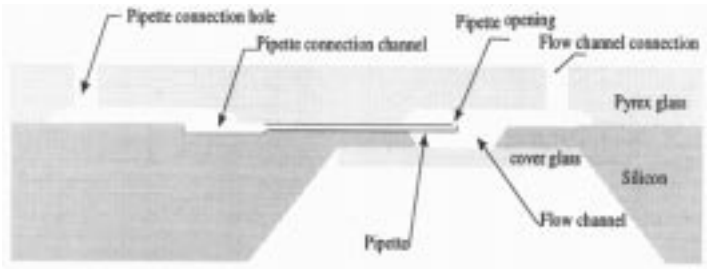


Fig. 4. Cross section of a flow cell consisting of integrated micropipette in a flow channel.

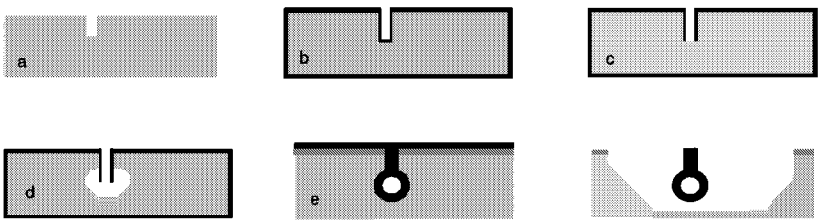


Fig. 5. Process outline of a micropipette using BCT (cross section).

6) Small sample volume, ca. 2 μl.

IV. Micromachining the Flow Cell

In Fig. 4, the general design of a micromachined flow cell is given. The fabrication of the flow channel in both Pyrex and silicon is based on bulk micromachining. The micropipettes are made of silicon nitride based on the buried channel technology (BCT) [14]. A powder blasting process [15] of Pyrex is used to enable the fluid connection for the flow channel and the micropipettes. The two wafers will be anodically bonded. The fluid interconnection between the flow cell and the setup holder uses a packing material made from a dry film resist layer.

A. Pipette Fabrication

The outline of the basic steps of the buried channel technology is given in Fig. 5. A 1-μm-wide trench, that is made in silicon by reactive ion etching (RIE) (step a) is coated with a protection layer (thermal oxide) (step b). The layer is removed from the bottom of the trench by RIE (step c), and the buried structure is made by an isotropic etch of the trench (step d). Then the protection layer is removed and the structure is made by growing in the trench a layer of LPCVD silicon nitride (step e). Next the surrounding silicon is etched away in KOH resulting in a micropipette (step f). Due to the BCT process, the opening of the pipette will be on the top side of the pipette by making the etch trench partly more wider.

The direct integration of the micropipettes in the flow channel is possible due to the fact that BCT is a single-wafer process, is self-aligned and uses one-sided processing without the need of complicated assembling techniques.

B. Different Micropipette Shapes

Based on the principle of BCT four different shaped pipettes have been processed (Fig. 6).

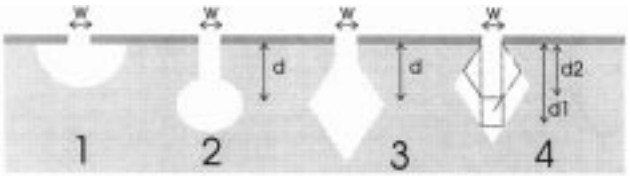


Fig. 6. Four different shapes for pipettes in silicon possible with BCT.

- Shape 1 can be made by an isotropic under etch of a slit etched in a silicon oxide mask [Fig. 6(1)]. A disadvantage of this shape is that when a bead with a DNA molecule is hold on top of the hole, the DNA may stick to the flat top of the pipette [Fig. 7(a), (b)]. A larger distance between the pipette opening, where the bead is captured, and the pipette surface would be preferable.
- Shape 2 can be achieved by an isotropic under etch of the trench done by RIE [Figs. 5(d), 6(2), 7(c), (d)] or by a wet etching. A problems with a wet etching process can be the wetting of the trench. Advantage of the isotropic etch is that the etched result is independent of the crystal orientation of the silicon with respect to the mask layout.
- When KOH etch solution is used [Fig. 6(3)], the walls of the channel will be very smooth (silicon [111] planes). Disadvantage is that the obtained result depends on the crystal orientation of the silicon.
- Shape 4 also makes use of KOH [Figs. 6(4), 7(e), (f), (i)] has the advantage that the size of the channel easily can be regulated by the trench depth, and there is no need for bottom etching of the trench. Disadvantage is again that the obtained result depends on crystal orientation.

In shape 2 and shape 3, the depth of the structure underneath the surface can be tuned by the depth (d) of the trench [Fig. 5(c)]. The trench depth is limited by the width (w) of the trench and by the maximum aspect ratio that can be achieved during RIE etching [18]. The other limit to the trench depth is the easiness in removing the trench bottom.

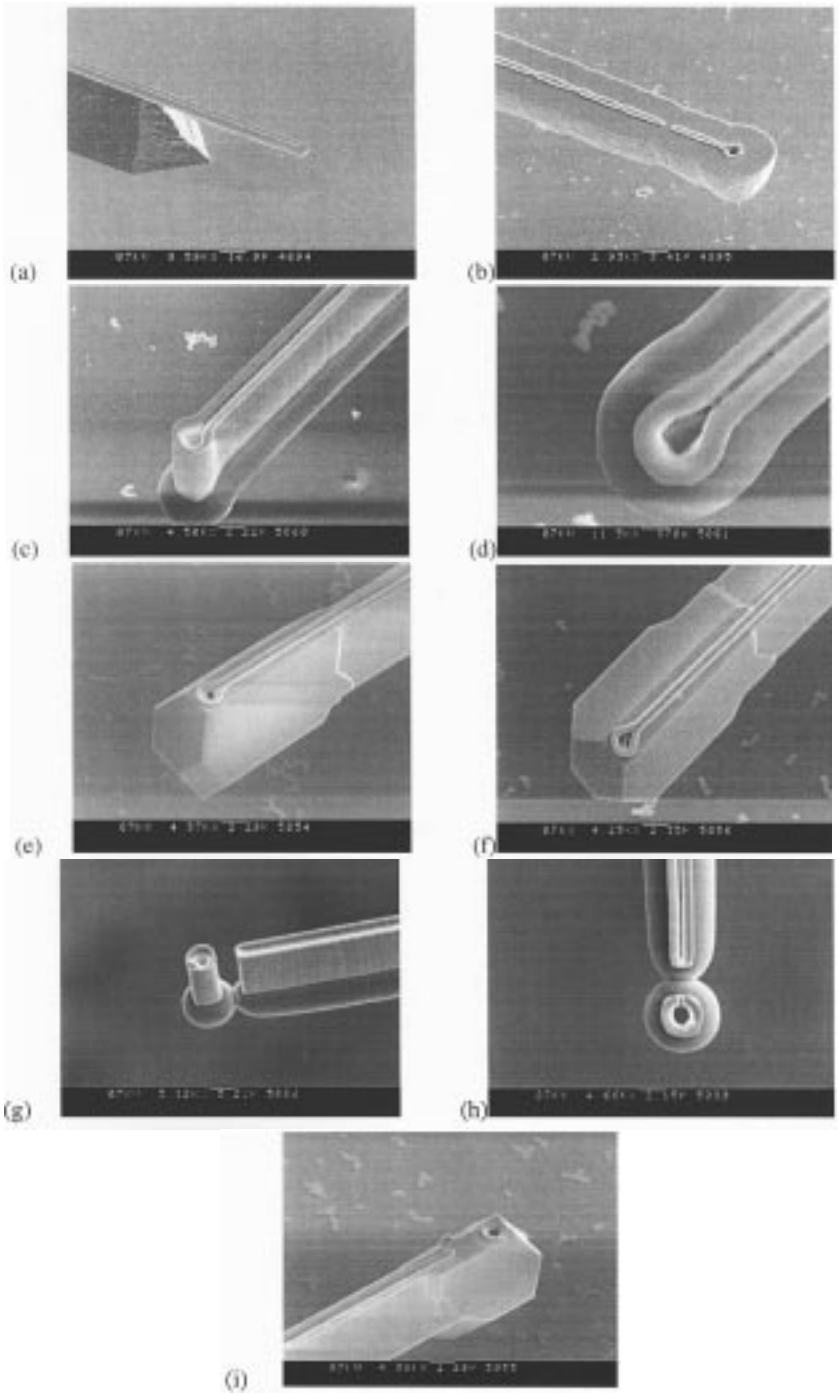


Fig. 7. (a) Free standing micropipette of shape 1; (b) detail of the pipette tip showing the hole with a diameter of 1 μm. (c) Free standing micropipette of shape 2, using mask layout I (opening 1 μm); (d) detail of this pipette tip (top view). (e) Free standing micropipette of shape 4, using mask layout I (opening 1 μm); (f) detail of this pipette tip (top view). (g) Micropipette of shape 2, using mask layout II to achieve a more circular-like opening; side view; (h) top view. (i) Micropipette of shape 4 (KOH shape), usng mask layout II.

C. Integration of Micropipette Opening

The mask layouts shown in Fig. 8(a) are used to integrate an opening for the pipette. All the process steps from Fig. 5 step (a) until step (e) are done with this mask. Cross sections in direction of B, C, D, and A, are shown in Fig. 8(b) and (c), respectively. The circular opening in the mask layout of type I is deformed by the influence of the trench as can be seen in Fig. 7(c), (d). Due to this artefact, a second mask layout, type II, has been integrated. As can be observed in Fig. 7(g)–(i), the mask layout type II gives better results for the pipette opening definition since the opening is separated from the trench.

The connection of the pipette opening to the pipette tube with mask type I is automatically done when the trench is etched (step (a) in Fig. 5). For the mask type II, until step (c), the two parts of the pipette are still separated. Due to the under etching of the trench in step (d) the two parts will connect [Figs. 8(c) and 7(g)–(i)].

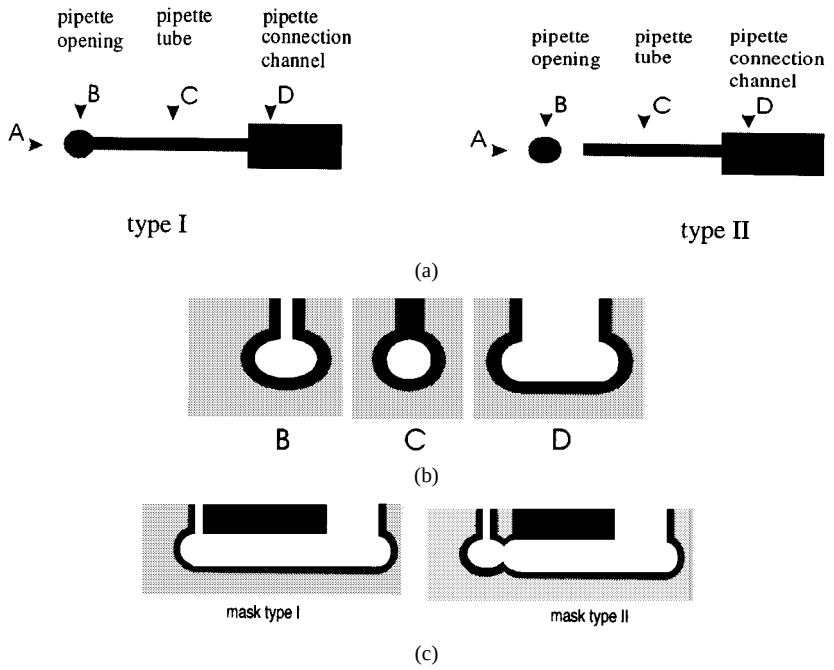


Fig. 8. (a) Two different mask layouts (top view) to integrate an opening in the pipettes made by BCT. (b) Cross section in the B, C, and D plane of the buried channel. (c) Integration of the micropipette opening: cross section of the pipette in direction of A using the two mask layouts.

Many micropipettes are simultaneously integrated in a flow channel of 100 μm height, 500 μm wide and 3 cm long (Fig. 9). This small channel volume, 2 μl, requires only very small sample volume. The micropipettes shown have a length of ca. 130 μm, width of 5–10 μm, and a circular-like opening of 1 μm.

D. Flow Channel

From Fig. 4 it can be seen that the micropipettes connections and the upper part of the flow channel are made in Pyrex glass. The Pyrex wafer is patterned and etched in 50% HF solution by using a 1 μm sputtered silicon layer as mask. The next step is the powder blasting through the Pyrex wafer creating the 300 μm diameter connection holes [15]. For this, a layer of dry film resist (Ordyl BF405) is deposited on the other side of the Pyrex wafer (not the structured side) and patterned with photolithography and developed in 0.2% Na_2CO_3 solution. Then, the Pyrex wafer is diced, the sputtered Si mask is removed by KOH and the flow channel side is anodically bonded to the silicon wafer in order to assemble the flow cell.

E. Holder and Device Connection

The fluidic connections between the flow cell and a holder uses a new packing material instead of a macroscopic connection (like a Viton O-ring causing a large dead volume). This packing material is, again, the dry film resist (Ordyl BF405). The dry film is patterned with photolithography. After drying, the film is applied onto the flow cell and heated to 100°C for a good adhesion. When the flow cell is mounted into the holder, a simultaneously clamping and heating of the Ordyl is done for a tight connection. A schematic representation of the connection between the flow cell and holder is shown in Fig. 10.

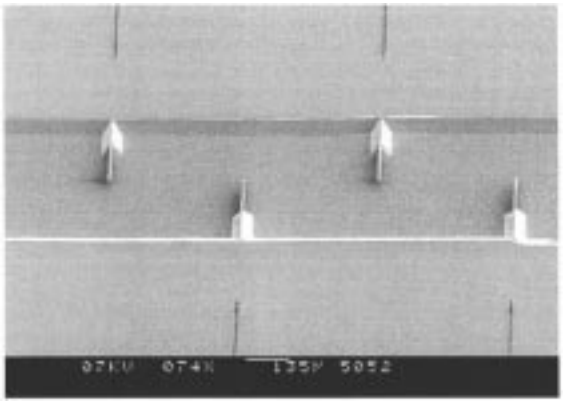


Fig. 9. Several micropipettes on their silicon support above the surface.

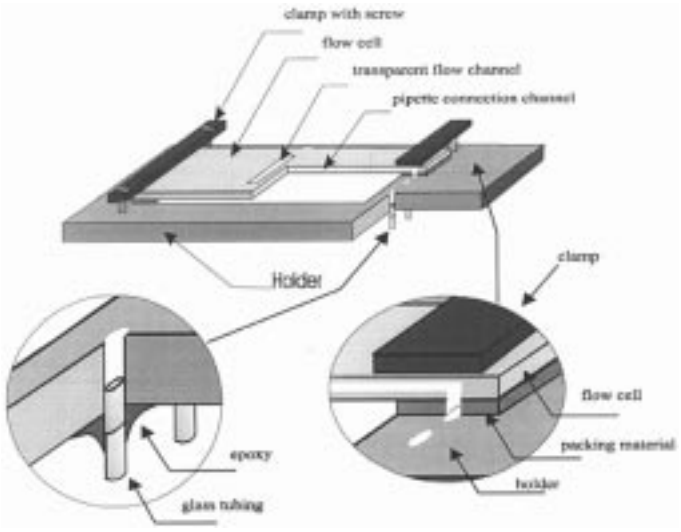


Fig. 10. Overview of the holder with details of connections.

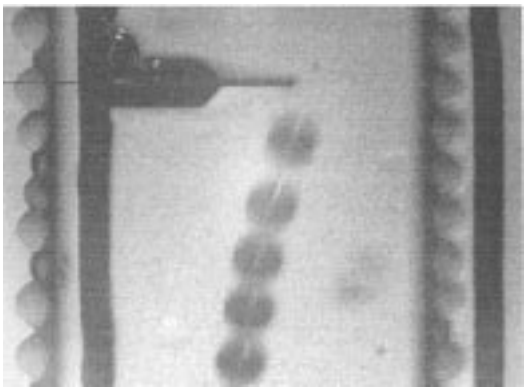


Fig. 11. Making air bubbles with a silicon nitride micropipette in a flow channel.

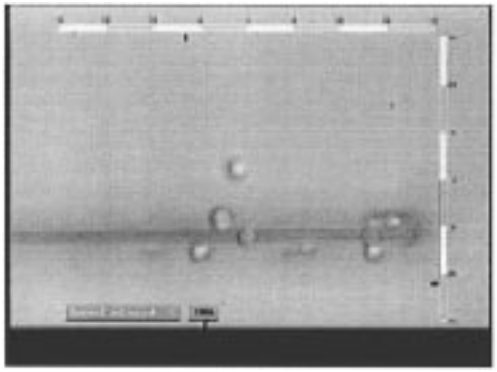


Fig. 12. Sticking of polystyrene beads on a silicon nitride micropipette.

V. Results and Discussions

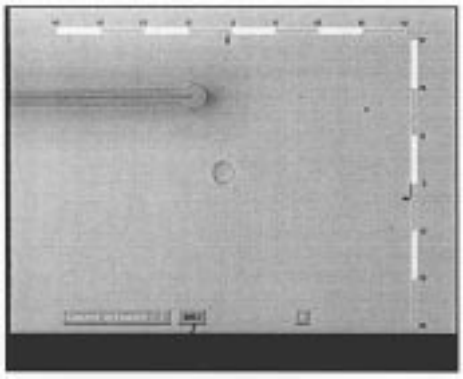
Tests, performed with shape 2 micropipettes, have shown that the pipettes are open (Fig. 11). As can be seen the micropipettes can be used to locally inject small air bubbles into a fluid flow.

From the first experiments with the polystyrene beads and micropipettes in a flow channel it could be seen that the beads were sticking to the silicon nitride. Fig.12 shows a lot of beads sticking to the micropipette. The strength of the sticking force is such that the beads could not be released with the optical tweezers ($\sim$70 pN). The beads on the pipette could easily be removed when the flow cell was washed with 1% SDS (sodium dodecyl sulfate) solution or with BSA (bovine serum albumin).

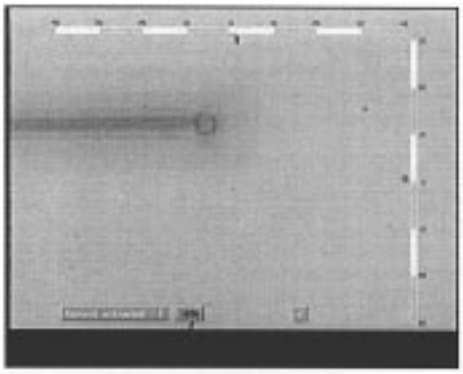
Fig.13(a) shows a micropipette and a bead that is gripped by the optical tweezers. Then, the bead is transferred to the pipette opening and gripped, Fig. 13(b).

In Fig. 14(a), the DNA molecule is held in between the beads, and the force sensor marker shows zero force. Of course, the DNA itself can not be seen using optical wavelength due to its extreme small diameter (2 nm). By moving the pipette away from the optical trap the DNA molecule is stretched, Fig. 14(b).

The force-extension curve obtained with the micromachined flow cell and micropipettes, Fig. 15(a), shows a similar behavior

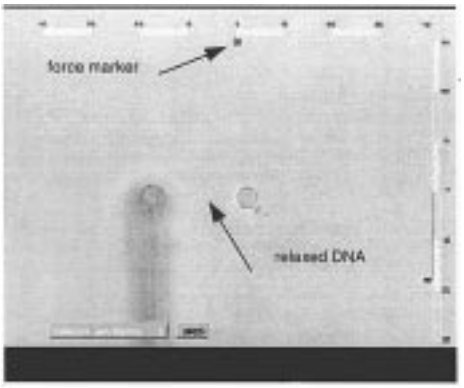


(a)



(b)

Fig. 13. (a) A 2 μm polystyrene bead hold by the optical tweezers next to the micropipette. (b) The bead is gripped by the micropipette.



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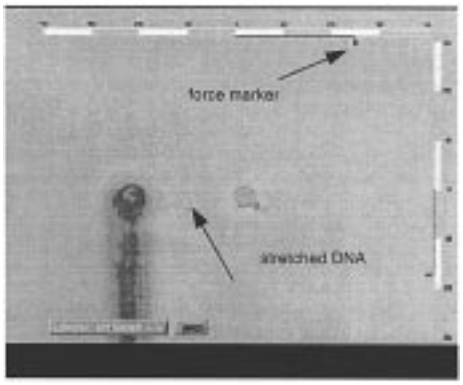
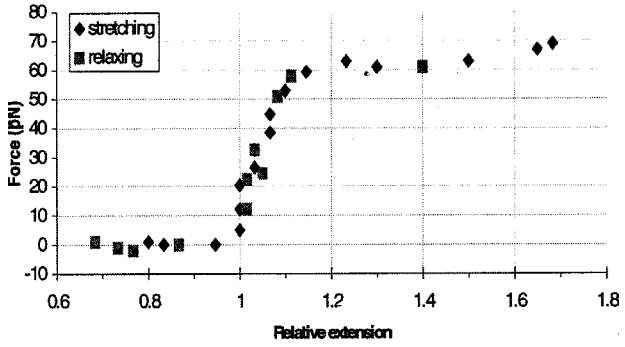
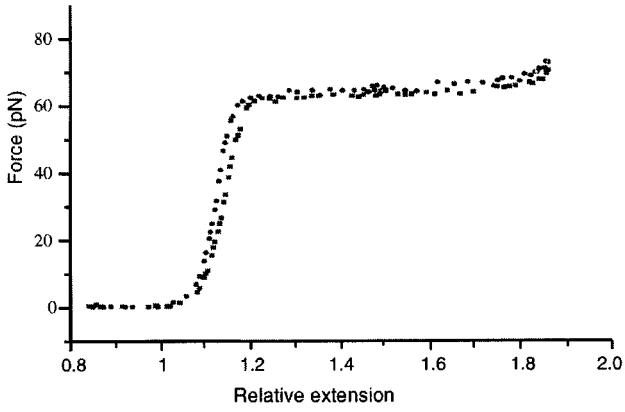


(b)

Fig. 14. Two beads gripped on a micromachined pipette and by the optical tweezers having a DNA molecule (not observable) hold in between: (a) no force applied and (b) 30 pN force applied.



(a)



(b)

Fig. 15. (a) Experimental stretch measurements with the micromachined flow cell and the micropipettes. (b) Experimental stretch measurements with the conventional flow cell and the capillary pipettes [13].

as the typical one [Fig. 15(b)] [13]. There are two curves. The diamond points represent the stretching of the DNA, and the square points are measured during the relaxation of the same molecule.

The behavior of the single molecule up to a few pN is the entropic elasticity as described by [11]. As soon the contour length of DNA is reached (relative extension $L/L_0 = 1$) the force increases very fast up to about 60 pN. For L/L_0 between 1 and 1.1 the DNA shows a spring-like behavior with a low stiffness. Above this level the DNA molecule is stretching out within a force of only a few pN.

An effect was observed when the optical trap was brought within 5 μm from the pipette: the light from the laser was deflected by the pipette. The light of the laser beam diverges rapidly below the bead given an incorrect force measurement. However, the present micropipettes (ca. 12 μm high, 5–10 μm width) are suitable for the study of the mechanical properties of long DNA molecules (>10 μm).

For chemical study of DNA, shorter DNA molecule (5 μm) has to be used. For this investigation, the micropipettes have to be downscaled. A smaller pipette (diameter 2–3 μm) can be constructed by etching a less deep trench with a smaller width (<1 μm) and reducing the etch time of the isotropic etch [Fig. 5(d)].

VI. Conclusion

We have demonstrated the possibility to integrate micropipettes into a flow channel to study mechanical and structural properties of DNA molecules. Moreover, various shapes of the micropipettes have been fabricated having the convenience of choosing for each type of experiment the best pipette shape and size. The conventional flow cell with glass capillary pipettes have been replaced successfully by this micromachined flow cell. Force-extension curves from both the conventional and micromachined technology were found to be in excellent agreement. For chemical study of DNA, the micropipette should be downscaled.

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