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Dynamic arraying of microbeads for bioassays in microfluidic channels

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Abstract

This paper proposes a new dynamic mode of generating bioanalytical arrays in microfluidic systems, based on ultrasonic trapping of microbeads using acoustic forces in standing waves. Trapping of microbead clusters in an array format within a flow-through device is demonstrated for the first time using a device with three integrated ultrasonic microtransducers. The lateral extension of each trapping site was essentially determined by the corresponding microtransducer dimensions, 0.8 mm × 0.8 mm. The flow-through volume was approximately 1 μl and the trapping site volumes about 100 nl each. The strength of trapping was investigated, showing that 50% of the initially trapped beads were still trapped at a perfusion rate of 10 μl/min. A fluorescence based avidin bioassay was successfully performed on biotin-coated microbeads trapped in the flow-through device, providing a first proof of principle of the proposed dynamic arraying concept. The dynamic arraying is believed to be expandable to two dimensions, thus, with a prospect of performing targeted and highly parallel protein analysis in microfluidic devices.

Keywords: Ultrasound; Microchannel; Trapping; Bead; Array; Proteomics

1. Introduction

With the sequencing of the human genome being completed, the task of mapping the proteome has been outlined as the next major milestone in life science research. Although the global proteome mapping effort is an important goal, yet more targeted protein expression investigations, closely related to disease development are still gaining the attention from a majority of the biomedical proteomic research community [1]. A recent trend is the search for biomarkers in biofluids derived from diseased tissue or natural secrets from organs related to or involved in the disease progress [2]. It is envisioned that the identification and abundance mapping of biomacromolecules/biomarkers involved in early disease states may very well provide a new approach to clinical diagnostics and/or an efficient route to the development of new drugs and disease treatments [3,4].

In line with the discovery of new biomarkers being early indicators of disease development, the need for techniques to screen samples for such biological components will increase proportionally. Hence, the recent and very intense development in the area of protein arrays [5,6]. Although, much focus has been put on the development of global protein microarrays analogous to DNA arrays [7], protein arrays composing directed biological questions may very well provide equally important information and in a more targeted approach answer the questions related to a biological pathway or a given disease through out its progress.

In order to successfully develop protein arrays, high quality affinity probes directed against the specific proteins/biomarkers that correlate to the disease state are needed.

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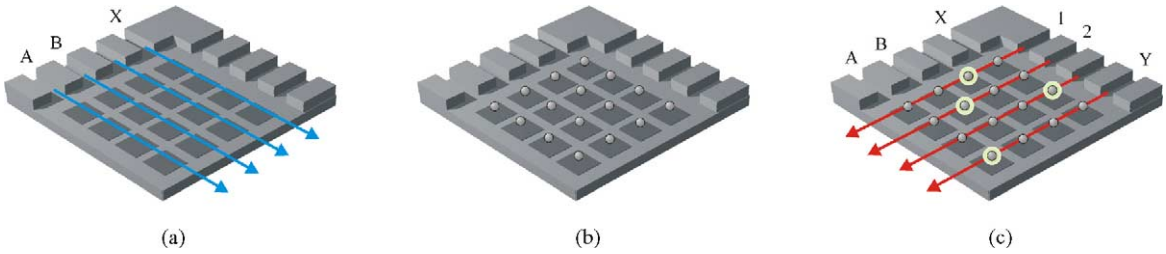

Fig. 1. Illustrations of the concept of dynamic arraying showing insertion of the solid phase of different specificity (a) through inlets (A, B, . . ., X), trapping of antigen specific bead clusters using the ultrasonic transducer array (b) and perfusion/incubation of sample (c) through inlets (1, 2, . . ., Y) followed by fluorescence read-out.

Thus, the development of antibody libraries has become a specific area of interest with several industrial players. Once the desired antibody library is developed and available, a technology for arraying these compounds for parallel read-out has to be presented. Today, ink-jet technology is one of the most common ways of producing two-dimensional arrays of biological compounds [7–9]. Individual antibodies can thus be deposited in an array pattern onto a flat surface, e.g. a glass slide, which is chemically modified to facilitate efficient immobilisation of antibodies [6]. These types of protein arrays are disposable, enabling a single screening of one biological sample for a given set of antibody–antigen interactions. Bioassays for protein identification in microfluidic systems using microbeads as the solid phase for immobilisation of antibodies have previously been performed by several groups, utilising the increased surface area, and thus the high binding capacity of the beads as compared to solid surfaces [10,11].

The use of functionalised microbeads for performing highly sensitive bioassays is an attractive approach to targeted protein analysis. In order to perform such assays in a flexible and reusable format, means of trapping and manipulating microbeads in microfluidic systems are sought. Several authors have in the past demonstrated manipulation and separation of particles or cells in fluidic systems by making use of acoustic forces in standing waves [12–15]. Acoustic separation of microparticles in micromachined devices has been reported [16]. It has been shown that cavitation, and related detrimental damage of biomaterial, can be avoided by using high frequency ultrasound above 1 MHz [17]. Thus, it is possible to use the same principle to extract erythrocytes from blood plasma and to eliminate fat particles from blood [18]. Neither of the above papers has however addressed the issue of trapping beads or particles in streaming microfluidic systems in order to perform bioassays. The possibility of trapping beads in a capillary using a focused ultrasonic transducer has been studied to enable separation and detection of trace amounts of proteins [19,20]. The trapping was performed by generating a standing wave in the length direction of the fluid flow through the capillary. A recent report from our group [21] describes the design and development of a microfluidic device with integrated piezoceramic microtransducers for localised and spatially controlled ultrasonic particle trapping. The integration of several microtransducers gives way for the creation of individually controlled trapping sites along the length of a flow channel, thereby providing means for the formation of biospecific bead cluster arrays.

This paper proposes a new dynamic mode of generating protein arrays using ultrasonic forces to trap the solid phase, making the simultaneous screening of a whole set of different biological samples possible. By performing the antibody/antigen interaction on chemically activated microbead clusters in a laminar streaming microfluidic system rather than on solid surfaces and by trapping such bead clusters of different antigen specificity (A, B, . . ., X) in an array pattern using acoustic forces, one can address each bead cluster array with an individual sample stream (1, 2, . . ., Y), as illustrated in Fig. 1. In this way, the solid phase (bead cluster), on which the bioassay is performed, can be disposed after completed analysis by simply switching off the bead trapping forces and displacing the beads from the analysis zone. After loading a new set of bead clusters into the array, the next assay can be performed. The concept of dynamically generated protein arrays can in principle be integrated and controlled in a closed microfluidic system that is highly amenable for automation. A core of the proposed protein array technology is the development of means for individually controlled trapping and release of microbead clusters.

The present work demonstrates a bead trapping microarray consisting of three piezoelectric microtransducers integrated in a microfluidic channel. The successful loading of an array and individual control of the bead clusters is demonstrated for the first time. The strength of the acoustic trap, i.e. loss of beads during streaming conditions at different perfusion flow rates is reported. Finally, a model bioassay using fluorescein-labelled avidin binding to biotin-coated beads is performed in the device, demonstrating successful on-line bead trapping and biochemical read-out in a flow-through format.

2. Experimental

2.1. Microarray device

The fabrication of the ultrasonic microarray device has been presented and discussed in detail in a previously published paper [21], and is thus only briefly presented herein.

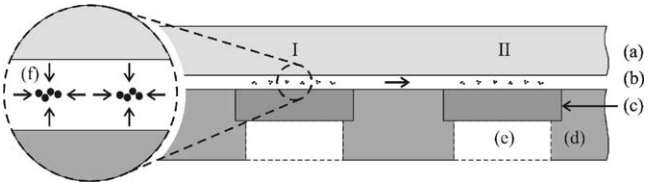

Fig. 2. Two trapping sites, I and II, designed as acoustic microresonators consisting of glass reflector (a), fluid layer (b), multilayer ultrasonic transducer (c), baffle (d) and air backing (e). The close-up shows a simplified view of the configuration of trapped bead clusters (f) at one of the trapping sites. Beads are trapped by acoustic forces (arrows in circular insert) due to pressure gradients in the fluid layer.

The device comprises an array of three individually addressable bead-trapping sites. Each trapping site is designed as an acoustic resonator consisting of a miniature ultrasonic transducer and a reflector, enclosing a bead conducting fluid layer. The resonator is designed to essentially obtain a pressure node in the middle of the fluidic channel above the transducer, keeping the particles away from the interior channel surfaces. The function is illustrated in Fig. 2, showing a cross-section of a resonator array. Previous work [21] has shown the existence of regions with strong laterally confining acoustic forces in the near field of the transducers that facilitate bead cluster trapping, since forces acting on the particles are proportional to gradients in the acoustic energy density [22].

The evaluated device, shown in Fig. 3, consisted of a microstructured SU-8/glass channel plate clamped to a printed circuit board (PCB) carrying the transducer array as well as the electrical and fluidic connections. The piezoceramic microtransducers were batch fabricated using a multilayer thick film prototyping process [23], based on computer numerically controlled (CNC) milling. Three transducers (0.8 mm × 0.8 mm × 0.2 mm) were mounted on the PCB, electrically connected to copper conductors and covered with epoxy. The epoxy was polished down to the surface of the piezoceramic elements after hardening, yielding a plane upper surface. Microstructured fluidic channel plates connecting to the fluid inlets on the plane polished transducer board were batch fabricated by lithographic structuring of SU-8 on a soda lime glass substrate followed by dicing. External fluidic connections were made on the backside of the PCB. After polarising the piezoceramic material, the transducer elements were connected to a function generator[1] through a control box, enabling fast switching of the drive signal to either element.

2.2. Microfluidic and imaging system

The microfluidic system was arranged as illustrated in Fig. 4. Beads were manually injected through 0.25 mm inner diameter polyetheretherketone (PEEK) tubing using a syringe. Distilled water (washing fluid) and sample was injected through 0.3 mm inner diameter Teflon tubing using two syringe pumps. The configuration of the microfabricated channel system is shown in the insert in Fig. 4, where beads were injected in (a), adjacent to the inlet for washing fluid (b). Beads and washing fluid were passing the transducers in the main flow channel, ending up in a common outlet (d). Sample was injected in an orthogonal flow channel with an individual inlet (c) and outlet (e), at the position of one of the three transducer elements (f). After filling the fluidic structure with water, excessive fluidic connections were sealed before injecting the beads.

The imaging was performed using a fluorescent microscope[2] supplied with a mercury light source and filters yielding exciting light at 470–490 nm and detecting light at about 515 nm, adapted for fluorescein isothiocyanate (FITC). The shutter was normally closed and opened only during the image captures. Also a confocal imaging system[3] was utilised for parts of the experiments.

2.3. Chemicals

Polystyrene beads[4] (6.7 μm mean diameter) with immobilised biotin were used in the bead trapping experiments. Also FITC-marked melamine beads[5] (5 μm mean diameter) were used in parts of the evaluation. A 23 μM solution of avidin[6] conjugated with FITC was prepared by dissolving the lyophilised powder in distilled water.

2.4. Bead trapping and detection

Beads were injected in the water-filled channel, and conducted to the trapping site by a fluid flow of 3 μl/min supplied from the wash inlet. One transducer element was activated, trapping the beads. The frequency generator was set at delivering a 10.8 MHz, 10 V p-p sinusoidal signal. The strength of trapping was evaluated by imaging the bead loss under increasing fluid flow. The fluid flow was increased in steps of 2 μl/min until no beads were visible in the region over the transducer element. To deal with stray light, a reference image of the empty trap was captured and the intensity in each point was subtracted from captured images.

The possibility of moving beads between the three trapping sites was studied by sequential trapping. Due to induced fluorescence in the epoxy surrounding the transducer elements, more strongly fluorescent melamine beads were utilised in this experiment to allow imaging of the complete array. Beads were injected and conducted to the first trapping site using a fluid flow of 3 μl/min, which was maintained throughout the experiment. Beads were trapped by the activation of the first transducer. The driving signal was then switched to the second transducer, to which the flowing fluid

[1] HP 33120A, Hewlett-Packard, USA

[2] Olympus BX51WI, Japan
[3] Olympus BX61WI with an FV300 confocal unit, Japan
[4] PC-B-6.0, Gerlinde Kisker, Germany
[5] Fluka 90641, Sigma–Aldrich Co., USA
[6] Sigma A2901, Sigma–Aldrich Co., USA

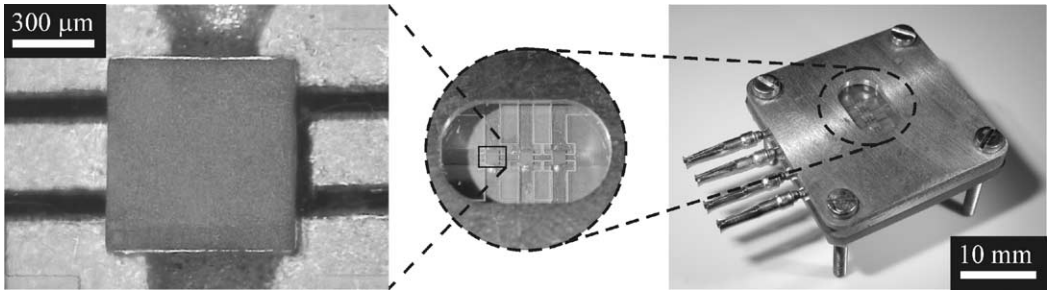

Fig. 3. Assembled device with the array of three transducers visible through the glass window.

conducted the beads. The procedure was repeated for the third transducer element before releasing the beads to the outlet.

2.5. Bioassay

A bead-based biotin-avidin assay was performed using one of the array trapping sites of the device. Biotin-coated beads were loaded into the trapping site and trapped as described above. The bead carrying flow was turned off, the common bead/wash outlet valve closed and the sample outlet valve opened. Avidin was perfused at 3 μl/min over the trapped beads through the sample channel and the fluorescent response was captured at time intervals of 5 s. After almost 2 min, the avidin flow was stopped, the valves switched and the washing fluid perfused at 3 μl/min for 40 s before releasing the beads. The perfusion of avidin was studied in a similar experiment repeated using an "empty" trap, i.e. without the insertion of beads. To diminish the effect of surrounding streaming and unbound avidin, the captured images of the beads were masked (using the same mask for each picture in a series), and the intensity was thereby measured over particularly stable bead clusters.

3. Results

3.1. Bead trapping

The channel height was 71 μm as measured by confocal imaging. Trapped particles in the channel were mainly positioned in the centre of the channel, 36 μm above the transducer. A small fraction of the particles was often found on the surfaces of the transducer and glass reflector. The lateral bead distribution was studied using the fluorescence microscope. A typical lateral bead distribution is shown in Fig. 5, where fluorescent beads are trapped in clusters in the fluid over the transducer element. Upon increasing fluid flow, bead clusters were pulled away from the trapping site (Fig. 6) with the measured relative bead area versus fluid flow plotted in Fig. 7.

The trapping of bead clusters by sequential activation of the three trapping sites is shown in Fig. 8. Due to exposure setting of the microscope, the beads appear smeared out when

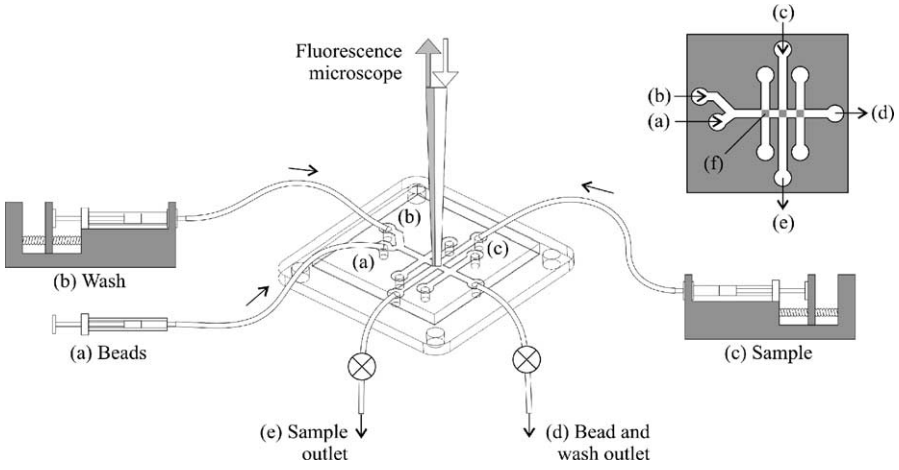

Fig. 4. Microfluidic and imaging set-up. Beads were injected in (a) and conducted to the trapping site by using washing flow (b). Sample was injected in one of the orthogonal flow channels (c) → (e). The outlets (d) and (e) were controlled by valves (X). The positions of the transducer elements are shown in the insert (f). A fluorescence microscope was used to monitor the trapping of beads.

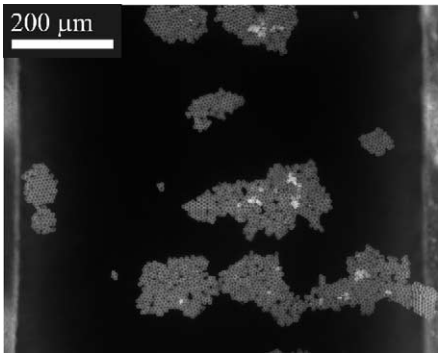

Fig. 5. Trapped bead clusters (lighter) above a single transducer element. The figure area covers essentially one transducer element.

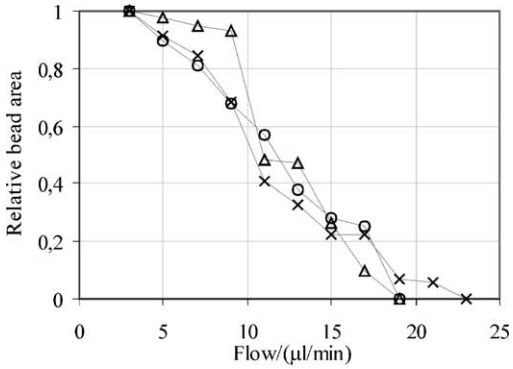

Fig. 7. Relative bead area of trapped beads vs. flow for three measurements (Δ, × and ◯).

moving from one trapping site to another (Fig. 8 (b), (d) and (f)).

3.2. Bioassay

The fluorescent intensity read-out of the bioassay over selected bead cluster areas is plotted in Fig. 9 (a). A similar fluorescence measurement sequence of avidin flowing into an "empty" trap, i.e. without trapped beads, is plotted in Fig. 9 (b).

4. Discussion

In order to enable fast switching of bead clusters and to minimise carry over from one bioassay to the next, it is essential to optimise the clearance of beads between subsequent assays. Thus, the bead clusters should preferably be trapped in the centre of the flow channel as this location has the highest flow and as the beads have no physical contact with the channel wall. The design of the microresonator with integrated miniature transducer elements in direct contact with the thin bead-conducting fluid layer has been shown to generate a pressure distribution with essentially a pressure node in the centre of the channel, together with periodic lateral pressure variations due to near field effects [21]. The measurements using confocal imaging confirmed that the beads were trapped in the middle of the channel, but also showed that a small fraction of beads were present at the transducer and reflector surface. This can also be seen in Fig. 8 where some beads were stuck at the middle trapping site during sequential trapping. It is anticipated that the position of the beads can be adjusted to be completely kept away from the walls by optimised driving conditions, and that improvements in transducer manufacturing will diminish individual variations between array elements. Also, by a proper selection of buffer systems, surface adherence can be substantially suppressed. The effect of the acoustic near field on the trapping behaviour is identified in Figs. 5, 6 and 8, where beads are shown to gather in clusters above a single transducer element. This implies that the distribution of beads in the trap will be influenced by the bead injection procedure. In the present device, beads were injected using a syringe and transported to the trapping site using flow from the wash inlet. Upon reaching the trapping site, the transducer was activated and beads were trapped. Beads were then sometimes still being supplied from the bead-carrying flow, giving a higher concentration of trapped beads to the left in the bead trap, as in Fig. 6 (a). This also explains the trapping behaviour during sequential trapping. In the bead trapping sequence, the drive signal was switched to the next array element instantaneously, and beads were therefore trapped upon entering the trapping site from the left. The sequential trapping series shown in Fig. 8 indicated that few beads were lost when switching between different trapping sites. Beads released from one transducer element passed in the direct vicinity of the next element due

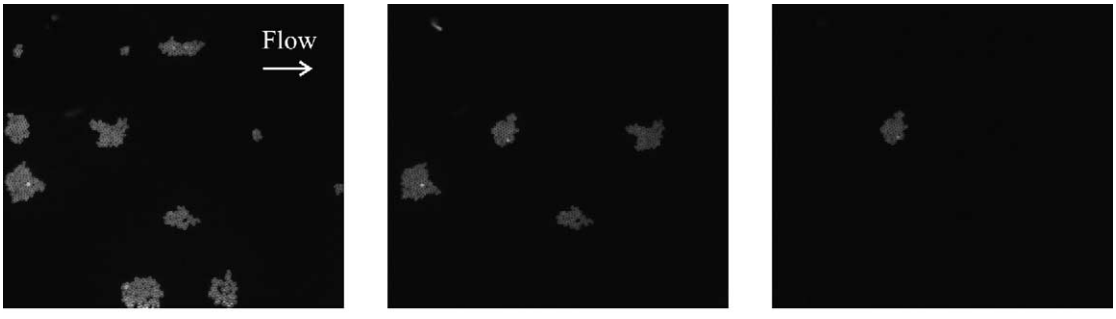

Fig. 6. Bead trapping at increasing fluid flow (a) 3 μl/min, (b) 11 μl/min and (c) 17 μl/min.

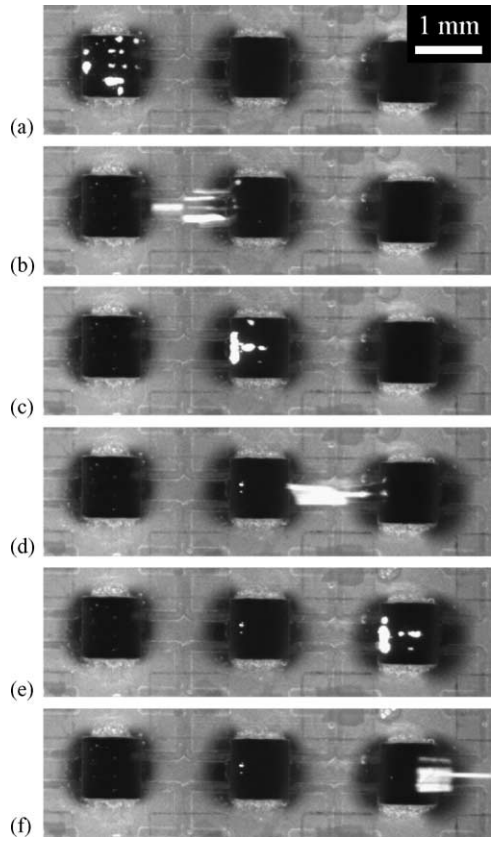

Fig. 8. Sequential trapping of beads in the microchannel (a, c and d). A continuous fluid flow during the sequence transported the beads between the trapping sites (b, d and f).

to the supposed laminar flow in the microchannels [24]. The issue of bead injection will be dealt with in future work. The same absolute amount of beads needs not be trapped at every trapping site, and therefore we believe conventional injection techniques to be adequate. If necessary, the distribution and amount of beads on each trapping site could be monitored by simple image analysis functions.

The measurements on the strength of acoustic trapping shown in Fig. 7 indicate an almost linear relationship of remaining trapped beads versus volumetric flow. Beads were drawn from the trapping site by increasing viscous forces due to increased fluid flow. When studying individual sequences of the trapped bead clusters (Fig. 6), it can be noted that the beads mainly were removed from the trap cluster by cluster, which gave a step-wise decrease in bead area for some measurements (Fig. 7). The clusters that were trapped at the highest flow speeds were most often confined over the centre of the transducer element indicating that trapping forces were stronger there. The measurements showed that the volumetric flow could be increased up to 20 μl/min (mean linear flow rate ≈ 4.7 mm/s) before all beads were removed from the acoustic trap, and that about 50% of the initially trapped beads were still trapped at a flow of 10 μl/min. Twenty microliters per minute corresponds to displacing the volume confined within the trapping site (about 100 nl) in 0.3 s.

The results from the bioassay show that avidin had bound to the biotin-coated beads, which can be seen as a measured increase in fluorescent response marked as Δ in Fig. 9 (a). About 40 s was needed to reach a steady state in concentration of avidin over the trapping site, as seen in Fig. 9 (b). This is probably due to a gradient in concentration of avidin in the supplying sample channel when starting the assay and to the parabolic flow profile within the channel. An optimisation of the fluidics with respect of sample delivery is expected to improve the time needed for performing this type of assay. Microfluidic techniques are in general considered to yield fast chemical reactions due to the short diffusion paths in small confined volumes. The flow-through volume of the device was in the order of 1 μl, depending on the channel used, and the active volume in a channel crossing was less than 100 nl. The detected intensity at $t = 0$ in Fig. 9 (a) may be caused by autofluorescence of bead material, contaminations of diffused avidin or scattering of light from the fluorescent epoxy surroundings. The minimisation of this background intensity will be addressed in future work, by considering

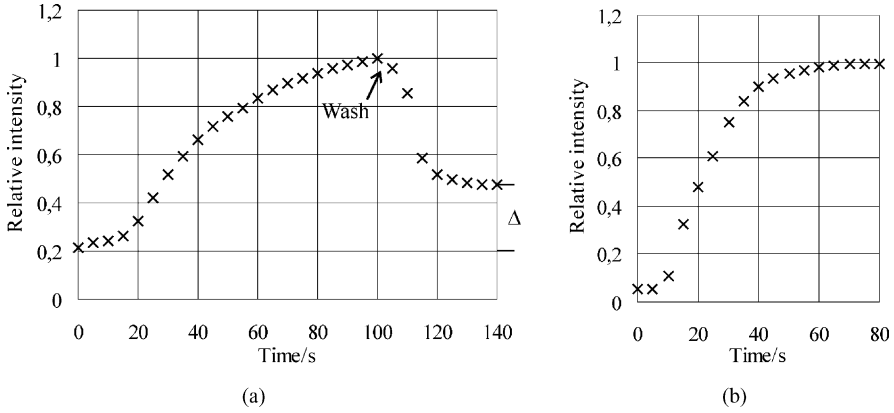

Fig. 9. Loading of FITC-tagged avidin over trapped biotin-coated beads with indicated response Δ (a). The switching from avidin to washing flow is indicated. The loading of FITC-tagged avidin into an "empty" trap is shown in (b). The plotted intensities are normalised to the maximum intensity in the series.

materials, design and detection schemes. In this proof-of-principle work, we have not yet raised the issue of detection limit using the proposed dynamic arraying technique. The concentration of avidin in the sample was in the micromolar region, and the technique is thought to enable the detection of much lower concentrations.

5. Conclusions

A new dynamic mode of generating bioanalytical arrays is proposed. Successful non-contact trapping of chemically activated microbead clusters in a microfluidic device has been presented. Bead clusters were trapped at individually controlled trapping sites using acoustic radiation forces originating from ultrasonic microtransducers integrated in the flow-through device. Studies on the strength of trapping showed that the flow could be increased to 20 μl/min (mean linear flow rate ≈ 4.7 mm/s) before all beads were pulled away from the trap by viscous forces. At a flow rate of 10 μl/min, about 50% of the beads were still trapped in their specific location. It is concluded that near field effects in the miniaturised system helped to provide strong lateral trapping forces, allowing bead trapping at considerably high perfusion rates. Performing a model bead-based bioassay using the device showed the prospect of using the technology. Biotin-coated beads were injected and trapped followed by perfusion of FITC-tagged avidin. The detection of avidin binding to the microbeads was successful. Future developments will focus on expansion of the arraying concept to two-dimensional ultrasonic transducer arrays including more detailed analysis on bead handling and cross contamination issues. Eventually, the development will enable on-line analysis of, e.g. proteins performed on biospecific bead arrays in a flow-through device.

Acknowledgements

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Biographies

Tobias Lilliehorn received his M.Sc. degree in Physics from Linköping University in 1998 and his PhD degree in Microsystems Technology at Uppsala University in 2003. He is now employed as a researcher in the micro actuator group at the Department of Engineering Sciences at Uppsala University, focusing on miniaturized piezoactuators for microfluidic applications.

Mikael Nilsson received his Master of Science in Engineering Physics in 2003 at Lund Institute of Technology. He is currently a PhD-student at the department of Electrical Measurements in Lund and his main research area is within microfluidics and on-chip ultrasonic manipulation of microparticles.

Urban Simu, born in 1971, graduated in 1997 with a M.Sc. in engineering physics and received his PhD degree in Engineering Science in 2002 at Uppsala University, Sweden. He belongs to the micro actuator group at the Department of Engineering Sciences, Uppsala University, as a researcher. His research interests are in processing of miniature components and actuation thereof using various functional materials. His main focus has been piezoceramic actuators for microrobotics and microfluidics.

Stefan Johansson received his PhD degree in Materials Science at Uppsala University in 1988. In 1994, he became associate professor (docent) and, in 2000, professor, both in Materials Science at Uppsala University. As one of the Swedish pioneers in micro-mechanics he has been involved in micro-fabrication and micro-robotics research for close to 20 years. During the last 10 years his research has been focused on actuation in micro and miniature 4 systems and he is heading the micro actuator group at the Department of Engineering Sciences at Uppsala University. He is author, or co-author, of more than 80 international research papers and he, together with industrial and academic partners, have filed more than 20 patents, of which a large part is already issued. In 1996 and 1997 he and a colleague received several prestigious national innovation awards. As a consequence they founded the spin-off company, Piezomotor AB, which today develops and produces miniature piezoelectric motors for industrial applications.

Monica Almqvist received her PhD degree in Electrical Measurements in 1999 and currently holds a position as research assistant at the Department of Electrical Measurements, Lund Institute of Technology in 2000. Her research has been focused on optical measurements of ultrasound fields, airborne ultrasound and ultrasound vector doppler tomography. The past years her main interest has been in two newly started projects: developing capacitive micromachined ultrasound transducers and ultrasonic trapping in microfluidic bioanalysis systems.

Johan Nilsson obtained his PhD in 1993 in Electrical Measurements on the topic Ink Jet and Droplet Technology at the Department of Electrical Measurements, Lund University, Sweden. Following the PhD, he got a post-doc employment at the same department where he headed the research in droplet formation characterizations and silicon nozzle development The topic for the research has since 1997 been microfluidics and microstructures with a focus on microsystems for protein analysis using mass spectrometry. He currently holds a position as Associate Professor at the Department of Electrical Measurements.

Thomas Laurell received his PhD degree in Electrical Measurements in 1995. He obtained a position as an Associate professor in 1998 and was later appointed Professor in Medical and Chemical Microsensors at the Department of Electrical Measurements, Lund Institute of Technology in 2000. Laurell currently leads the microtechnology and nanoproteomics group at the department. His research focuses on nanobiotecnnology and Lab-On-A-Chip technologies e.g microstructured components for biomedical monitoring/analysis, implantable neural electrodes and micro components for liquid/cell sample handling in chemical microsystems, i.e. dispensing, injecting, and sampling of picoliter volumes as well as aqoustic manipulation of particles and cells in microfluidic systems. In the past years a strong focus has been put on new miniaturised technology for nanoproteomics and masspectrometry, aiming at accurate picoliter sample handling and preparation for submicroliter proteomic analysis of low abundant proteins. Also, new approaches to high density, high sensitivity protein microarrays and chip integrated microbioassays has a strong focus. For these developments the Laurell group recently set-up a lab devoted to microfluidics and nanoproteomics developments.