BioMEMS for Future Drug Discovery Needs

a report by
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Introduction

Billions of dollars are spent finding ‘blockbuster’ drugs by pharmaceutical companies. Due to the potential riches that can be earned from these blockbusters in the global healthcare market, pharmaceutical companies are increasing the dollars spent each year on research and development (R&D). About US$400–800 million and 10 years is spent by each of these companies to bring a drug to market for which only one out of five lead drug compounds make it to final clinical use.¹ Hence, there is tremendous pressure within these companies to ensure an improved ‘success rate’, reduced cycle time and lower R&D costs.

Towards this end, there is a drive towards technologies that support miniaturisation and high throughput, which enable faster drug target discovery and drug development. Miniaturisation allows numerous experiments to be carried out using smaller quantities of expensive reagents and test samples. High-throughput screening and massive parallelism increase the speed at which numerous combinations of experiments yield the blockbuster drug compounds.

BioMEMS for Drug Discovery

Using Micro Electro Mechanical Systems (MEMS) fabrication technology, it is possible to make structures with micron-sized features that enable mechanical, electrical, thermal or chemical functionality using substrate materials such as silicon, glass or plastics. Moreover, since it is an offshoot of microelectronic fabrication technology, it is fundamentally suited towards precisely controlled, mass manufacturing. When applied within the pharmaceutical, life sciences and healthcare application fields, components made using this technology are commonly referred to as ‘bioMEMS’ devices. These devices often take the form of microarray chips, microfluidic chips, lab-on-a-chip, or µTAS (micro Total Analysis System), drug delivery components and enable miniaturised instruments on chips the size of a few millimetres on edge to 1mm in thickness. They can perform analytical, synthetic, amplification and detection procedures requiring only a tiny volume of chemicals and in a fraction of the time of conventional instrumentation. These components are often an integration of electrical, fluidic and optical elements within the bioMEMS instrument.

In the past two years, the doubling of bioMEMS patent applications is mainly attributed to new markets for proven drug discovery technology. The widespread use of bioMEMS devices has quickly been accepted by pharmaceutical companies as a rapid and accurate solution for screening for compounds and thereby increasing the speed of development of new therapeutic pharmaceuticals.² Apart from higher speed, advantages of using bioMEMS devices include lower cost of reduced use of reagents and labour, greater control and modularity.³

BioMEMS devices also create new applications within these arenas and accelerate the rapid growth of these markets. BioMEMS devices have been applied to a variety of steps in the drug discovery pathway. From the areas of genomics to proteomics, many laboratory instruments can be miniaturised onto a bioMEMS chip. This is yet another advantage of MEMS technology since it can effectively integrate multiple functional blocks together, allowing quick and inexpensive performance of complex multistep analytical protocols, which traditionally require a host of different machines. Finally, the mass manufacturability of MEMS technology permits low per-unit-cost components with very accurate and repeatable dimensional control that are vital for effective sample mixing and

separation. The lower unit costs permit single-use disposable devices, thereby preventing the risks associated with cross-contamination from reuse.

In the field of drug discovery, key bioMEMS devices are microarrays, microfluidic chips, and micro capillary electrophoresis (CE) chips. The microarray marketplace is growing rapidly and these devices are being used widely. Microarray technology allows both miniaturisation and high-throughput processing for applications such as drug discovery, gene expression, genotyping, mutation screening, gene synthesis and proteomics. Intriguing results are beginning to emerge from the use of DNA microarrays to classify subtypes of cancer and to guide treatment decisions. Once they are optimised further for classifying disease, determining the most appropriate treatments, their market potential could be significant.

Microfluidic devices fabricated using MEMS offer numerous application potential such as high-throughput drug screening, clinical diagnostics and genetic analysis. Passive elements such as enclosed channels, conduits, nozzles and reservoirs can be fabricated using micromachined substrates such as silicon and glass, which are then bonded together. Active elements such as valves and pumps can also be fabricated using the same processing steps, thus integrating an entire microfluidic system. When dealing with small volumes, an enclosed microfluidic system offers the benefit of a variety of processing options such as sorting, mixing and separation of tiny sample volumes as well as containing evaporation losses that are significant when dealing with microlitre and nanolitre volumes. These microfluidic structures can be integrated with electrodes to form capillary electrophoretic systems for rapid assay development.

**MEMS Foundries**

The entry barrier to manufacture the bioMEMS device for healthcare and pharmaceutical applications, however, is high. Moreover, biomedical companies usually do not have captive MEMS fabrication capabilities since the bioMEMS device is typically just one of many components that need to be integrated into their final product offering. As a result, a significant portion of these biomedical companies are strategically partnered with a MEMS foundry facility for the development and manufacturing of their mission-critical bioMEMS devices.

Most biochips with microfluidic structures are fabricated with bulk micromachining technology using wet and dry etching techniques to provide a more robust fabrication method with higher structure flexibility but with a lower cost structure than most high-aspect ratio micromachining technologies. Applied MEMS has core competencies in bulk micro-machining and robust wafer/wafer bonding technologies. Some popular materials used for bioMEMS devices are silicon and glass. Silicon serves as a multipurpose substrate that can be micro-machined and can house microfluidic features as well as integrated conductors that enable electrodes, bond pads, etc. Moreover, it can be subjected to surface treatments to enable biocompatibility or to possess appropriate surface chemistry properties. Glass or pyrex have the advantages of being highly suitable top caps that are transparent, easily machined using MEMS, laser ablation or ultrasonic drilling and also biocompatible. Glass, being an electrical insulating material, facilitates having electrically conductive layers deposited and patterned on it. Through the use of these materials, microarrays, microfluidics, microfluidic CE chips and micro biomedical tools such as nozzles and needles can be fabricated.

**Case Study – XeoChip®**

Taking advantage of Applied MEMS demonstrated foundry capabilities, Xeotron has partnered with Applied MEMS to create its proprietary in situ synthesised DNA oligonucleotide (oligo) microarray technology for a broad range of applications. The core of this technology is an in situ parallel combinatorial synthesis within the three-dimensional (3-D) nanochambers of microfluidic chips (Xeochip®) and involving photo-generated reaction chemistry and digital photolithography. This enables an extremely flexible, cost-effective and yet highly industrialised process.

The XeoChip® is fabricated at Applied MEMS using MEMS bulk micromachining technologies (see Figures 1 and 2). Channels connecting the synthesis chambers are 56µm in diameter and have been etched into the silicon with a cover glass bonded onto the upper surface, creating 8,064 individual, 3-D reaction chambers. Each chamber is connected in parallel by fluid distribution channels, allowing parallel reagent flow to all reaction sites. The DNA synthesis in the chambers utilises a photo-reactive process where a digital micro-mirror device is used to shine light on specific individual reaction chambers at the appropriate time. This technology allows the production of high-quality custom oligonucleotide microarrays with quick turnaround and low cost. These microarrays are typically used in gene expression experiments where ribonucleic acid (RNA) levels from up to 8,000 genes can be monitored, in parallel. The XeoChips® are used with existing commercial detection equipment.

dramatically lowering entry costs and allowing greater access to more researchers.

Each chamber is an isolated site for chemical synthesis or bioassays. This microenvironment significantly enhances rates of intermolecular interactions, such as hybridisation. The microfluidic flow through the XeoChip® is pressure driven and controlled by a programmable solvent manifold.

These microfluidic chips provide several attractive benefits for use as biological microarrays:

- **flexibility** – different sets of DNA sequences can be easily synthesised;
- **controllable temperature and flow conditions**;
- **readable by most commercial detection instruments**;
- **easy-to-handle because molecules are inside the chip, not on the surface**;
- **small inner volume, less than 6µl per chip**; and
- **highly efficient molecular contacting environment**.

**Probe Synthesis Within the XeoChip®**

Each XeoChip® or microarray consists of 63 x 128 features (reaction chambers). The fluidic channels within the chip have been designed for optimal, even flow of reagents throughout each feature of the array. Xeotron uses its patented photogenerated reagent (PGR) during oligonucleotide synthesis with standard phosphoramidite chemistry in conjunction with a maskless, digital micro-mirror device (DMD) projector (see Figure 3) to effectively synthesise any DNA sequence at any feature on any chip. The combination of microfluidic chip, PGR chemistry and DMD projector enables a highly flexible chip platform with robust performance and good reproducibility. Coupling efficiencies in excess of 98% allow the synthesis of oligos up to 100 bases in length in a few hours.

**Use of XeoChips®**

The microfluidic chip is inserted into a chip holder for use in Xeotron’s microfluidic hybridisation station. The hybridisation station allows multiple chips to be hybridised and washed at the same time. For typical expression analyses, arrays are hybridised to Cy3 and Cy5 fluorescently labelled cDNA or cRNA. Following hybridisation, the chip holder can be transferred to a microarray scanner for fluorescent image capture (see Figure 4).

**Figure 4** presents an example of a XeoChip® used in differential gene expression of brain versus skeletal muscle samples. This XeoChip® contains 254 oligos representing cancer-related genes in 30 replicates throughout the chip. Use of the chip yields uniform spot intensities (see enlarged image, Figure 4) and a well-differentiated gene expression pattern of the two tissue samples. Red features indicate over-expression of that gene in muscle, and green, in brain, while yellow indicates approximately equal expression. The circular features are readily analysed with most commercially available image analysis software, to gain an estimation of gene expression levels between two biological samples.

As demonstrated with the Xeotron application, the microfluidic MEMs chip provides an ideal medium for manufacture and use of tools to study changes in gene expression levels. This is just one of many applications that can make use of DNA biochips. Similarly, synthetic peptides may also be synthesised within these chips. The bioMEMS XeoChips® are invaluable tools for use in the expanding the fields of genomics and proteomics.
Due to increasing cash-conservation and time-to-market pressures of today’s global economy, many biomedical companies are requiring their foundry partners to offer solutions that significantly reduce both the cost and time of bioMEMS device R&D cycles and that lower the perceived entry barrier to using MEMS technology. In order to address these concerns, Applied MEMS, Inc. introduced a family of bioMEMS technology platforms (known as Applied BioMEMSTM) based on standardised fabrication processes that reduce the costs and cycle times of proof of concept, product prototyping and volume production phases of bioMEMS device commercialisation. Unlike integrated circuit electronic chips, MEMS devices are inherently 3-D in structure and encompass multiple physical and energy domains. This often necessitates a custom and non-standard process to be developed for each application need. Therefore, our standardised Applied BioMEMSTM technology platforms are targeted on very specific and prominent product families of bioMEMS devices for healthcare and pharmaceutical applications.

Applied BioMEMSTM Technology Platform

In order to address the most prevalent bioMEMS device applications, our initial Applied BioMEMSTM technology platforms are divided into four families:

- **MicroArray family** is formed on a single silicon wafer as the platform for sample screening, sample identification and similar spotted array applications.
- **MicroFluidic family** for lab-on-chip, microreactor, DNA/protein chips and similar applications. The microfluidic chambers, channels and ports are formed on a single silicon wafer, which is bonded to a glass capping wafer.
• ElectroMicroFluidic family for electrophoresis, chemical sensing and similar applications. The microfluidic channels and ports are formed on a single silicon wafer, which is bonded to a glass capping wafer that contains integrated electrodes.

• 3-D MicroFluidic family for complex 3-D microfluidics (drug delivery), micropumps, microvalve and similar applications. There are two independent levels of microfluidic chambers, channels and ports that are formed on two bonded silicon wafers, which are bonded to a top glass capping wafer.

The MicroArray and MicroFluidic platforms have recently been introduced and the resulting demonstrator chips are shown in Figure 5. The ElectroMicroFluidic and 3-D MicroFluidic platforms will be introduced later in 2004.

Each of the technology platform families is based on a standardised fabrication process utilising silicon and glass and results in a device that is compatible with optical read-out techniques. There are user design guidelines for each of the technology platforms that provide the foundry customer with maximum flexibility in customising the chip for their application, while simultaneously reducing costs and cycle time by at least 30% through the use of standardised processes. This procedure is user-friendly, requiring the foundry customer to only provide the chip-level artwork along with a few user-defined design inputs (as per Tables 1 and 2). This methodology supports the entire bioMEMS device commercialisation process from proof of concept through low-volume prototyping to high-volume production.

One obvious disadvantage of a standardised technology platform approach is that it cannot address all possible bioMEMS devices for healthcare, life science and pharmaceutical applications. In this situation, where the foundry customer requires additional functionality or features, they would commit to customised wafer fabrication runs that include the necessary design/process development cycles. For some of these customised fabrication run situations, Applied BioMEMS technology platforms can be used as stepping-stone foundations that help minimise the amount of customised design/process development cycles required to develop the bioMEMS device.

Conclusion

MEMS technology is ideally poised for the miniaturisation of devices and components used routinely in instrumentation for drug discovery and development as well as other life sciences applications. The implementation of these bioMEMS devices enables low-volume usage of expensive reagents, high-throughput parallelisation and integration of many different components onto one instrument at a fraction of the cost of conventional systems. Applied MEMS recognises the needs and requirements of the field of drug discovery and can provide partnerships with pharmaceutical and bio-component companies to develop and take to production customised bioMEMS solutions. This was exemplified by the development of the bioMEMS XeoChip® developed and produced for Xeotron Corporation. Moreover, Applied MEMS also offers standardised technology
platforms that help lower the entry barriers into this arena specifically through the MicroArray, MicroFluidic, ElectroMicroFluidic, and 3-D MicroFluidic Platform technologies. The use of either of these bioMEMs solution pathways with MEMS foundries such as Applied MEMS help pharmaceutical companies to lower drug discovery and development costs, achieve lower per-unit cost, offer a high degree of manufacturing control, along with miniaturisation and high-throughput processing. These aspects lead to lower overall costs, reduced cycle times and faster time to market.