

Micro & Nanotechnology

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An Integrated Multifunctional Lab-on-a-Chip Platform for High Throughput Optical Mapping of DNA

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Direct Linear Analysis (DLA) technology employs continuous microfluidic elongational flow to stretch and optically map individual DNA molecules. Sequence specific tagging of DNA molecules with bisPNAs enables genomic differentiation between species. We report on the operation of a microfluidic lab-on-a-chip platform with the integrated functionality of sample concentration, fractionation, and high throughput optical mapping. Integration of the components on a single chip enables high throughput analysis of sub-nanogram samples. Previously described DLA devices [1] had throughput rates that were directly proportional to the initial sample concentration. Integrated on chip concentration in conjunction with tunable sample delivery flow rates to the DLA component allows for dynamic optimization of throughput to 12,000 kbp/s, independent of the initial sample concentration. In addition, fractionation of the sample enhances information throughput by discarding shorter fragments with lower information content prior to the optical mapping step. This integrated microfluidic device has been demonstrated in conjunction with a macrofluidic upstream sample preparation chamber in an automated system. This research was supported by the Department of Homeland Security Science and Technology Directorate.

[1] Phillips et al, Nucleic Acids Research, 2005, 33 (18), 5828.

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Development Of A Cell Sorting Device Based On The Integration Of Porous Poly(Dimethylsiloxane) (PDMS) Membranes Into Layered Microfluidic Devices

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Layered microfluidic devices integrated with semi-porous membranes have been widely used for mass transport control, immunoassays, and blood cell sorting. The placement of a semi-porous membrane at the interface of two channel layers is crucial to minimize unwanted crossover of fluid flows between microchannels while allowing diffusive mixing of reagents. Several methods have been reported to seal off the crevices inevitably generated because of the thickness of the membrane. For example, the application of PDMS pre-polymer as a mortar layer could prevent the leakage along the membrane. This method provides robust and reliable bonding between two PDMS layers. However, in the case of thicker membranes and/or narrower channels, the mortar layer can clog the channels easily. We introduce an alternative strategy of directly using PDMS as a porous membrane itself to fabricate monolithic microfluidic devices. In this case, the integration of a porous PDMS membrane can be completed without clogging microchannels. To prepare porous PDMS membranes, a photoresist is utilized as posts on a silicon wafer. Therefore, a thin film of porous PDMS can be prepared by spin coated on the wafer. This method allows varying sizes of pores on a single membrane, compared to commercially available porous membranes with a fixed pore size. In addition, the wafer can be repeatedly used to create porous membranes. We demonstrate the use of this method to fabricate a cell sorter where a porous PDMS membrane between two layers of microchannel. This porous membrane has two porous regions: 10 μm and 20 μm regions. Thus, a cell sample (lymphocytes) loaded from the top microchannel can be filtered into small or larger size of cells through the porous membrane, and collected from the bottom microchannels.

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3-D Microfluidic Technique for Patterning Cells

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We developed a technology that can pattern single cells in two-dimensional space, where each cell is placed in a well-defined spot. The basis of our technique is a microfluidic system that can simultaneously capture a large number of cells from solution, position each with sub-micron precision, and transfer the patterned cells to a substrate. The critical component of the system is a polymer membrane containing a pattern of microscopic holes, whose diameters are slightly smaller than that of a single cell. One side of the membrane is immersed in a solution of cells, and gentle suction is applied from the other

side. The resulting fluid flow carries cells toward the holes of the membrane. When a cell reaches the membrane, it blocks a hole. Thus, the fluid flow, along with the residual cells, is redirected toward the remaining unblocked holes, until each hole is plugged by exactly one cell. Once the membrane is laden with cells, it is brought into contact with an adhesive surface. The suction is released to transfer the cells. Repeated application of this patterning process can yield complex structures of cells of different types.

Such spatial control of single cells will allow the study of intercellular interactions, as in embryogenesis and cancer. With the ability to program cell-cell interactions within and amongst multiple cell types via spatial localization, we will study how the interplay between geometry and genetics affects observed phenotype. This technique can also be used to create cellular microarrays for high-throughput data acquisition. Ultimately, we hope to build three-dimensional tissues *de novo*, patterned slice by slice, and cell type by cell type.

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The Toxic Effects of Quantum Dots on Embryogenesis in *Caenorhabditis elegans*

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Quantum dots have the potential to be used in medical applications such as tumor targeting and directed drug delivery. Their high molecular brightness, tunable emission spectra and photostability are just a few of the properties that make these nano-sized semiconductor particles attractive candidates for such applications. However, before quantum dots can be employed for therapeutic or diagnostic purposes, their potential toxicity needs to be thoroughly investigated. Such toxic effects may arise from their size or from the inherent toxicity of the materials that make up their core. In this study, the toxic effects of quantum dots on embryogenesis have been explored using the *Caenorhabditis elegans* (*C. elegans*) embryo as a model organism. Quantum dots are introduced into this nematode by microinjection and are then incorporated into its developing oocytes. Preliminary results suggest that the level of toxicity on embryo development is strongly dependent on the composition of the nanoparticles, on its coating, and on its propensity to aggregate. Additionally, it has been observed that the embryo uses a technique to package the quantum dots into isolated aggregates during development. The dynamic behavior of quantum dots in the *C. elegans* oocyte has also been studied using fluorescence correlation spectroscopy.

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Collaboratory for Structural Nanobiology (CSN), Nanoparticles Database

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Nanotechnology is the science and engineering field of functional systems at the molecular scale. This covers the manufacture of functional materials, devices, and systems through control of matter over the nanometer scale (1 to 100 nanometers) and the study of novel properties and phenomena developed at that scale. Many existing technologies depend on processes that take place in the nanoparticles, components that have very high surface areas, making them ideal for using in composite materials, reacting systems, drug delivery, developed cancer treatment and energy storage and many others. Due to the significant progress of this discipline, the initiative to develop a web-service database emerges, with structural and experimental information about nanoparticles. This project has been created as a result of a multidisciplinary team effort. Here you will find downloadable structural files, related research data, and resources for visualization of different nanoparticles such as dendrimers, buckyballs, nanotubes and metallic particles.

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A Nano-assay To Measure Modification Of Cysteine Residues In GST-fusion Proteins

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Cysteine residues are the target of numerous posttranslational modifications and play important roles in protein structure and enzymatic function. Because of this, much research on the biochemistry of proteins is dependent on understanding the activity and state of these residues. Many current methods for measuring modified and unmodified cysteine residues in proteins are cumbersome and often lack sensitivity, requiring large amounts of protein. We have developed a highly sensitive and simple assay that accurately measures the relative amounts of free cysteine residues in GST-fusion proteins using 96 well glutathione-coated plates. Free-unmodified cysteines are labeled and visualized using biotin and HRP-conjugated streptavidin. Our assay can be used to quantify the extent of reactions targeting -SH groups in proteins. We demonstrate this