The microplate market past, present and future

microplates today – the global market

Microplates and the peripheral markets of liquid handling and detection technologies exist within almost all laboratories performing assays. This article discusses what, if any, are their growth expectations and whether there are new technologies on the horizon that could make the microplate obsolete.

By Dr Peter Banks

Today, microplates are one of the most commonplace of all disposable labware. Its most common format consists of 96 individual wells arranged in eight rows and 12 columns with dimensions defined by the American National Standards Institute[1] through an initiative sponsored by the Society for Biomolecular Sciences in 1996. There are a myriad of microplate types, including different well densities from several wells to several thousand wells per microplate; coloured microplates for different optical readouts (ie black for fluorescence; white for luminescence); solid bottom wells or clear bottom wells for top- or bottom-reading fluorescence, respectively; different plastics (polystyrene, polypropylene, etc); various coatings (ie reduction of non-specific binding, tissue-culture treated, etc) and so on.

The annual global market for microplates is approaching $500 million globally and dominated by several large companies such as Corning, Greiner Bio-One, NUNC and a large number of smaller companies focusing on specialty products or microplates designed for specific applications. In addition to this market, peripheral markets focus on the provision of instrumentation, in the form of liquid handling devices and microplate readers, specifically designed to use microplates as analysis vessels.

The liquid handling market encompasses a wide range, from hand-held pipettors that can address either individual or multiple wells simultaneously to semi- to full-automation solutions that dispense multiple reagents and/or aspirate contents from full columns of microplate wells or complete microplates simultaneously. This market is slightly larger than the microplate market itself and is estimated to be $600 million. Numerous companies provide products into this market including Tecan, Eppendorf, Mettler-Toledo, PerkinElmer and Beckman Coulter.

Microplate readers range from single mode detection devices akin to the first absorbance readers that appeared on the market more than 30 years ago to highly sophisticated multi-mode readers capable of performing absorbance, luminescence and a wide range of fluorescence-based modes including intensity, fluorescence resonance energy transfer (FRET), time-resolved fluorescence (TRF), the variant TR-FRET and fluorescence polarisation. Some readers have been designed to process microplates in a matter of seconds for applications such as high throughput drug screening. This market is slightly smaller than the microplate market at about $300 million. The top five companies in this market are PerkinElmer, Inc, Thermo Fisher Scientific, MDS Analytical Technologies, Tecan and BioTek Instruments, Inc.

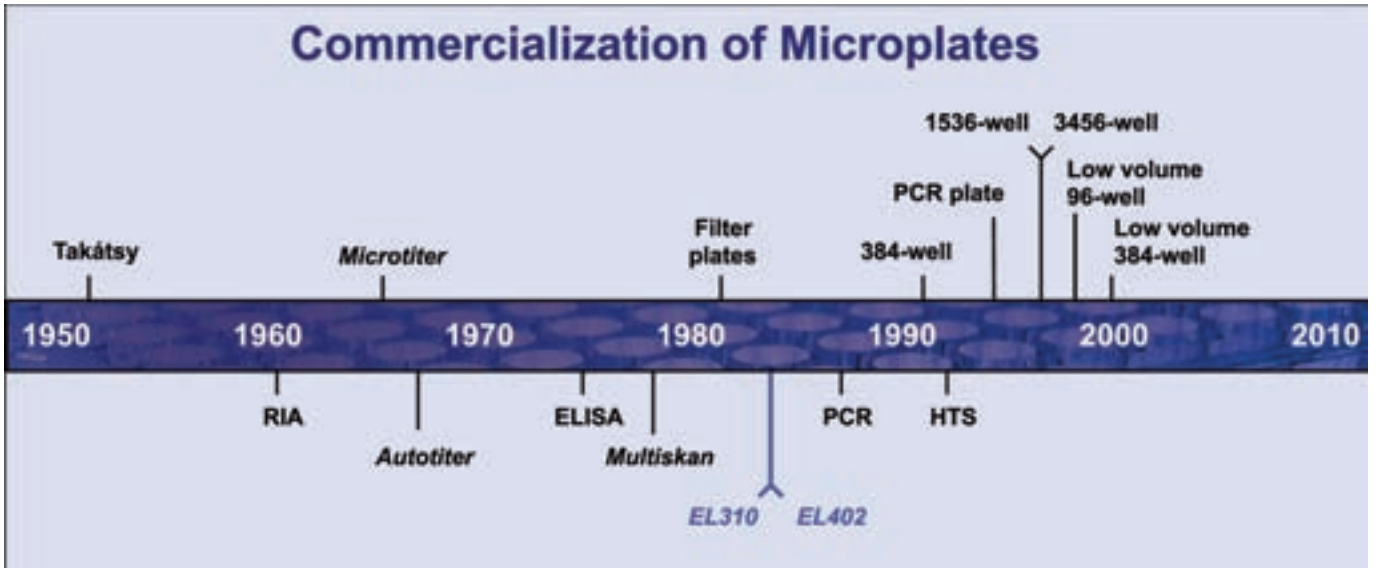

Figure 1
Timeline of microplate and complementary instrument development

The beginning and growth of the market[2]

The first microplate was hand-made in 1951 by Hungarian physician, scientist and inventor Gyula Takátsy. A serious influenza epidemic in Hungary required physicians to find a fast, economic and reliable test method for the identification of the influenza virus. Standard test methods involving reagent tubes and dilution series were too unreliable, tedious, expensive and time-consuming. Using a side-by-side arrangement of wire metering loops, Takátsy was able to fill multiple sample tubes with a defined sample volume at the same time, thus significantly increasing the sample throughput of his laboratory. This model was soon replaced with an easy to use geometry with 8 x 12 wells – the first 96-well microplate (**Figure 1**).

These acrylic plates were individually machined and thus difficult to produce in large quantities. Injection moulding of plastics was developed in the 1960s and was the manufacturing basis of the first commercial 96-well microplate, Microtiter, offered by Cooke Labs (now known as Dynex Technologies) in 1965. Moulded acrylic microplates quickly were replaced with polystyrene, the most common plastic used in microplates today. Microplate usage was largely driven by applications in virology and serology, for example in hemaglutination inhibition where the microplates were useful vessels for performing serial dilutions. The first automated liquid handling device, the Autotiter, was developed in 1967 by Astec Inc (now known as Tomtec), and simply automated serial dilutions much the way Takátsy had performed them manually with his wire loops more than a decade earlier.

Enzyme-linked immunosorbent assays (ELISA) were developed in the mid-1970s as an alternative to radio-immunoassay (RIA) techniques. ELISAs fuelled growth of the use of immunoassays in both research and clinical markets, and microplates were considered the best vessels in which to perform the assays. This growth also created the need for microplate readers. LabSystems (now part of Thermo Fisher Scientific) developed the Multiskan photometer specifically for reading 96-well microplates used in this market. This device marks the beginning of the microplate reader market that we know today.

The microplate, liquid handling and reader markets grew rapidly in the 1980s with numerous companies offering products ranging from different coatings on microplates, filter plates and a wide array of instrumentation. BioTek Instruments entered the market at this time with the EL310 microplate absorbance reader and the EL402 microplate washer (**Figure 2**), both specifically designed for performing ELISAs. The 1980s also saw the development of new enabling technologies such as the polymerase chain reaction (PCR) by Kary Mullis. This again led to the development and use of new microplates, specifically designed for performing PCR.

With the advent of high throughput screening (HTS) for small molecule drug discovery in the 1990s, the market demanded microplates with higher well densities for increased sample throughput. The pharmaceutical industry widely adopted HTS methodologies in the early 1990s where large

libraries of small molecules (up to 106 compounds at the time) were screened for binding to putative drug targets, typically as recombinant purified proteins. The explosion of genomic technology at the time created a vast number of possible drug targets leading to a bottleneck in the drug discovery process at HTS. To alleviate this bottleneck, the 384-well microplate was developed which increased the number of wells by a factor of four on the same footprint as a 96-well microplate. These 384-well microplates were rapidly adopted, and spurred the development of even higher well densities such as 1,536- and 3,456-well microplates by Whatman (now part of GE Healthcare), and by a collaboration between Whatman and Aurora Biosciences (now known as Vertex Pharmaceuticals), respectively in 1996.

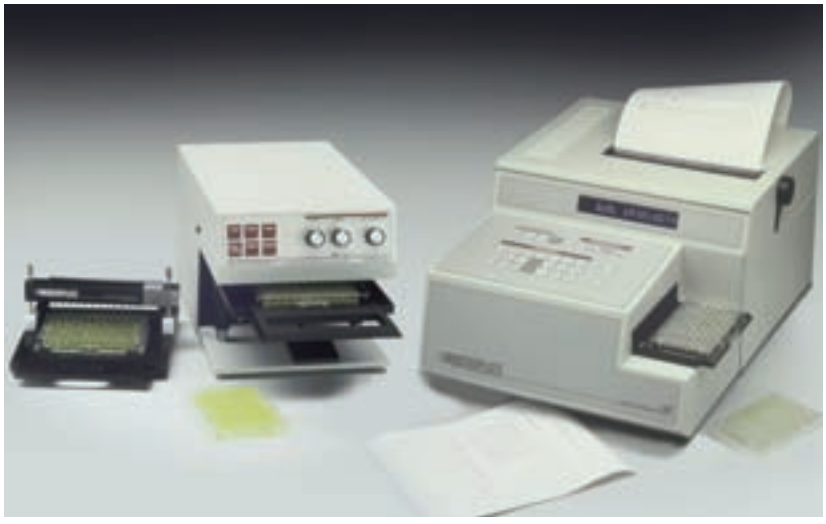

Figure 2 (above)
EL402 and EL310 microplate instruments from BioTek Instruments, circa 1984

Figure 3 (right)
Human Genome U133 Plus 2.0 array. Courtesy of Affymetrix

Difficulties, particularly in liquid handling, limited early adoption of microplates with higher densities than 384-well, which could still use devices designed for 96-well operation. By the time liquid dispensing technologies could deliver sub-microlitre volumes with adequate precision necessary for operation in 1536-well densities, the need for ultra high throughput was limited to a small segment of the market. However, the benefits in miniaturisation available with higher well density, namely smaller assay volumes leading to reduction in costs of reagents, fuelled the development of low volume 96- and 384-well microplates.

In this decade, other scientific advances and new technologies have led to new uses of microplates. For example, the development of RNAi technology has led to genomic screening efforts on a scale similar to HTS. The old HTS paradigm of screening large libraries of small molecules against purified proteins has been replaced, in large part, with assays of greater biological relevance using cells where the drug target is in a milieu more representative of what would occur in the human body. This has driven the need for specialty microplates for cell usage, liquid handling devices that can dispense and wash cells and microplate readers that can measure optical readouts from the bottom of the microplate well. In addition, many researchers want more information per well through multiplexing efforts. A number of technologies have been developed to achieve this including Luminex Corporation's xMAP technology that can measure up to 100 different analytes per well

The future for microplates and peripheral markets

In 2008, most industry pundits forecast continued growth for the microplate and peripheral markets at least in the next few years. The current global recession may confuse these forecasts somewhat, yet the stimulus package from President Obama, which provides a bonus of $21.5 billion in science and research spending[3], should relieve at least US markets. Economic climate aside, are there technology threats here or on the horizon that could make the microplate obsolescent?

Microarray technologies burst into the marketplace in the 1990s, led by Affymetrix and its GeneChip products (**Figure 3**). GeneChips assist researchers in quickly scanning for the presence of particular genes or markers or changes in their expression levels in a biological sample using arrays of thousands of oligonucleotides synthesised on a quartz slide using photolithographic techniques. These microarrays are used to determine

which genes or markers exist in a sample by detecting specific pieces of mRNA or DNA that has undergone some biochemical assay. A single chip can be used to do thousands of experiments in parallel. These genomic analysis applications are widely used into this decade.

Efforts to translate the format to arrays of proteins, which would be directly competitive to microplate and peripheral markets for immunoassay analysis, have been largely unsuccessful in market penetration. Customers wanting the multiplexing capability of protein arrays have largely adopted the Luminex xMAP technology due to flexibility of analyte choice, which uses microplates as the reaction vessel for its assays.

While there is still a need for high density arrays for gene expression analysis, the explosive growth of microarray technologies in the 1990s has been replaced by modest growth or even decline – better growth is seen in focused arrays, which tend to be less expensive. Some focused arrays use printed arrays at the bottom of a microplate, on a glass slide, or various bead-based technologies. This latter market dynamic is apparently evident to Affymetrix also due to the recent acquisition of Panomics which uses the xMAP technology in conjunction with its Quantigene assays for focused gene expression analysis.

A corollary technology based on the use of photolithography to develop microfluidic channels in chips, the so called 'lab-on-a-chip', also heralded a new age in the 1990s. The ability to have myriad channels etched on the chip allows for on-board liquid handling and the ability to perform multiple analyses per chip (ie a channel would be equivalent to one microplate well). Purported applications include real time PCR, biochemical and cell-based assays and immunoassays, which is a direct threat to the microplate market. Caliper Life Sciences is probably the most successful company to have developed a commercial offering, the LabChip system, based on this technology. Yet the LabChip actually uses microplates as storage vessels for reagents from which the 'lab-on-a-chip' (**Figure 4**) sip from, thus the LabChip is actually complementary to the microplate market. Cellectricon has also developed a chip-based microfluidic system named DynaFlow for hERG safety testing of lead compounds in preclinical drug discovery. It also plans to release a high throughput variation of the technology in 2009 in collaboration with AstraZeneca, which will address ion channel drug discovery in general. Yet DynaFlow HT will impact the microplate markets insignificantly. It will typically compete with closed systems like IonWorks provided by MDS Analytical Technologies which do not contribute to the microplate and peripheral markets. The use of 'lab-on-a-chip' technology in other applications remains the focus of academic development.

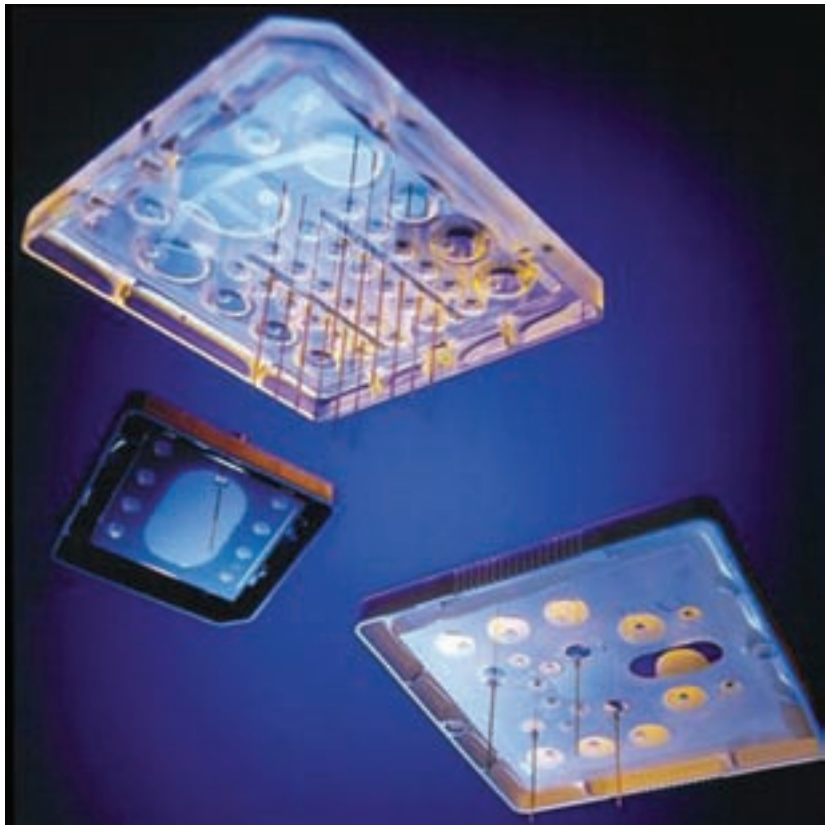

Figure 4
LabChip Chips: Single, 4- and 12-Sipper Chips. Courtesy of Caliper Life Sciences

Label-free technologies based on surface plasmon resonance (SPR, **Figure 5**) such as that offered by Biacore (now part of GE Healthcare) do not use a microplate format and compete on an effective basis with microplate-based technologies performing immunoassays for applications such as biotherapeutics drug discovery and development. Compared to small molecule drug discovery, biotherapeutics have had numerous successes in the pharmaceutical market, especially for immunotherapeutics. Currently there are about 100 companies developing more than 190 antibody drugs for more than 40 different cancer

Figure 5
Biacore CM5 sensorchips. Courtesy of Biacore (GE Healthcare)

References

1 ANSI/SBS 1-2004: Footprint Dimensions; ANSI/SBS 2-2004: Height Dimensions; ANSI/SBS 3-2004: Bottom Outside Flange Dimensions; ANSI/SBS 4-2004: Well positions (96-, 384-, 1536-well).

2 Manns, Roy. Microplate History 2nd Edition May 1999, presented at MipTec-ICAR'99, May 17-21, 1999, Montreux, Switzerland; Astle, Thoma. Recollections of Early Microplate Automation. Journal of the Association for Laboratory Automation, 5, 30-31 (2000).

3 Hossain, Farhana, Cox, Amanda, McGrath, John and Weitburg, Stephen. The Stimulus Plan: How to Spend $787 Billion. The New York Times, Feb 24, 2009.

4 Bioseeker Group, Abs in Oncology: Drug Pipeline Update 2006.

indications[4]. Yet other label-free technologies compete in the same space as Biacore that use standard microplates. ForteBio's Octet platform uses Bio-Layer Interferometry (BLI) technology to enable real-time analysis of biomolecular interactions in a flexible, easy-to-use format with similar binding affinity data as Biacore products. Thus one company's products impact the microplate industry negatively, the other, positively.

Numerous technologies have been devised over the years for higher throughput capability and miniaturisation to reduce reagent costs. Yet it is difficult to miniaturise to assay volumes below what is typical of 1536-well microplates (2-10µL). While acoustic liquid handling systems have the ability to dispense volumes as low as several nanolitres with satisfactory precision, evaporation is still one of the main problems – sub-microlitre assays typically require controlled environments for humidity, at an added expense. Also, cell-based assays become problematic as too few cells can be added to the assay to generate appropriate amounts of reporter necessary for detection. Furthermore, while minimising costs per assay point is still a market driver, increasing sample throughput beyond what is possible with standard microplates is of dubious worth for most applications.

In general, the microplate and peripheral markets in liquid handling and detection comprise a very large market of almost$1.5 billion. The technologies exist in the infrastructure of almost all labs performing assays. It is extremely difficult to envision these microplate-based technologies being replaced anytime soon. DDW

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