# COMPACT MICROFLUIDIC PROBE SYSTEM WITH SELF-ALIGNED MOUNTED HEADS FOR DIRECT USE ON INVERTED MICROSCOPES

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## ABSTRACT

The microfluidic probe (MFP) is a scanning technology for local (bio)chemical processing of surfaces by hydrodynamically confining nanoliter volumes of liquids. To catalyze the broader use of this technology, we here present a compact MFP that can be placed on a standard inverted microscope. This system has self-aligned mounting heads for increased ease of use. We demonstrate the efficacy of the compact MFP by selectively etching thin films on macroscopic topographies.

**KEYWORDS:** Microfluidic probe, surface processing, hydrodynamics, local chemistry.

## INTRODUCTION

The microfluidic probe (MFP) is a non-contact, scanning technology enabling localized (bio)chemical reactions on surfaces by hydrodynamically confining nanoliter volumes of liquid. This technology is suited for interacting with surfaces (e.g. cells, tissue sections) immersed in liquids. Using the MFP, we earlier demonstrated $\mu$m-scale patterning of proteins, manipulation of cells and multiplexed micro-immunohistochemistry [1]. We, as well as other groups working with the MFP, so far have primarily focused on applications driven by problems in biology and medicine [2,3,4]. To catalyse the broader use of this technology, it is necessary to reduce the footprint of the bulky current MFP setups [5] and to create a compact, portable and user-friendly system. This will likely enable its routine use in standard "non-microfluidic" research and diagnostic laboratories akin a stand-alone tool. Here, we present a compact MFP (cMFP) which can be placed on the stage of a standard inverted microscope providing easy and rapid access to the MFP technology, when required, without the need of modifying or assigning a dedicated microscope setup. In addition, we present a strategy for patterning curved surfaces thereby now enabling interactions with macroscopic topographies.

## COMPACT MICROFLUIDIC PROBE SYSTEM

For the cMFP, we decreased the size of an entire MFP scanning system to 175 mm × 100 mm × 140 mm (smaller than a shoe box) which is compatible with an inverted microscope stage, Figure 1. The substrate holder is modular and suitable for microscope glass slides and Petri dishes. The MFP heads comprise precise through holes (mounting vias) for self-aligned mounting and vias for fluidic connections, Figure 2. To interact with common substrates used in biology, the travel range was chosen to be 50 mm × 50 mm × 25 mm with scanning velocities between 0.2 $\mu$m/s and 7 mm/s (Figure 3a) enabling different modes of processing. The cMFP is controlled either via a custom LabView user interface, a joystick or a scripting module.

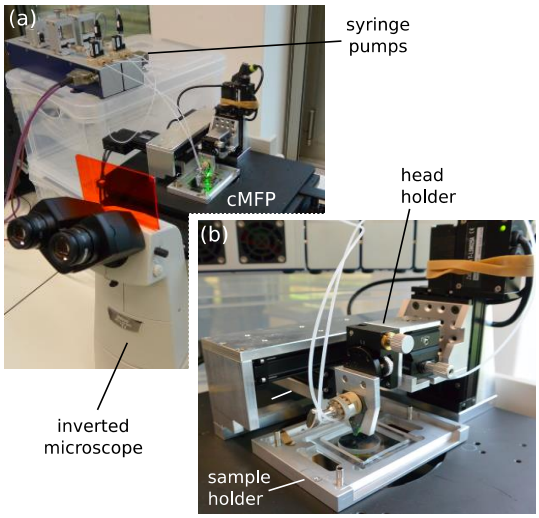


***Figure 1.*** *(a) Photograph of a cMFP mounted on the stage of a standard inverted microscope. (b) Zoom on the cMFP scanning system. The Z-stage (head holder) controls the distance between the head and the sample and the X-Y stage (sample holder) allows scanning 50 × 50 mm$^2$ of the sample of interest.*

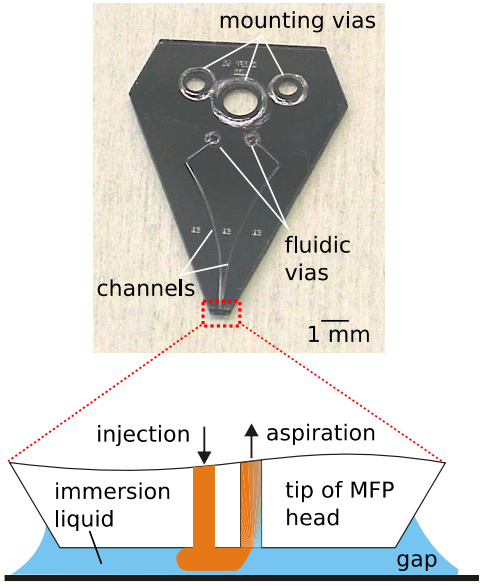


***Figure 2.*** *Microfabricated silicon-glass MFP head with precise through holes for mounting and vias for fluidic connection. Shown below is the working principle to hydrodynamically confine a processing liquid (orange) in the presence of immersion liquid (blue). The apex of the MFP head is positioned 20-30 µm above the surface and injection of the processing liquid is lower than the aspiration. This results in the formation of a local flow envelop of the processing liquid within the immersion liquid.*

**RESULTS AND DISCUSSION**

For calibration, a microfabricated glass slide with rulers and crosses in Cr was used to estimate the accuracy in positioning of the MFP head, Figure 3.

For typical operating conditions, the accuracy of the scanning system is ±8 $\mu$m (example: for a travel range of 5 mm at 7 mm/s, the accuracy was ±6.25 $\mu$m) which is comparable to the dimensions of mammalian cells, therefore being suitable for performing a range of cell-based assays.

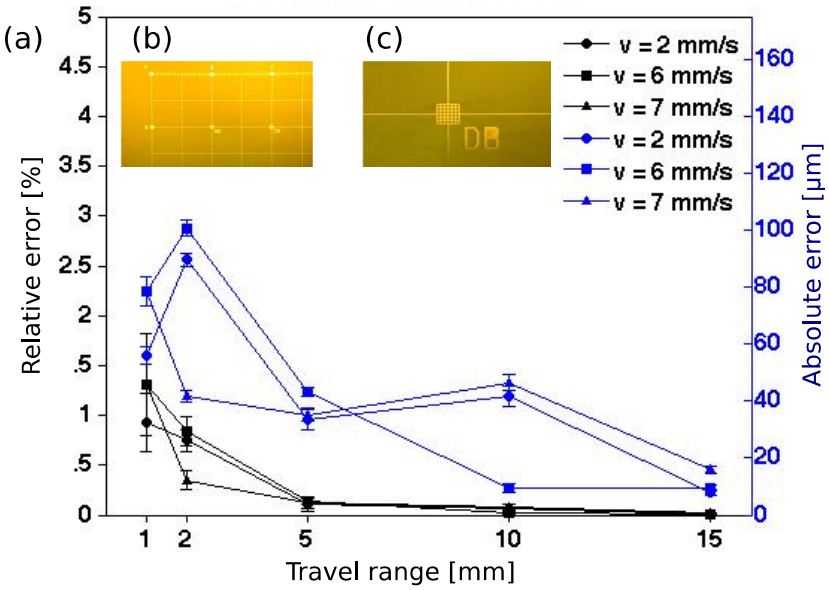


***Figure 3.*** *(a) Graph depicting the accuracy in positioning the MFP head (actual position compared to the command) along the X-axis. The error bars represent the 95% confidence interval. (b) Photograph of the calibration grid patterned on a microscope slide (4× magnification). Coarse divisions are 0.5 mm. (c) Zoom on the crossings (20× magnification). The smaller grid is split into 5 µm divisions.*

We performed local chemical reactions on planar and curved surfaces. For samples with macroscopic topographies, the height variation is either known *a priori* or can be measured, for example, with an optical profilometer. This topographical information was used to adjust the Z-distance (height) automatically with a precision of ±10 µm preventing mechanical contact between the head and the surface. Patterns of lines and dots were created on a photoresist coated plano-convex lens having a radius of 258.4 mm by hydrodynamically confining 25% TMAH, Figure 4a. In addition, metalized planar and curved glass surfaces were locally etched using NaOH (1M), Figure 4b,c.

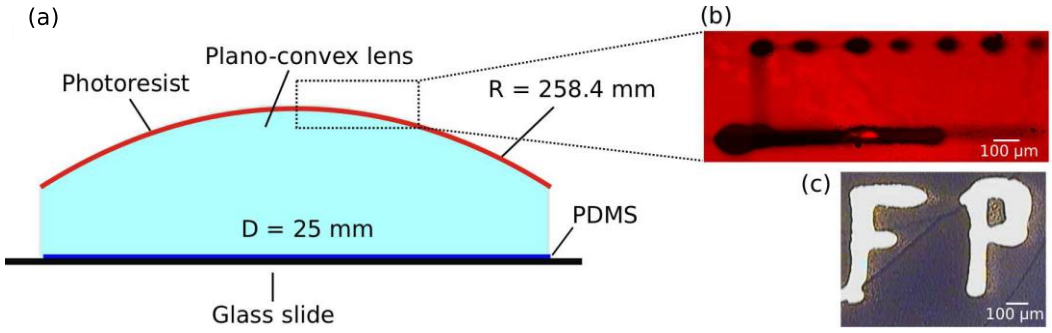


***Figure 4.*** *(a,b) A plano-convex lens (45280, Edmund Optics) coated with photoresist (15 µm, WLP1015, Dupont) was patterned using a MFP head having 50 × 50 µm apertures. A flow confinement of 25% TMAH (Sigma Aldrich) was generated and local etching performed along the curvature of the lens to create patterns at different scanning velocities (0.1 to 6 mm/s). (c) Patterns on a 50 nm aluminium-coated glass slide, etched with a 1M solution of NaOH.*

## CONCLUSION

The cMFP is compact, accurate, user-friendly and represents a powerful surface processing technology to be used with any inverted microscope. Based on the results, we believe it may even be feasible to microfabricate deep structures at specific locations on irregular samples using the cMFP.

With the cMFP, we are now closer to our objective of making the MFP technology better suited as a multi-functional research tool for the broader scientific community.

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