VLSI MICROFLUIDIC WELL PLATES FOR COMBINATORIAL CHEMISTRY

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ABSTRACT
Well plates with microliter-sized well are routinely used for a wide range of chemical and biological screening experiments. Further downscaling as enabled by microfluidic networks will increase the number of conditions that can be screened with the same amount of often-precious material. Here we present a microfluidic well plate composed of pL-sized wells designed with a novel actuate-to-open (ATO) valving architecture. This reusable well plate can discretely mix 200 pL half-wells in a 4x4 matrix to test for sixteen possible combinations. The device has also been integrated with a photonic crystal biosensor to determine binding events that occur upon mixing.

KEYWORDS: Integrated, Microfluidic, Combinatorial Chemistry, Valves

INTRODUCTION
Over the last several years VLSI (Very Large Scale Integrated) microfluidic networks have been developed and adopted for a wide range of applications, including protein crystallization, bacterial chemotaxis, and single-cell microinjection studies [1,2,3,4]. The pneumatic valves in these chips require positive pressure to close a fluidic channel; termed actuate-to-close (ATC) valves. These chips require continuous attachment to a peripheral pressure source and individual feed lines for each reactant. Microfluidic networks with valves that are closed at rest and open by applying negative pressure, termed here as actuate-to-open (ATO) valves overcome these challenges. ATO valves have been used sporadically in single channel configurations [5,6], but not in VLSI microfluidic networks. Development of a microfluidic chip capable of mixing and screening an array of reactants using very small volumes will further economize high throughput screening efforts that involve valuable reagents, since more experiments can be performed with less starting material.

DESIGN AND FABRICATION
Here, we show the massively parallel integration of ATO valves in VLSI microfluidic networks comprising individually addressable, 400-picoliter wells that are completely sealed at rest (Fig. 1). Each well is comprised of two 200-pL half-wells that are connected to vertical and horizontal fill lines respectively, enabling the creation of combinatorial libraries of chemical compounds, e.g. A1B1 to AnBn. Reactants are pulled into the chip from inlet ports upon vacuum actuation of the set of valves (red and orange valves in Fig. 1), thus eliminating the need for reactant feed lines required when using ATC valves. After filling, mixing of the adjacent 200-pL half-wells is accomplished by repeated actuation of a third set of valves (black).
RESULTS AND DISCUSSION

ATO valves exhibit a hysteresis with respect to actuation pressure when opened and closed, which can be influenced by parameters such as channel width, area of valve seat, and surface properties. Valve operation with valve seat area based on valve seating calculations for channels 75, 100 and 125 μm wide (Fig. 2, blue, green and red respectively). To open, the strong adhesion between the PDMS valve seat and the glass substrate must be overcome, whereas a small vacuum is sufficient to keep the valve open against the tensile strength of the PDMS.

We integrated a chip comprised of a 4x4 array of 400-pL wells with a patterned diffraction grating-based BIND sensor described in previous work [7]. We successfully validated its functionality in a combinatorial protein / antibody binding assay.
using mixed arrays of protein against three IgG antibodies (Fig. 3). An advantage of using ATO valves is that after filling and incubation, the chip can be decoupled from all peripheral lines and transported to a reader for detection of binding events.

![Sensor image after mixing of the adjacent components. Proteins adhere strongly to a certain matching IgG antibody, resulting in a red-shift in the right half-well compared to the left half-well. A strong association is shown in (2,2) and (3,1), and weaker binding is seen in (2,1) and (3,2), all as expected. (The red shift in the left most column is an artifact that we have since resolved.)](image)

**CONCLUSIONS**

We report the first example of integrated VLSI microfluidic networks with ATO valves, which simplifies their use with respect to portability, integrated control and dead volumes. In addition, we show the chip’s feasibility in combinatorial screening applications with a protein-antibody assay. This chip opens up the use of microfluidic chips for high throughput screening applications in which as many conditions as possible need to be screened with a precious target, such as certain disease-related proteins for drug screening, of limited availability.

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**REFERENCES**


