Integrated Microsystems for Microfluidics/BioMEMS: Cellular Sample Handling and Analysis

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Abstract

SUMMiTTM technology has evolved over the last decade into one of the most capable surface micromachining technologies [1]. Our current technology development efforts are aimed at integration of microfluidic, mechanical, optical and electrical/electrochemical capabilities in this technology base.

Technology

Standard SUMMiTTM technology provides five polysilicon layers that are independently patterned that allows the creation of intricate structures. This allows the designers to have a very flexible design space; however, there are designs which require the creation of electrically insulated chambers and/or mechanical structures. To address these new device and application requirements, we have made modifications to the baseline SUMMiTTM technology, shown in Fig.1, which enable the creation of insulator lined, transparent microfluidic channels/cavities along with complex mechanical, optical and electrical structures (Fig.2) [2].

Figure 1. (a) Standard SUMMiTTM layers and (b) modified flow. Incorporation of low stress silicon nitride layers allows the creation of complex microfluidic/mechanical structures with optical access and the ability to create almost any arbitrary field inside these structures. Electrodes that are in contact with the fluid inside the channel allow direct (electrochemical) access to the microenvironment.

Devices

The microsystem components fabricated include valves (Fig.3), an accumulator (Fig.4), pumps (Fig.5), channels (Fig.6) and a microtransfection device (Fig.7) [3] as technology demonstration prototypes. These devices are also geared towards being the base components in a microfluidic/BioMEMS design toolbox.

Figure 2. Reticle set of prototype devices (channels, electrodes, pumps, valves, microtransfection device) fabricated using the modified flow.

Valves are critical in many different sample/fluid handling systems. The first prototypes we have fabricated are flapper valves that open in the forward direction and close in the opposite direction. By designing the seats and flaps in subsequent polysilicon layers, check valves that function both in and out of plane directions have been realized. We are currently fabricating electrostatically actuated valves that will allow gating and proportional flow control functions.

Some of the preliminary data for a check valve is also shown in Figure 3. This valve was pressurized in the reverse direction (flow coming out of plane), and after the pressure was equalized on both sides of the valve, the syringe pump was started in the forward direction (flow into the plane). The valve did not open immediately, a pressure difference of 10mbar was required to open the valve which translates to a force of $7.5\text{N}/\text{um}^2$ at the valve seat/flap interface.

Similar pressure vs. time data is also given for an accumulator structure in Figure 4. This structure was formed by a 500um diameter, 0.6um high cavity. The top of the structure is formed by a 0.8um thick silicon nitride layer. The pressurization and discharge of air from this cavity (through a surface micromachined channel) is shown in the figure.

Figure 3. (a) Inlet and outlet valves constructed using polysilicon layers. Polysilicon springs provide the restoring force for the valves. Outer diameter of the valve structure is 135 μm , and the valve height is 3 μm . (b) Flow testing of a valve with the nitride layer removed to allow access to the ambient. The valve was over-pressurized in the reverse direction, the valve opened after a pressure difference of 10 mbar was reached in the forward direction (which translates to 7.5 nN/ μm^2 at the valve seat).

The valves shown above are incorporated into the membrane pump design in Figure 5. Inlet and outlet ports are on the left and right sides of the circular structure, which are connected through Bosch etched holes and the valves sit on top of these connection ports. Etch release holes (four circular

Figure 4. Accumulator. A built-in pressurized fluid storage structure - this chamber consists of a 500 μm diameter, 0.6 μm (initial) height region covered by a 0.8 μm silicon nitride membrane. This chamber was connected to a surface channel to route the chemical of interest into a manipulation chamber. Data shown was taken while charging this chamber with air at flow rate of 1.2 $\mu\text{L}/\text{min}$. After the charging was stopped, flow through the 1 nL volume channel was observed as the pressure dropped.

Figure 5. A membrane pump realized using the modified flow. Inlet/outlet valves are inside the cavity and actuation electrodes are placed above the silicon nitride layer (1 mm diameter, 6 μm above the surface).

openings in the middle) are formed during the same process step and are sealed by the fixture/package that holds the chip.

Some of the most interesting and promising features in surface/photo/electro-chemistry also start becoming dominant and/or feasible in the scale of the devices described here. Several devices have been designed and fabricated to investigate these effects (Figure 6). Electokinetic pumping, dielectrophoretic separations, travelling wave setups, magnetic particle manipulations and electrochemical modification of the electrodes/channel contents are some of the concepts that are being addressed by these designs.

Figure 6. (a) A flow channel with electrodes of varying shapes and spacing to create almost any arbitrary field inside the channel for pumping, separations and in-channel synthesis/reactions. (b) Close-up SEM of polysilicon electrodes formed around the silicon nitride channel structure.

The microtransfection device was also designed and fabricated to demonstrate the integration capabilities offered by this technology (Figure 7). In this device, microfluidic, electrical/electrochemical, optical and mechanical components are integrated to perform manipulations on individual cells in a continuous flow fashion. Cells enter the device through one of the Bosch etched connections from the back of the wafer, travel through the manipulation section which has the electrostatically actuated mechanical manipulator and a second fluid entry/exit port, and exit the device on the other side. All of the structure is enclosed by nitride, which allows optical access, electrical insulation and through a passage, mechanical coupling to the actuator that is placed outside of the fluid flow.

Figure 7. Microtransfection device which shows the integration of microfluidic channels, mechanical/electrical structures and optical access. The mechanical manipulator is actuated by a high performance comb drive coupled with a displacement multiplier. Electrodes are positioned before and after the manipulation section. Mechanical manipulation is intended to temporarily disrupt the cellular membrane allowing delivery of large molecules into the cell that would normally be excluded. The last figure shows bovine red blood cells flowing through the manipulation region.

Another device that has been designed to manipulate individual cells is the patch clamp array (Figure 8). In this device, cell localization regions are defined by holes etched in the nitride layer, and the vacuum applied through the cavity below is used to capture cells. Silicon substrate behind the cell localization region has been removed to provide optical access for transmission/reflection and fluorescence microscopy with multiple electrodes for simultaneous electrical measurements and manipulations. Devices with further enhancements that involve incorporation of new mechanical structures for coupling to the cells are currently being designed and fabricated.

A critical part of the overall system integration involves packaging and assembly of components such as the ones described here. The methodology we are pursuing for integration is best illustrated by its analogy to the current microelectronic systems; the channels that are formed in plastic or glass integration substrates are analogous to the printed circuit boards and the integrated microfluidic devices are analogous to the integrated circuits, performing specialized functions. The packaging methodology will be very dependent on the final function – for example, an environmental sensor will have to interface with the ambient, requiring specialized collection/sample delivery options. We are pursuing several options in generating these packaging systems, including polymers, plastics and injection molded structures (Fig.9) [6].

Conclusions

Microsystems are expected to play a key role in the impending global technology revolution [7]. The completion of the human genome project has signaled the start of the hard part of this work: figuring out the details of the cellular machinery that is encoded by the genome and the overall “system” view starting with proteins, leading to cells, tissue, organs and finally the whole organism. The devices and the technology described here are aimed at providing the next generation of tools for the

Figure 8. (a) Cross section of the patch clamp array. (b) Cell localization structure with a PDMS cage to hold the sample fluid. Four cell capture regions are visible with two electrodes below each hole in the center. The two larger holes are for fluid delivery/extraction and there is a larger sample delivery port on the top right portion of the device. (c) Red blood cells are being delivered into the device and are captured on the holes with the flow out of the lower left port. Silicon substrate behind the cell localization region has been etched to provide through-device optical access. Impedance based measurements for detecting cell capture and modification, electrochemical modification of electrodes/cells, multiple sample introduction/removal and fluorescence based measurements are currently under way.

biological and medical sciences in pursuit of these goals, starting with tools for measurement and manipulation of a single cell.

Figure 9. Packaging approach involving the microdevice, polymer/plastic based fanout part, molded or ceramic package and the circuit-board with fluidic and electrical interconnects.

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