Advances in Micro-Devices for Biomedical Applications

The advancement of Micro-Electro-Mechanical-Systems (MEMS) technology and micro-fabrication process has enabled the design and fabrication of components and integrated bio-systems with unique functionalities and applications. With advanced process integration and as dimensional tolerances of the micro-fabricated devices are improved, new bioassay schemes can be envisioned for various applications which requires precise and predictable control of bioassay kinetics (mixing, separation, capturing, collection, sensing). New applications and potential opportunities include point-of-care (POC) rapid diagnosis, drug discovery, and patient-specific therapeutics [1], lab-on-a-chip (LOC) and organ-on-a-chip (OOC) devices [2].

Sensera Inc., an integrated fast-turnaround designer and manufacturer of high performance micro-fabricated devices, assists its customers in meeting the stringent engineering and manufacturing requirements of this emerging biomedical product market sector through unique core capabilities including:

- Biocompatible and durable surface modification methods and processes to produce hydrophilic and hydrophobic surfaces on various underlying layers and materials;
- Micro-fabricating microfluidic molds and flexible replicates with lateral dimensional tolerance of 50nm.
- Hermetic seals and wafer bonding at low bonding temperatures, typically 150C-300C and as low as ambient temperatures, with a specialized sealing medium and process.

Sensera is experienced in working collaboratively with customers from various market sectors, including a biomedical industry, for prototyping, productization, scalable and manufacturable micro-fabrication process development and product manufacturing.

Surface Chemistry Control for Biomedical Micro-Devices

Transport properties of a liquid medium through flow channels are governed primarily by the liquid's viscosity and the pressure gradient across the channels in macroscopic flow systems. In such traditional flow systems, a variety of components and subsystems, such as membrane filters, mixers, pumps, reaction chambers, are used to separate, collect, mix and carry out chemical reactions between various constituents.

However, as the characteristic size of the flow channel is decreased, the behavior of the flowing medium is greatly influenced by the chemistry of the flow channel surfaces. When the mean free path of the molecules in the flowing medium approaches the characteristic size of the flow channel, the flow can no longer be treated as a *continuum*. In this regime, which is often the case with micro-fluidic devices, micro-channel surface chemistry can greatly influence flow behavior of the flowing medium.

By utilizing this unique micro-channel flow behavior, much smaller and highly efficient micro-fluidic devices can be designed and produced by intelligent engineering of the surface chemistry. For example, two different flowing media can be mixed, reacted, and separated *in-flow* within the micro-channel by controlling micro-channel surface chemistry as shown in **Figure 1** and demonstrated by Hibara, et.al. [3]

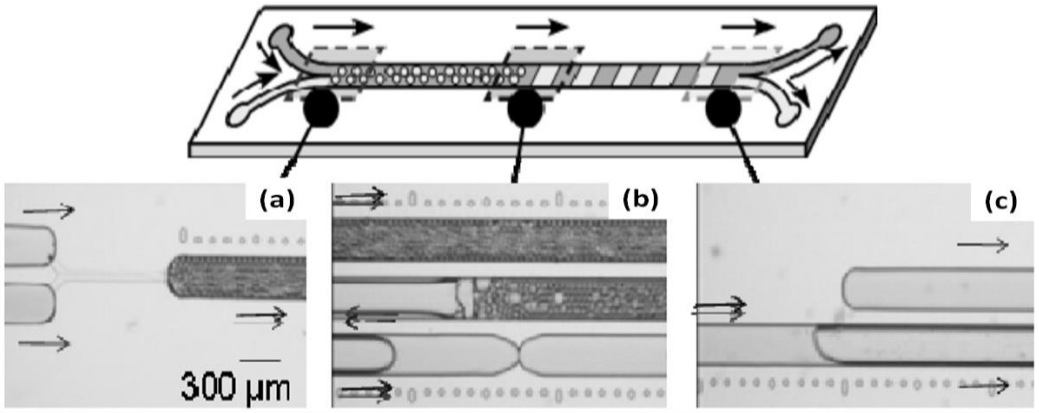

Figure 1: ***Demonstration of in-flow (a) droplet formation, (b) droplet-to-plug conversion and (c) separation of two-phase liquid by controlling surface chemistry of micro-channels. [3]***

Further, new liquid transport and reaction schemes which do not require conventional flow handling and control components can be envisioned and designed. For example, complex organ-level functions were mimicked on the 'breathing' lung-on-a-chip micro-fabricated system, as shown in **Figure 2**. [4] These examples demonstrate that extremely compact and high efficiency micro-fluidic systems can be designed and fabricated by the engineering and processing of micro-channels with controlled surface chemistry. Therefore, a convenient method of producing micro-channels with controlled chemistry, such as their hydrophilicity and hydrophobicity, is highly desirable to fully leverage and implement the advantages of micro-fabricated biomedical systems.

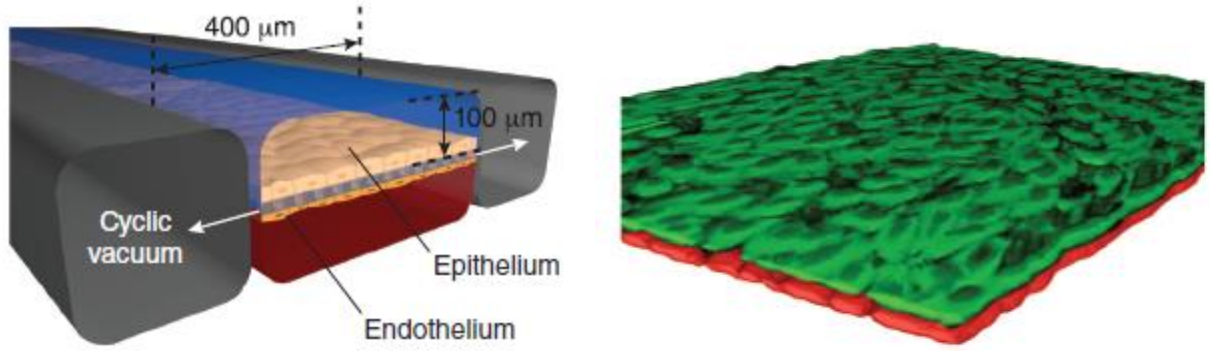

Figure 2: ***A schematic view of the 'breathing' lung-on-a-chip that recapitulates the alveoli-capillary interface (Left) and the fluorescence confocal 3D reconstruction (Right). [4]***

The degree of hydrophilicity, or water wettability of a surface, is generally quantified by water contact angle (WCA) measurement. The hydrophilicity/hydrophobicity of most solid material surfaces is primarily determined by functional groups on the surface. Some surface functional groups exhibit a high stability (or durability) toward environmental conditions and changes, such as temperature, relative humidity, pH, etc., while others do not. Some materials are inherently hydrophilic (small WCA) or hydrophobic (large WCA). Even for similar materials, the hydrophilicity/hydrophobicity can significantly differ depending on the history of the material. Therefore, proper design and engineering of the micro-fabrication process is critical for producing micro-channel devices with controlled surface chemistry for specific hydrophilicity/hydrophobicity.

At Sensera, we developed a method of producing hydrophilic and hydrophobic surfaces for various applications which are durable, applicable to large areas, bio-compatible and micro-fabrication process compatible. We have established an extensive data base and processing capabilities to control hydrophilicity/hydrophobicity of the solid surface. The approach can be application-specific selection of materials or surface modification processing. As shown in **Figure 3**, excellent inherently hydrophilic (WCA 11.3°) and hydrophobic (WCA 127.5°) surfaces are obtained by selecting glass substrates with different constituents. Further, super-hydrophilic (WCA 2.4°) and super-hydrophobic (WCA 141.4°) surfaces can be produced by plasma surface treatment and by nano-texturing of the glass surface, respectively. Sensera offers a micro-fabrication process to integrate these hydrophilic/hydrophobic surface treatment methods, including other well-known super-hydrophobic surfaces [5,6] into micro-fabricated biomedical devices.

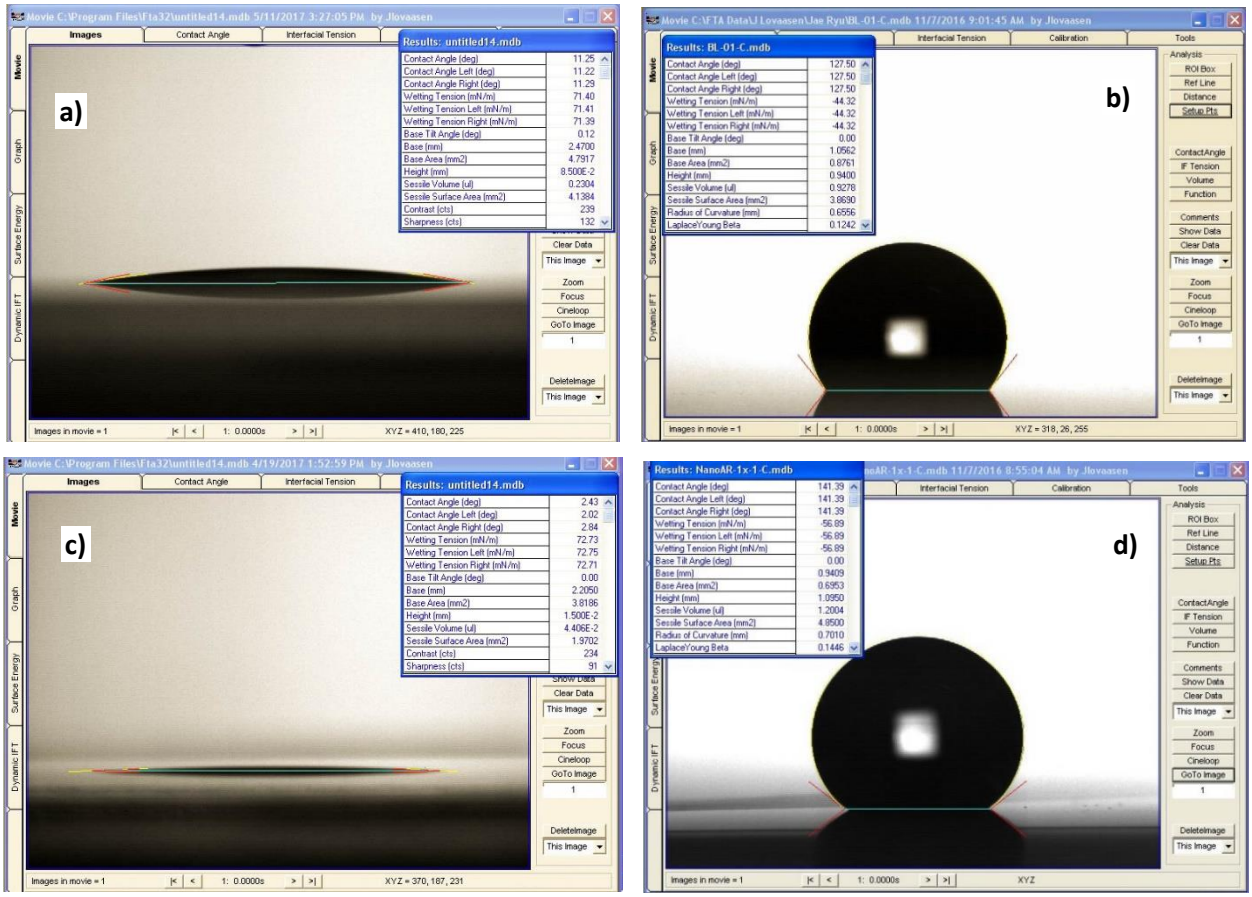

Figure 3: ***Various bio-compatible materials which are used for micro-biomedical systems: (a) inherently hydrophilic glass wafer; (b) inherently hydrophobic glass wafer; (c) super-hydrophilic plasma treated glass; and (d) super-hydrophobic nano-textured surface.***

Microfluidic Molds and Micro/Nano-Imprints

The cost of micro-fluidic devices must be sufficiently low to support their widespread use for the intended applications of drug discovery, patient-specific drug delivery, rapid diagnosis, organ-on-chip, etc. Biomedical micro-fluidic devices are typically manufactured by using flexible replicates or stamps which are produced via micro-molding or imprinting using micro-fabricated master molds. [7] In the well-established micro/nano-imprinting process, the micro-fabricated master mold is the costliest element. Multiple flexible stamps, typically numbering 5 to 10 pieces, can be produced from one master mold, as shown in **Figure 4**. After 5 to 10 replications, the master mold may be damaged or degraded and is the discarded. In the case where the cost of the master mold is very high, multiple rigid replicates, typically 3 to 4 pieces, are produced from the master mold. Usually, more than 10 flexible stamps are produced from each rigid replicate which is generally more durable than the master mold. Therefore, over 40 flexible stamps can be produced from one master mold by using the relatively low cost intermediate stage rigid replicates.

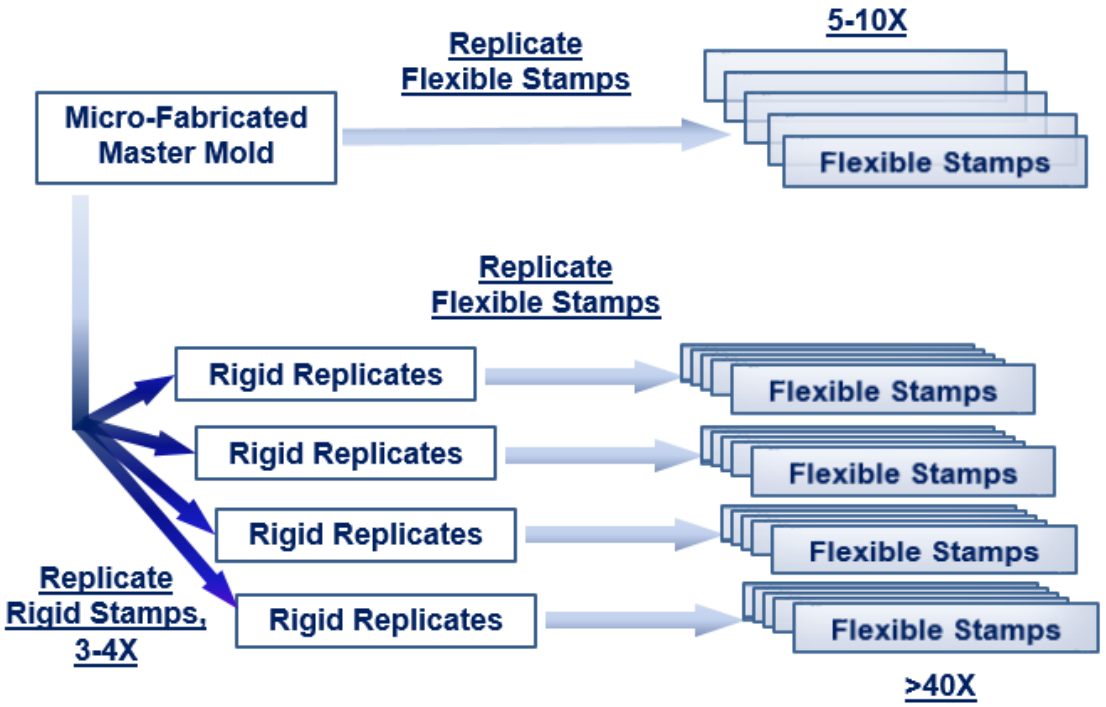

Figure 4: Typical pathways to produce multiple flexible stamps from a micro-fabricated master mold for micro-fluidic devices.

The intermediate stage rigid replicate can be constructed by using less fragile and more mechanically durable materials such as nickel or other engineering plastics. The preferred scenario to produce multiple flexible stamps for a micro-fluidic device application will depend on multiple factors, including:

- Fidelity requirements or functional specifications of the flexible stamp;
- Dimensional tolerances, both lateral and vertical, of the flexible stamps;
- Complexity, lead time and cost of the master mold;
- Volume requirements of the flexible stamp;
- Specific assembly procedure and functional complexity of the micro-fluidic device.

Sensera brings extensive design and hands-on experiences with micro- and nano-imprinting processes, micro-molding, rigid and soft replicate production, and flexible stamp fabrication procedures.

Bio-Compatible Packaging and Seals at Low Process Temperatures

Packaging of many biomedical micro-fluidic devices requires a low temperature die or wafer bonding process. A low temperature bonding process (T<50°C) is required to assemble biomedical devices when temperature-sensitive bio-molecules and/or organic layers are integral to the device. Typical materials to be bonded for biomedical devices include:

- Inorganic-to-inorganic, such as silicon-to-silicon, silicon-to-glass (including silicon dioxide) and glass-to-glass;
- Organic-to-inorganic, such as silicon/glass and polymer; and
- Organic-to-organic, such as polymer and polymer.

Depending on materials to be bonded, a suitable bonding process can be designed and implemented for manufacturing. Currently, many different types of wafer/die bonding techniques and processes are available and some are widely used at an industrial scale, [8] while others are in engineering development. [9] Pros and cons of these well-established and emerging technologies for packaging biomedical micro-devices/systems are summarized in **Table I**.

Techniques	Typical Temp. (°C)	Pros	Cons
Anodic	>300	• Strong bonds • Hermetic seals • High yield	• High Temp. • Long bonding time • High voltage
Glass Frit	>300	• Hermetic seals • Rough surface ok • High yield	• High Temp. • Long bonding time • Wide sealing area required
Adhesive	>150	• Versatile • Rough surface ok	• Non-hermetic
Surface Activation	~R.T.	• Low temperatures	• Very flat surface required • Limited applicability
Thermal Compression	~R.T. - 300	• Hermetic • Low temperatures • Rough surface ok	• Specific bonding medium required • High force

Table I: Bonding Techniques Used in Biomedical Microsystems

It is clear that the preferred bonding technique is primarily determined by both process compatibility of the parts to be bonded and the required seal performance of the assembled devices. If low bonding temperatures (near R.T.) are required, adhesive bonding or gold-based thermal compression bonding are good options. Surface activation bonding (SAB) is widely used in many micro-fluidic devices, especially in a prototyping stage. However, reproducibility and process yields for various large volume products are not yet fully established.

Anodic bonding and low temperature adhesive bonding are used at Sensera primarily for various electro-optic and biomedical devices. We are in development of near-room temperature thermal compression bonding and surface activation bonding for biomedical device applications.

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