The Abdus Salam International Centre for Theoretical Physics

United Nations Educational, Scientific and Cultural Organization

IAEA

310/1828 310/12

Workshop on Biomedical Applications of High Energy Ion Beams

Co-sponsored by: ICGEB and University of Surrey

12-16 February 2007

Venue:
Adriatico Guest House Giambiagi Lecture Hall
ICTP, Trieste, Italy

Using Ion Beams to Analyse Biomedical Materials on the Micro and Nano Scale

Frank WATT
National University of Singapore, Singapore

Photonics applications

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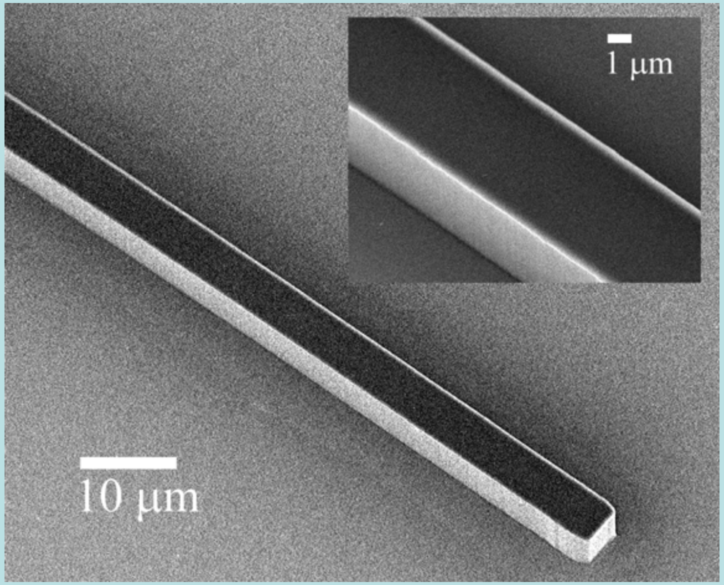
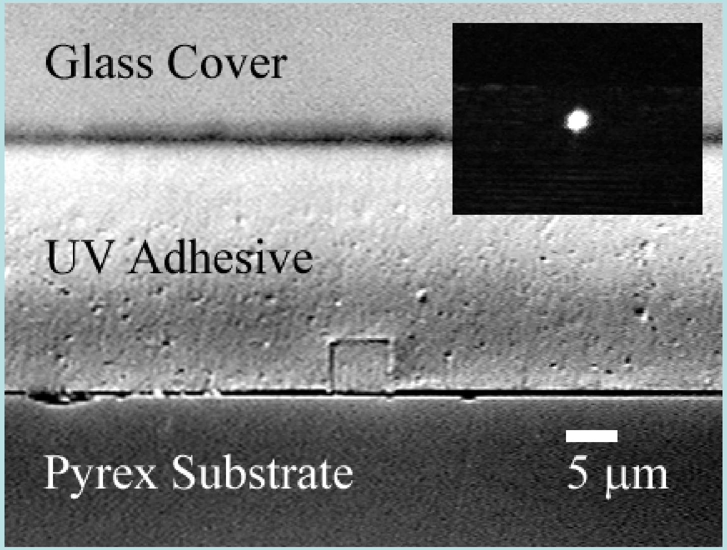
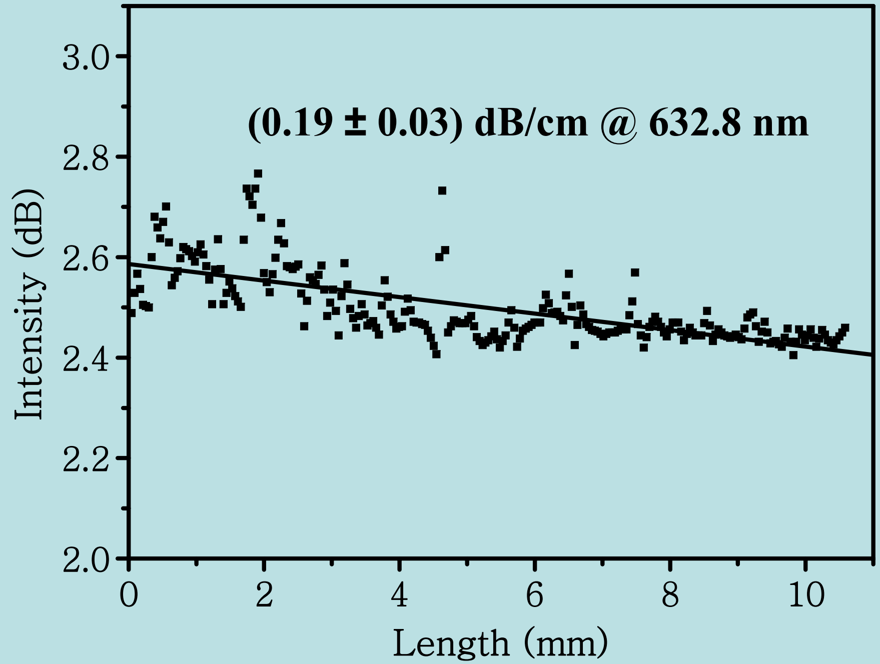




The waveguides fabricated using p-beam writing have smooth and vertical sidewalls, and exhibit low loss



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Photonics applications

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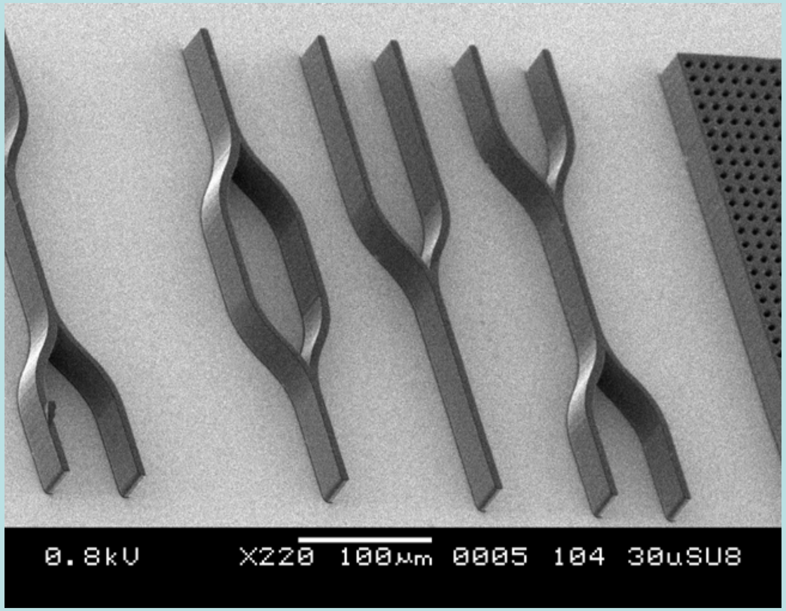
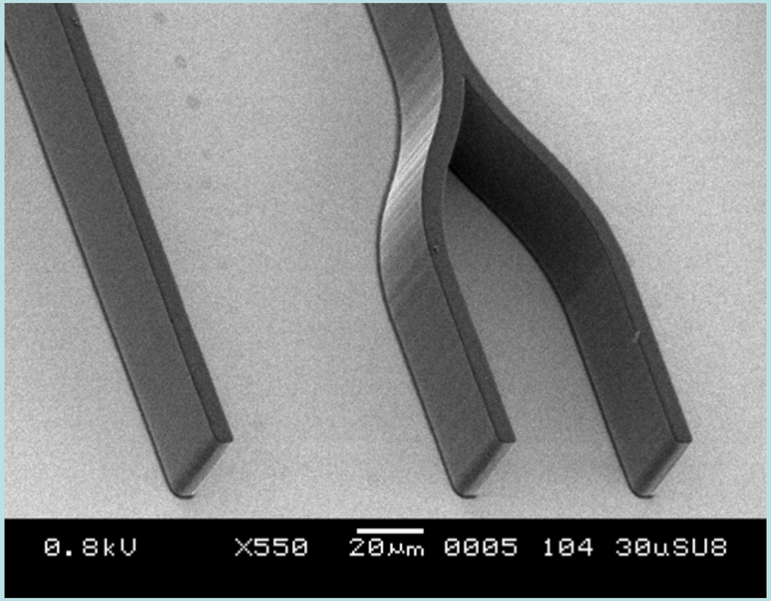
Free standing waveguides and optical components:





Test **waveguide structures** showing the side wall smoothness and orthogonality that can be achieved using p-beam writing. These structures were fabricated in a 30 µm layer of SU-8 spin coated on a silicon wafer.

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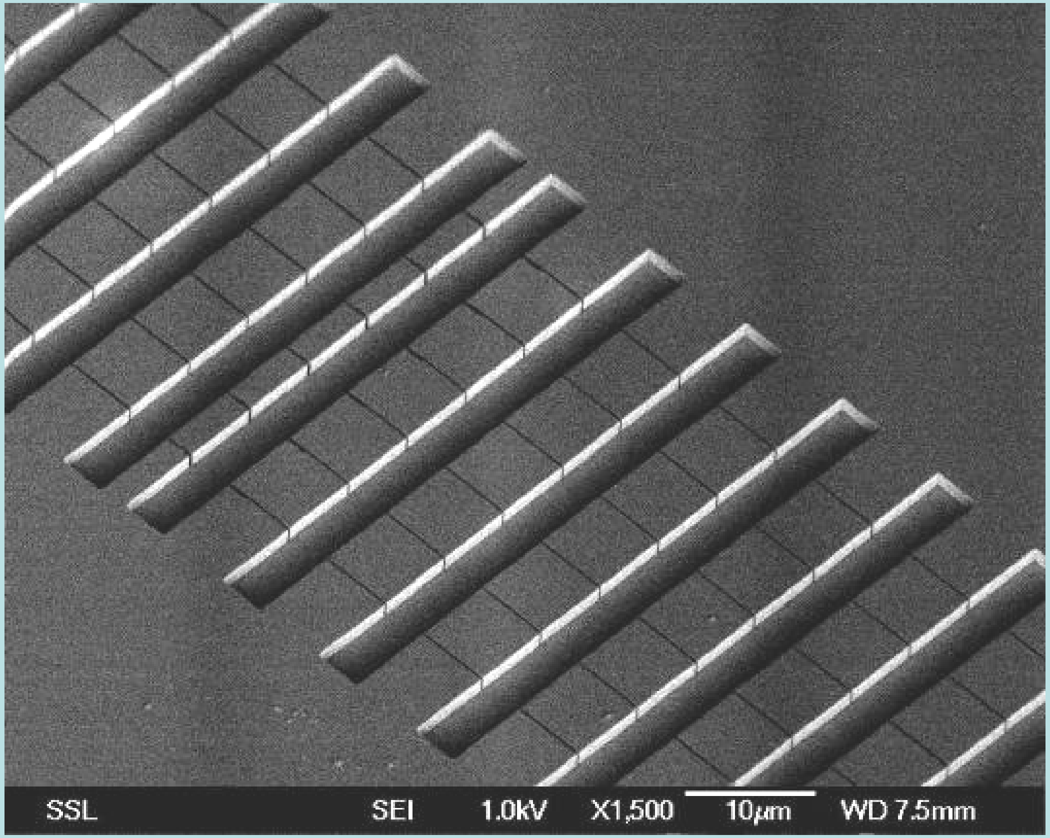
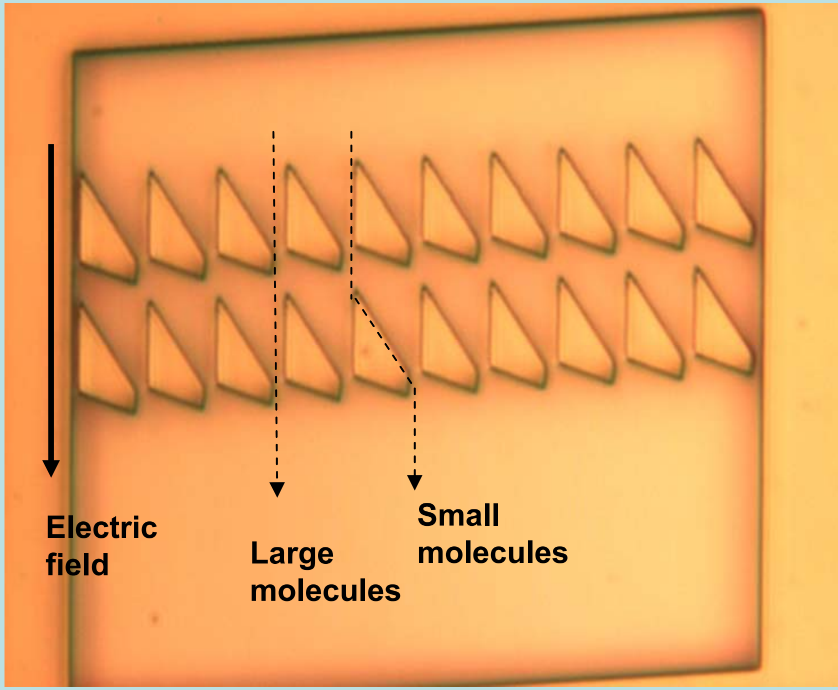
Biochip applications

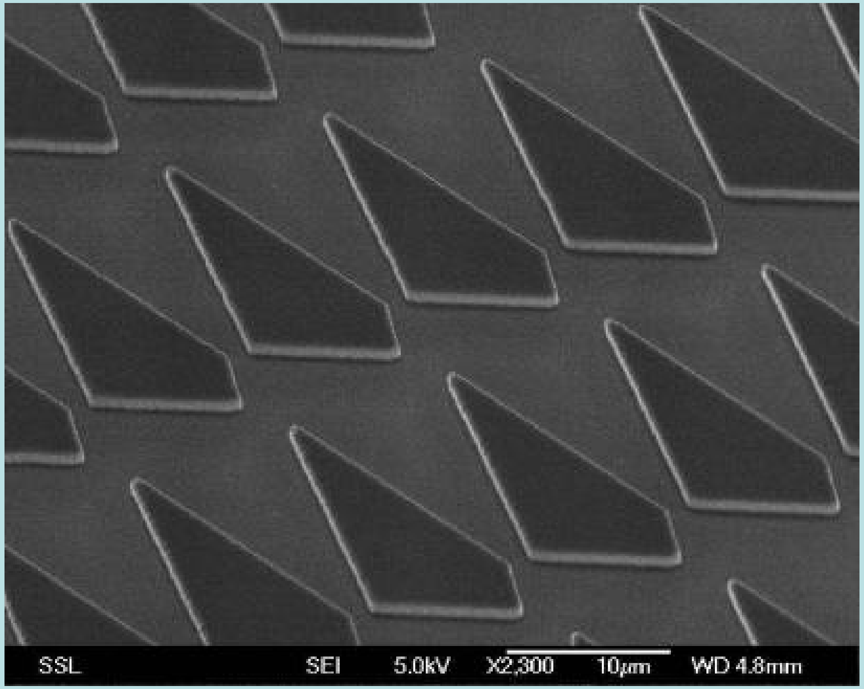


DNA – Protein sorting using entropic trapping

A series of reservoirs are connected by 100nm wide channels: When an electric field is applied along the channels, the DNA is stretched through the nanochannels at a rate which depends on the size and unfolding characteristics of the DNA.

Biochip applications





DNA – protein ratchet sorter: Using a combination of Brownian motion and Electrokinetic force, large molecules drift vertically through the obstacles, whereas the smaller molecules are ratcheted to the right.

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Advanced applications

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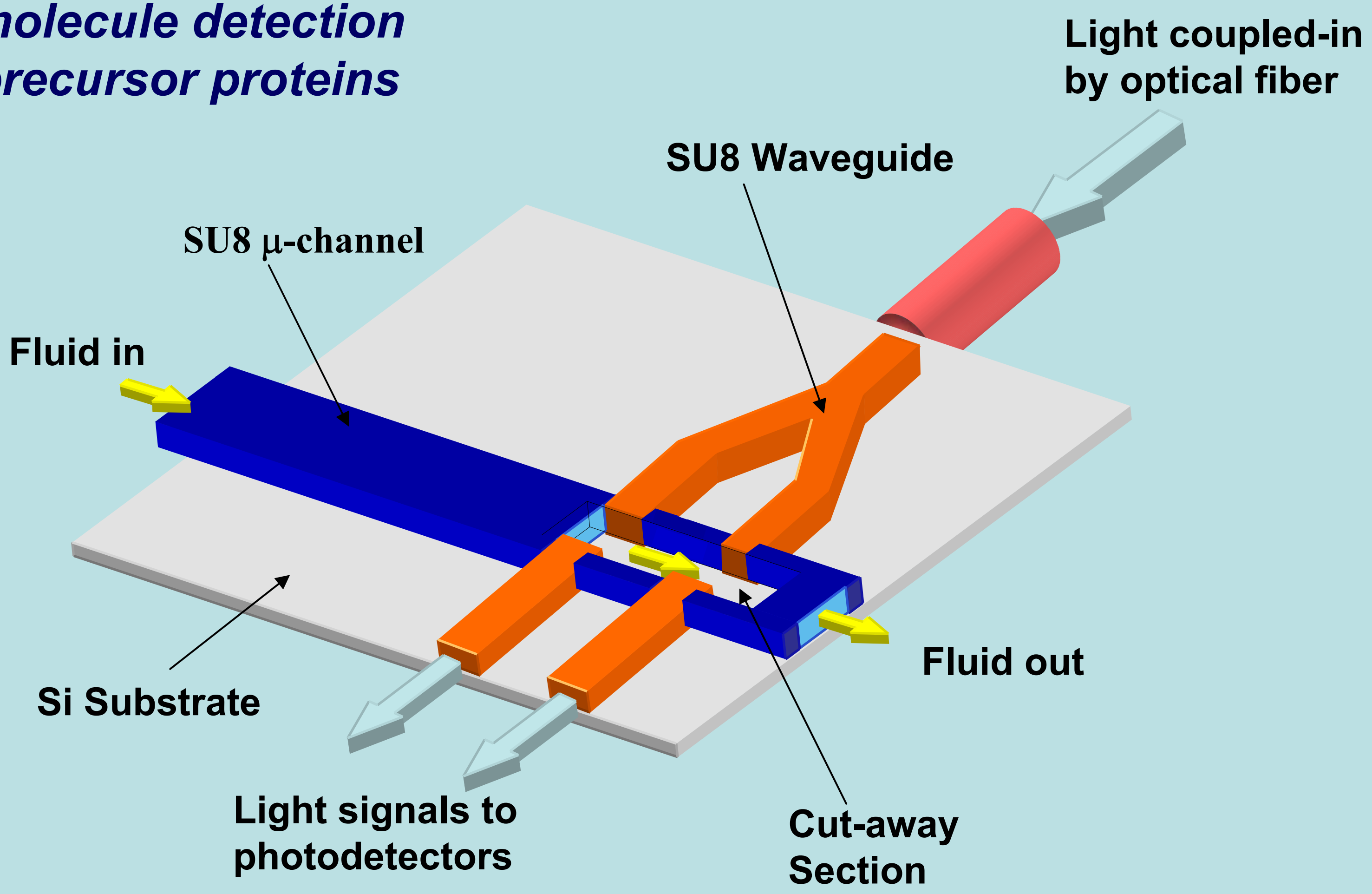
Integration of micro-photonics with μ-fluidics

Single molecule detection for AD precursor proteins



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Advanced applications

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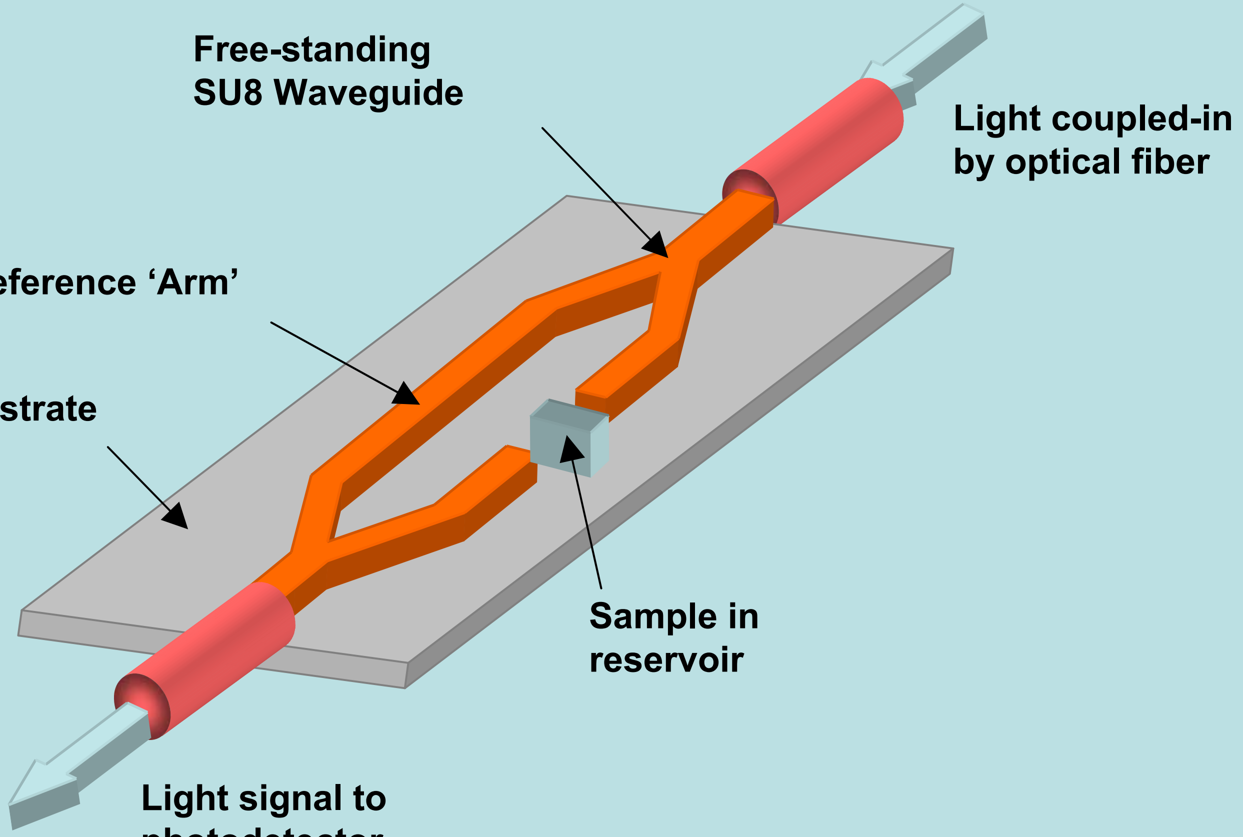

Waveguide Sensors:

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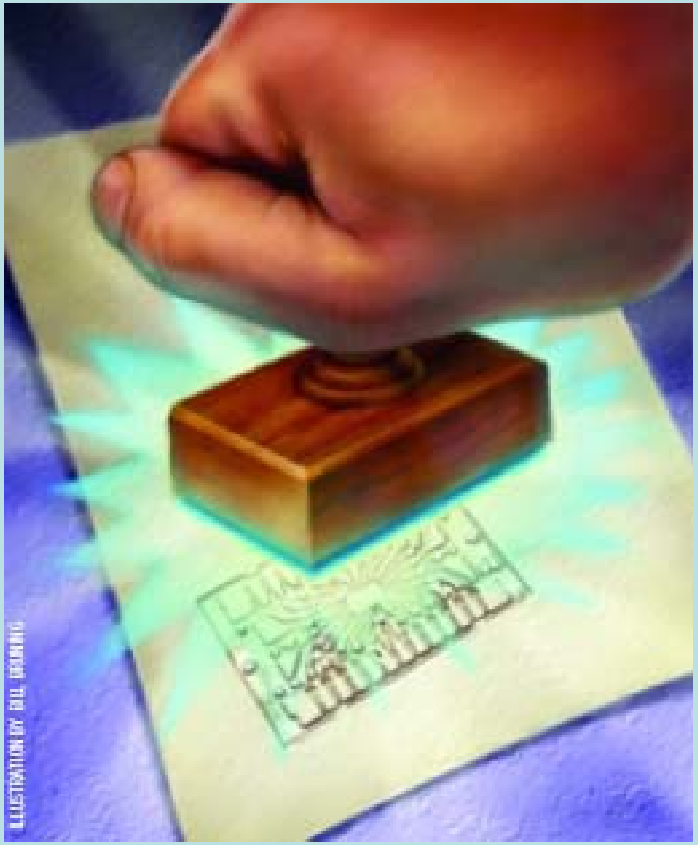
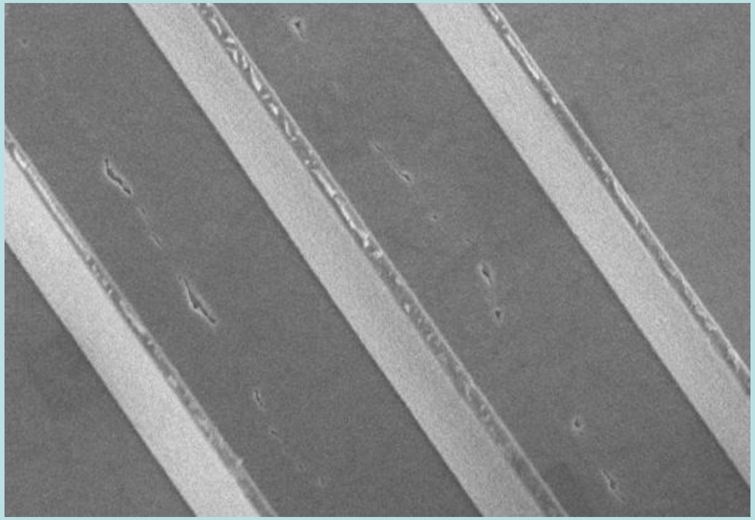
Imprinting and molding

Proton beam writing is as fast (or maybe faster than) e-beam writing. However these techniques are serial techniques (writing structures one at a time).

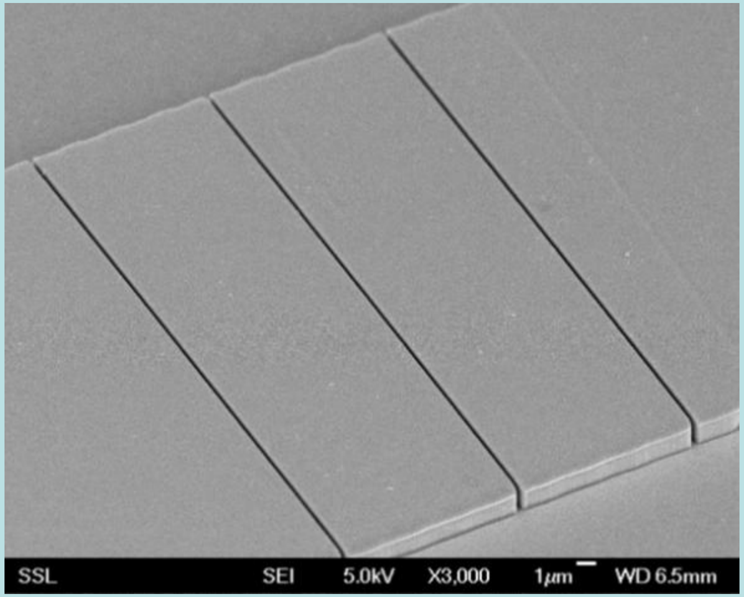
If we use p-beam writing to make stamps and molds for imprinting, then we can mass produce devices…..



IMPRINTING

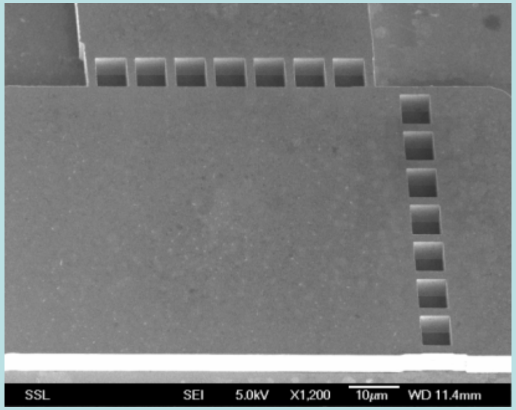


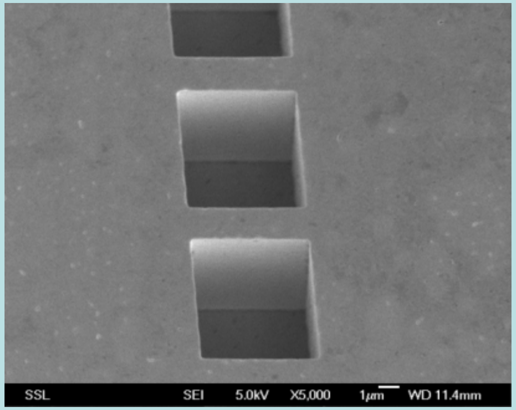
- A structure is made in PMMA using proton beam writing.
- The structure is electroplated to make a metallic (nickel) negative – eg 100nm nickel stamp, 2 microns deep.
- The PMMA is chemically removed



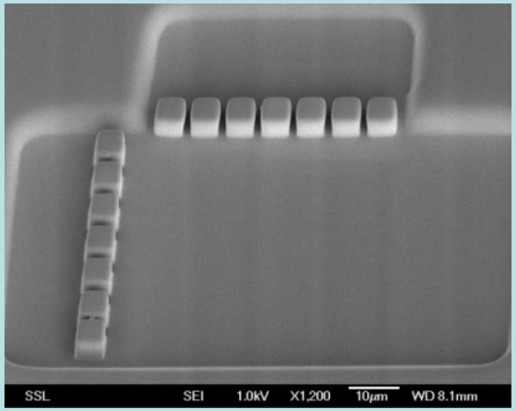
An imprint of the nickel stamp is made in polymer using hot embossing – heating the polymer up to its plastic temperature and pressing the stamp into the hot polymer.

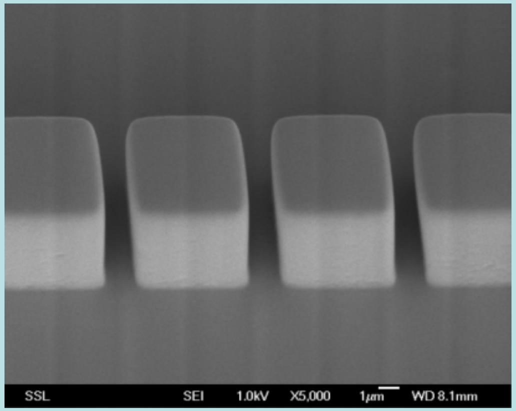
MOLDING





- A structure is made in PMMA using proton beam writing.
- The structure is electroplated to make a metallic (nickel) negative -
- The PMMA is chemically removed leaving a high quality 3D stamp.





PDMS is poured into the mold, allowed to set, and released. The structure can be bonded onto glass eg to form a biochip cell sorter……

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Biosensor applications

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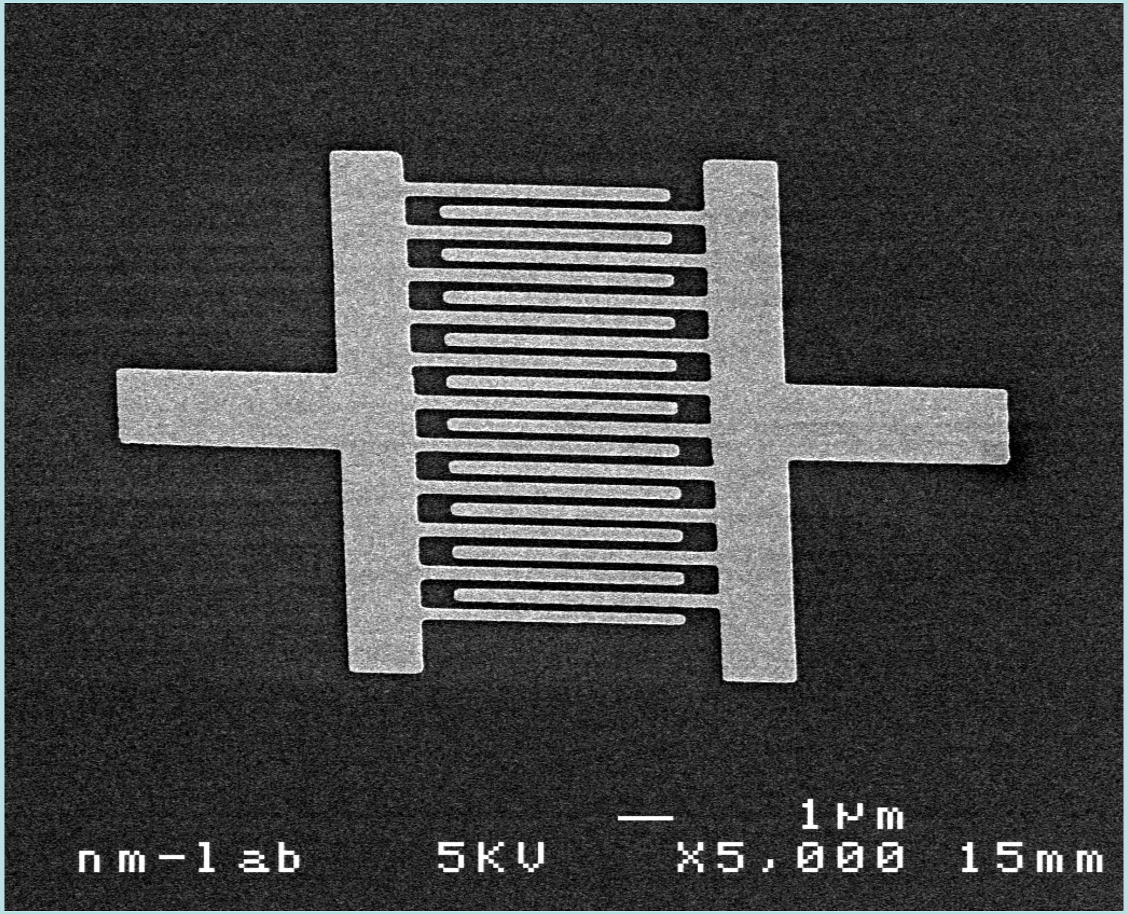
SEM image of a prototype inter-digitated nano-biosensor structure with 85 nm gaps, using proton beam writing and metal lift-off.

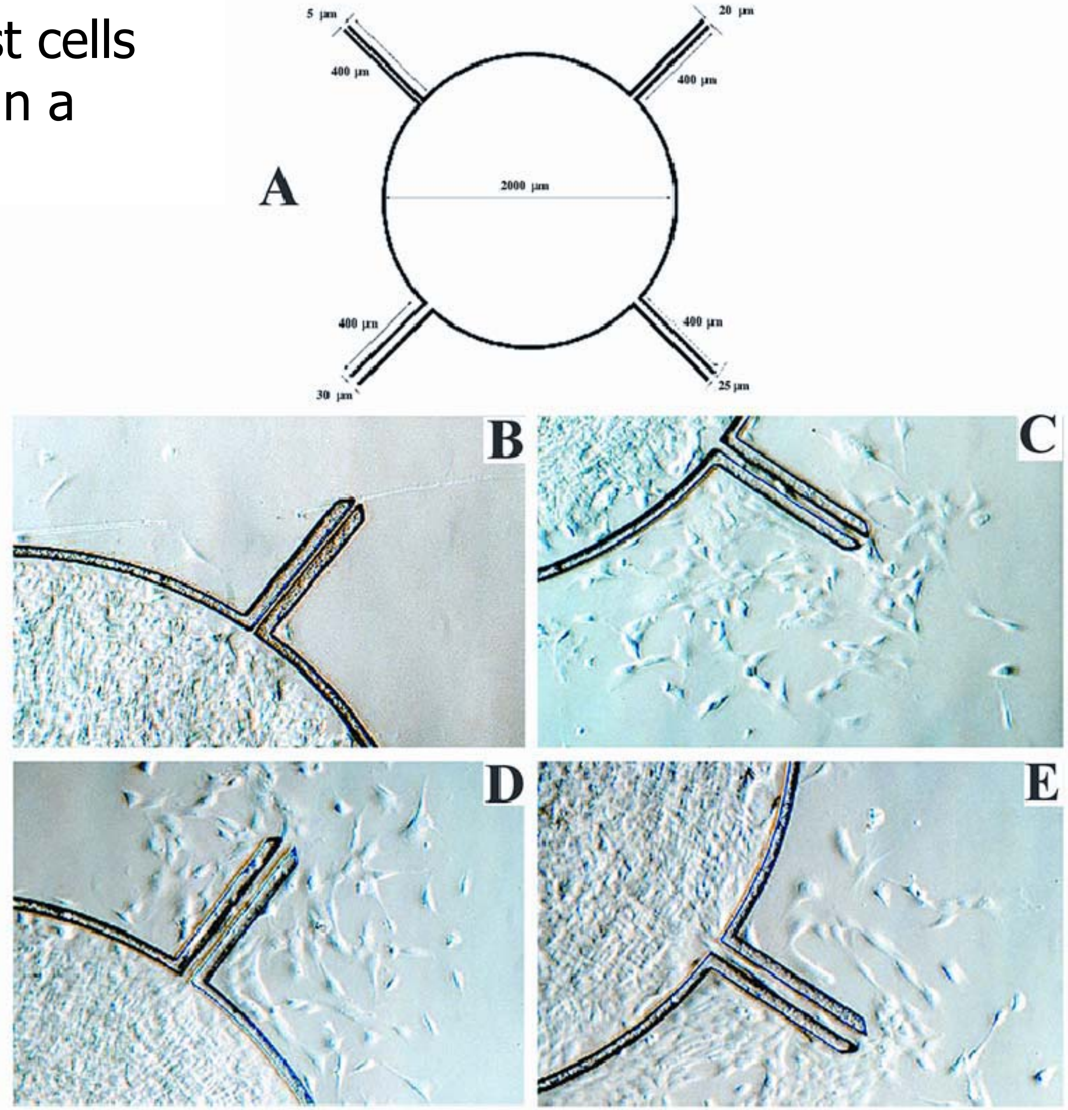


Lithography of high spatial density biosensor structures with sub-100 spacing by MeV proton beam writing with minimal proximity effects.

Nanotechnology 15 (2003) 223-226. HJ Whitlow, ML Ng, V Auzelyte, I Maximov, L Montelius, JA van Kan, AA Bettiol and F Watt.

Cell behaviour studies

Fibroblast cells trapped in a 'corral'



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Cell behaviour studies

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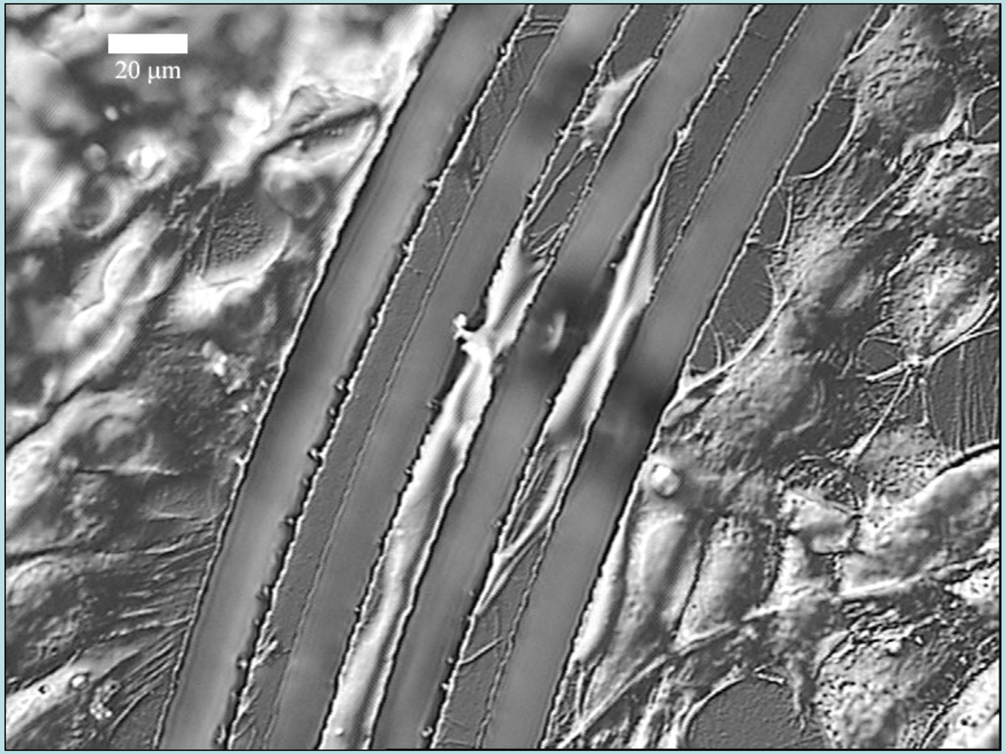

Cells align on ridge structures that are narrower than the natural cell width…. Tissue engineering applications

CIBA Cell biomechanical studies

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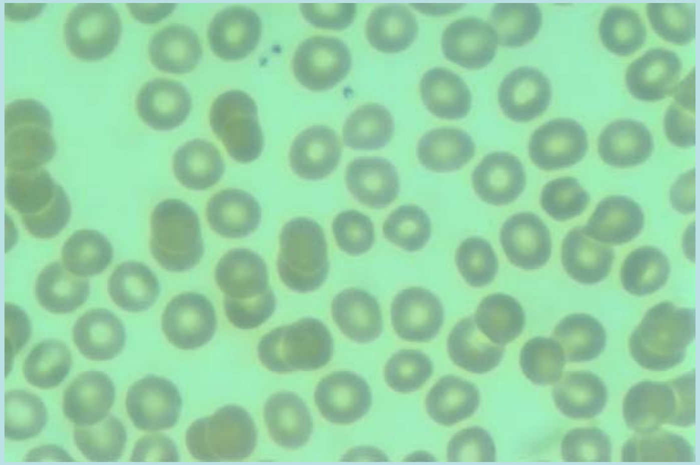
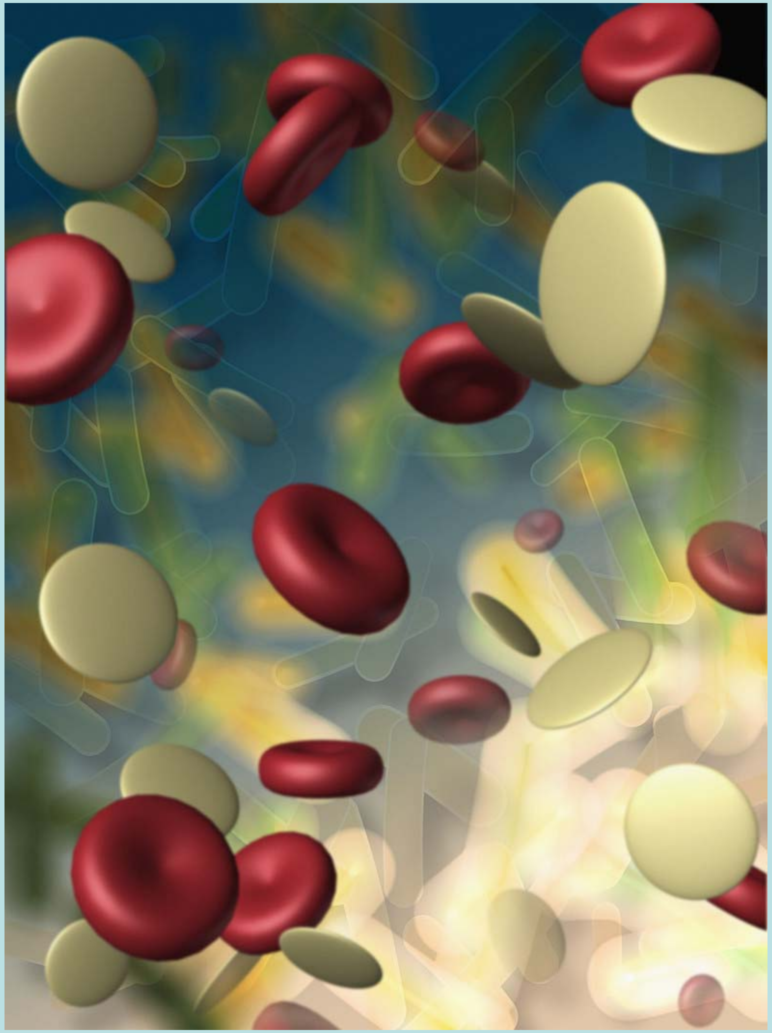
Human Red Blood Cell behavior in PDMS microchannels:

Biomechanical properties

Biconcave shape observed
under optical microscope





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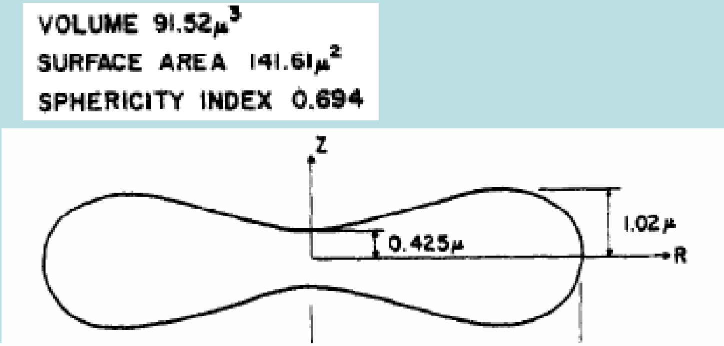
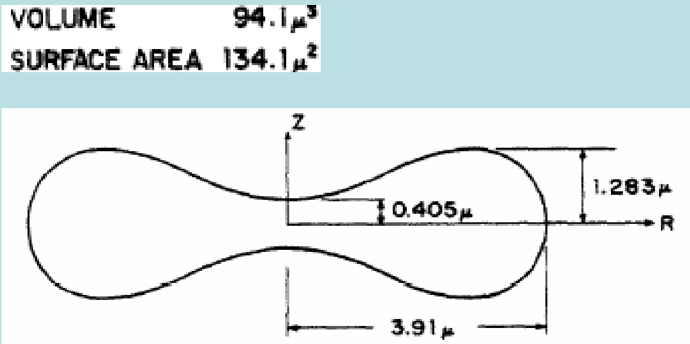
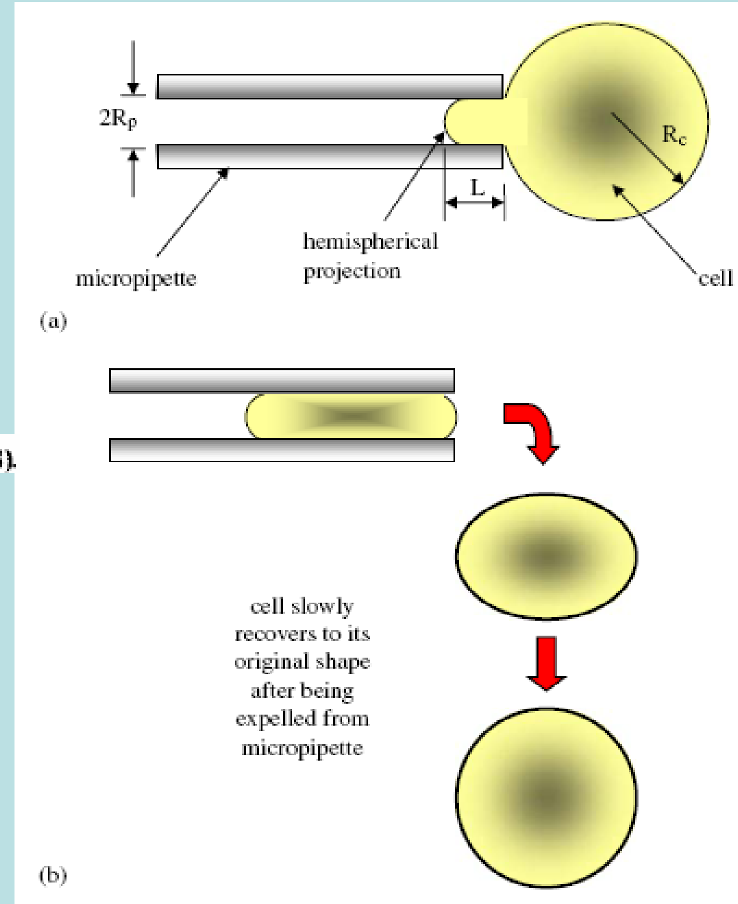
Red blood cell shape and its viscoelastic transporting model



Unstressed shape of the red blood cell, adapted from Fung and Tong (1968).



normal red blood cell shape measured by Evans and Fung (1972).



Viscoelastic behavior of a red blood cell through micro capillary

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Channel Design

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- Four kinds of PDMS channels (made from a metallic mold fabricated using p-beam writing and electroplating) were designed to study the cell deformability:

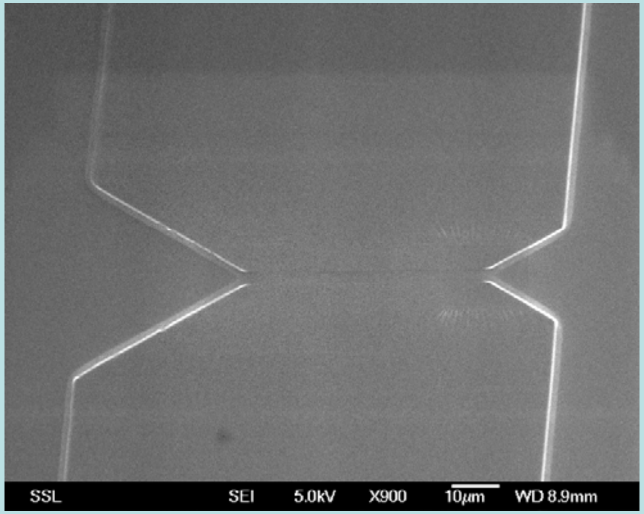
8μm(w) x 2μm: no deformation

6μm(w) x 2μm: slightly stretched

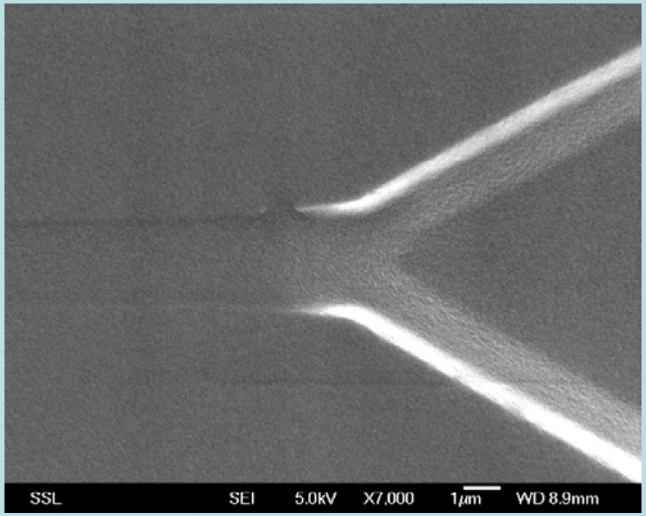
4μm(w) x 2μm: notable stretching

2μm(w) x 2μm: maximal stretch in microchannels;

52μm(L): sufficient traveling distance to monitor single cell movement.



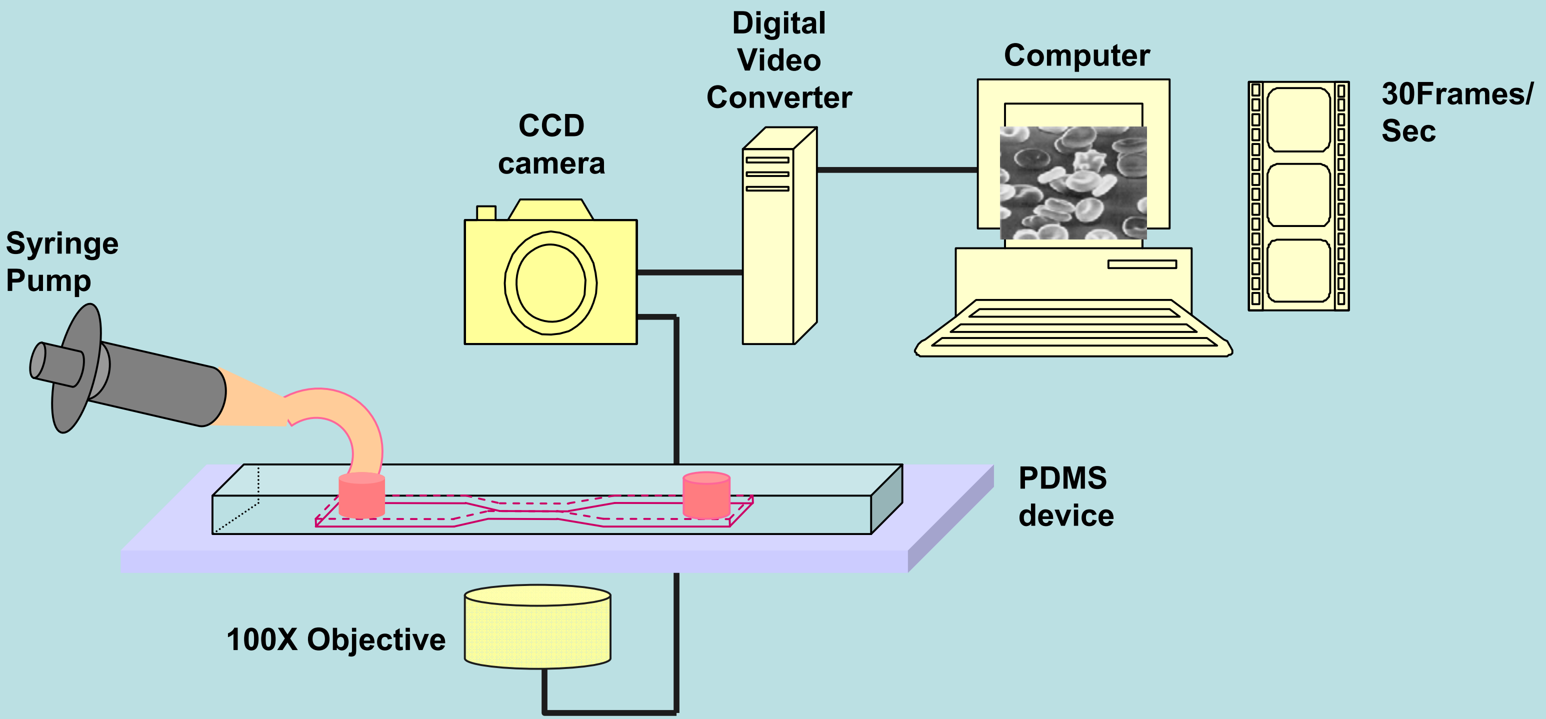
(a)



(b)

SEM images of 2um wide PDMS channel

Experimental set up and sample preparation



Preparation of blood sample:

Drawing fresh blood in micro liters from healthy adult;

Diluting with 1XPBS (1mM Phosphate Buffered Saline) to 3~5% ;

Vibrating mixing for 1 min.

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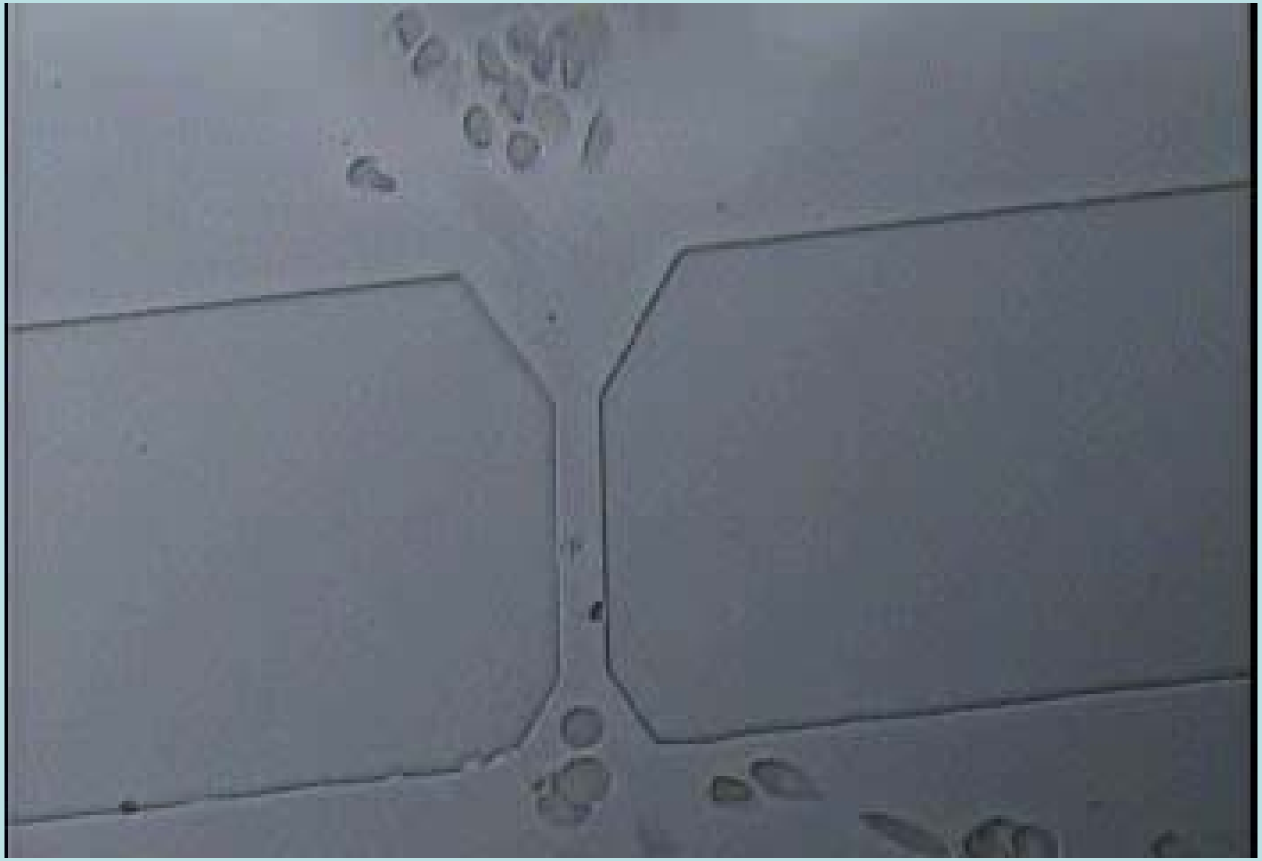
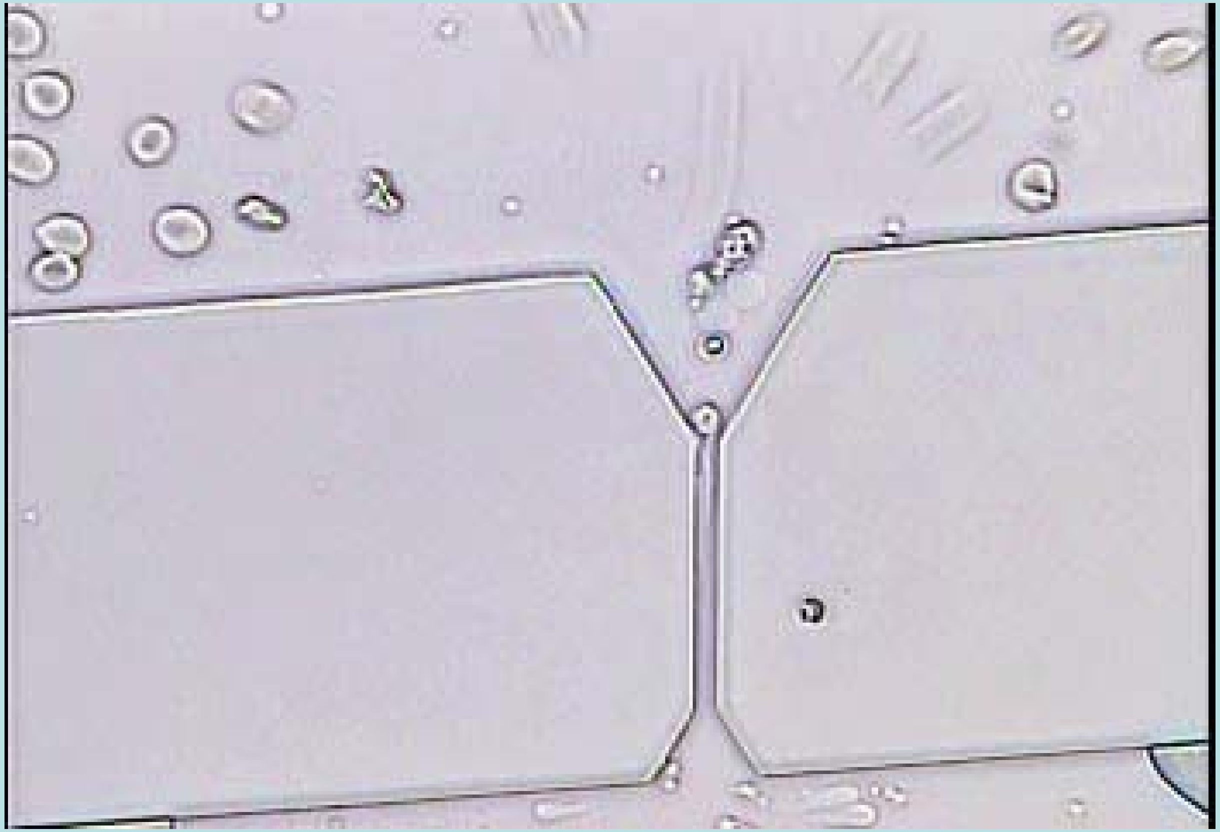


8µm(w) x 2µm: no deformation



6μm(w) x 2μm: slightly stretched

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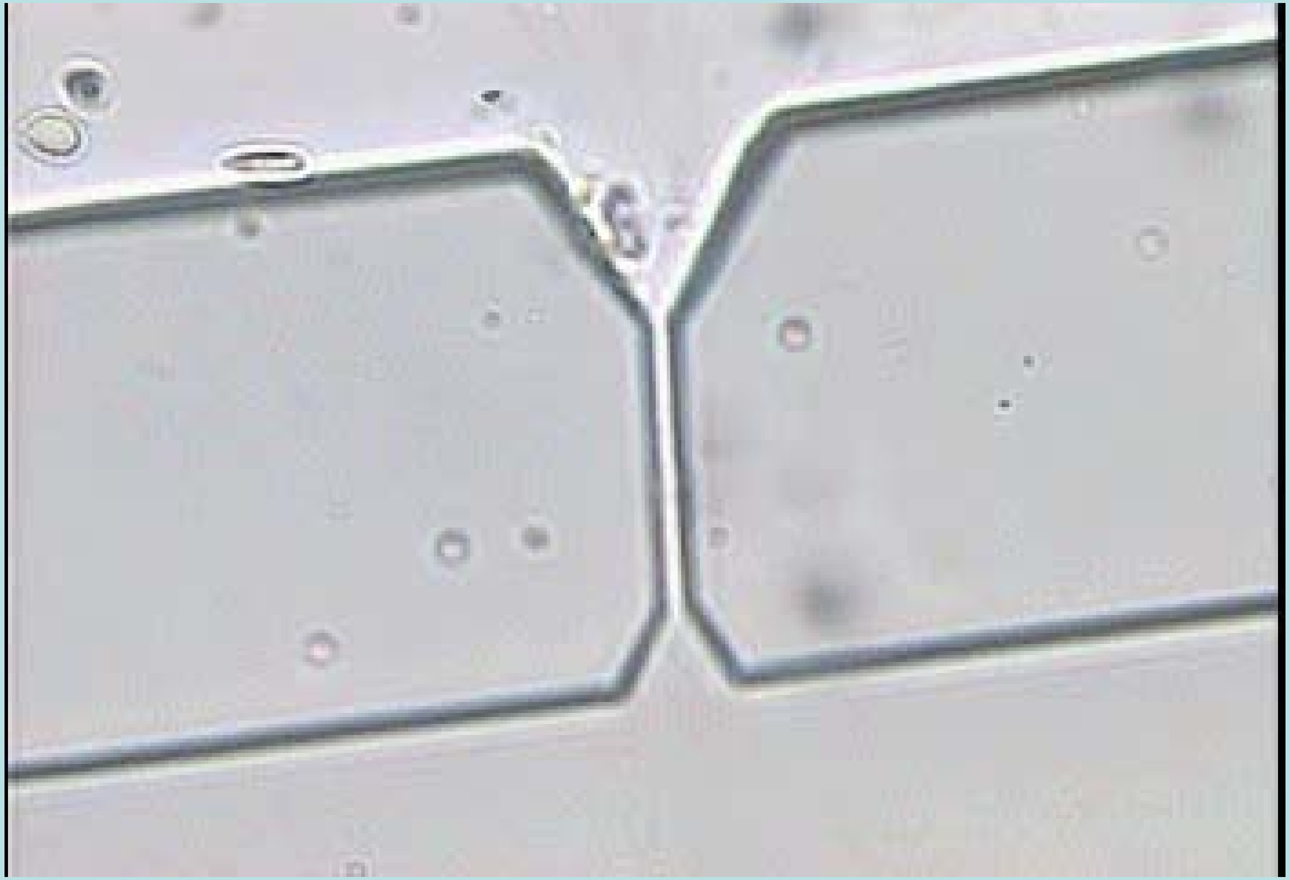
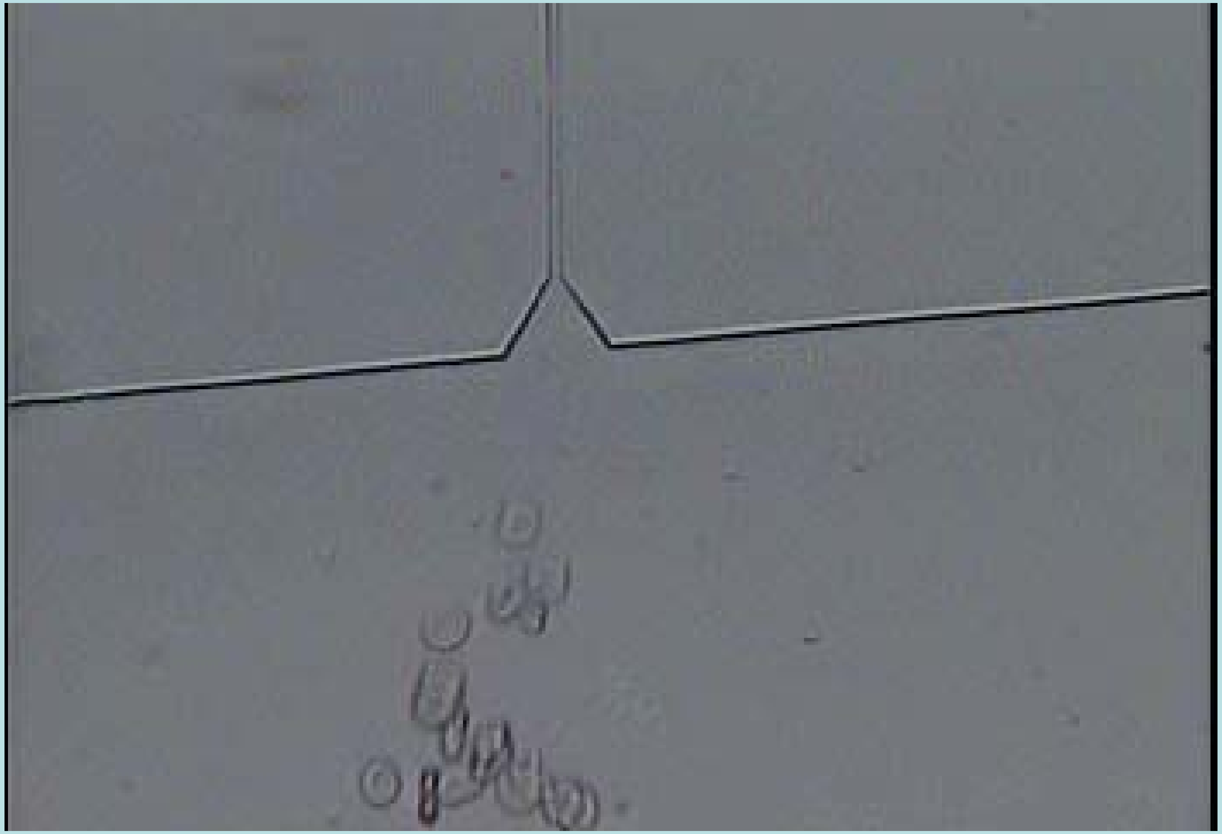


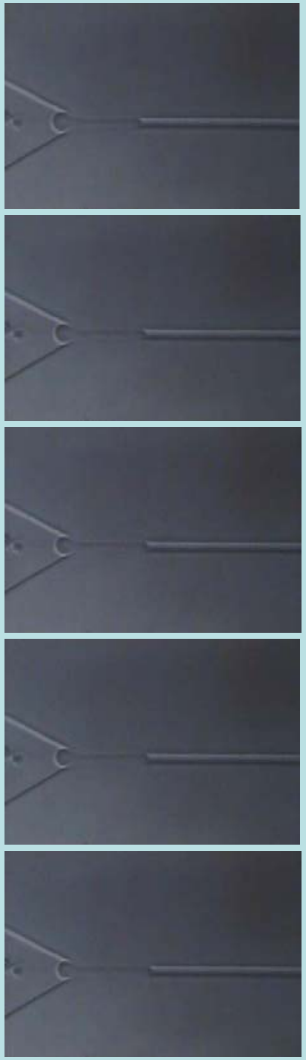
4μm(w)x 2μm: notable stretching



2μm(w) x 2μm: maximal stretch in microchannels;

2µm(w) x 2µm: maximal stretch in microchannels;

Captured pictures showing cell deformation at capillary entrance



Time (ms)

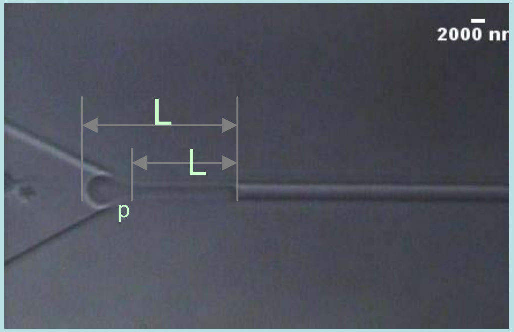
t =0

t= 132 ms

t= 264 ms

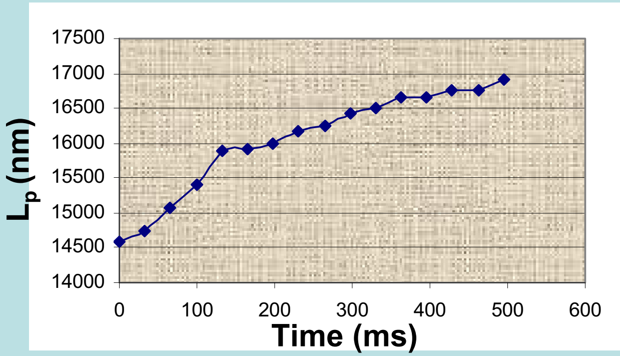
t= 396 ms

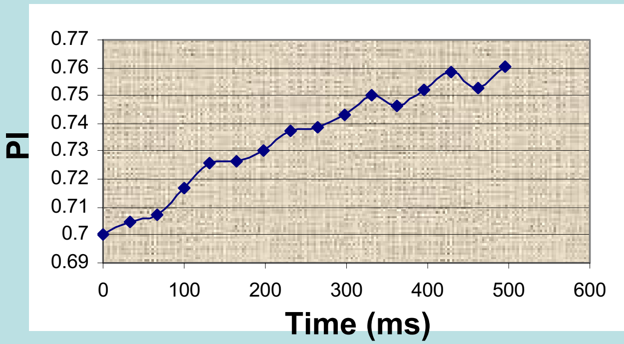
t= 495 ms

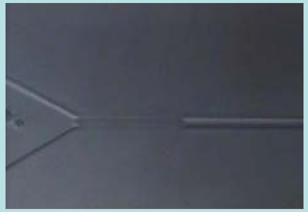


Projection index

$$(PI) = \frac{Lp}{L}$$







$L_{average} \approx 24.83um$

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Conclusions:

Proton beam writing: Great potential for 3D fabrication down to the nano-level….10nm and below: Great potential for biochips: Integrated microfluidics + photonics, tissue engineering substrates……imprinting for mass production….

But: we still need further technological developments:

- **No commercial instrument exists as yet……..**
- **We need user-friendly instrumentation, operation + easy maintenance**
- **Improvements in proton ion source, aperture design, lens systems, target stage stability, beam control software….**
- **Small 'footprint'…..**

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Acknowledgments

Asst Prof Jeroen van Kan (CIBA)

Asst Prof Andrew Bettiol (CIBA)

Dr Shao Peige (CIBA)

Dr Kambiz Ansari (CIBA)

Dr Chammika Udalagama (CIBA)

Assoc Prof CT Lim (Biomechanics lab)

Ms Wang Liping (CIBA)

Assoc Prof Ge Ruowen (Biological Sciences)

Silicon micro-dragon:

Resonant cavities written in porous silicon, patterned laterally using proton beam writing and vertically using alternating etch currents.