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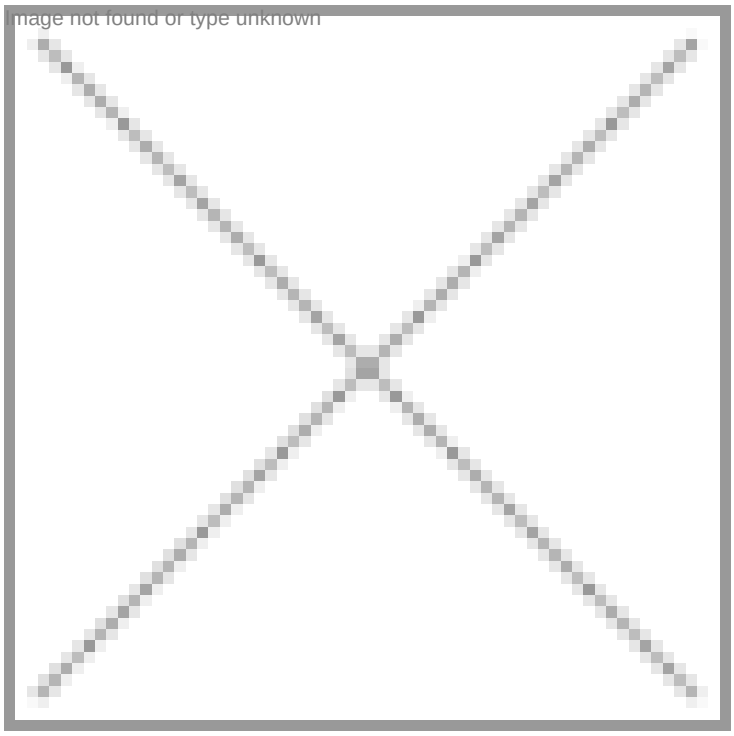

Developments in life science instrumentation and market scenario

Life science research in India has been the driving force propelling growth in the analytical instrument market. This has resulted in the development of new products and applications as well as the opening up of new markets

Biotechnology has been practiced for hundreds of years all over the world for developing crops and cattle with desirable traits. However, modern biotechnology is less than 50 years old. In the last decade especially, a number of important milestones have been crossed in the area of life science research; the sequencing of the human and other model organism genomes being just one of these discoveries. With the development of these new approaches, not only are life science research laboratories experiencing significant gains in productivity, but biotechnology companies are developing products that would have been inconceivable even a few years ago.

Genomic, proteomic and drug discovery applications focus on complex biological systems and exploit molecular processes for furthering basic scientific knowledge, developing new diagnostic tools, and increasing the efficiency of drug development. The key platforms employed for these applications include: DNA sequencers and synthesizers, PCR and Real-time PCR machines, microarray platforms, systems for in vitro and in vivo cell analysis including imaging systems as well as sample preparations instruments.

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DNA sequencing

The Human Genome Project (HGP) has had a major impact on the life sciences, resulting in the development of new applications and tools used across many areas of basic and applied life science research. This has also led to the entry of a number of new players into the DNA sequencing market which has fragmented this market significantly. With a number of new applications and workflows now made possible, a variety of platforms are available from different vendors.

Over the last decade significant improvements have been made to DNA sequencing technology. Some of these landmark improvements include shifting from radioactively labeled nucleotides to more safe fluorescent dye labels as well as the move from slab gels to capillary electrophoresis (CE) based analysis.

Even entry-level DNA sequencing platforms currently available in the market completely automate all the sequencing tasks that were time-consuming and laborious. Filling the capillary with gel (polymer), sample injection, electrophoresis, real-time detection of labeled DNA strands and converting raw data into analyzed data are all steps that are now automated. This allows researchers to focus on discovery instead of spending time on the technique itself and downstream data analysis. Further advancements include increased throughput, widely accepted standards for internationally acceptable data and significant reduction in "per sample" cost. This has resulted in the development of increasingly versatile applications,genotyping, SSCP and methylation studies to name a few.

The development of more efficient and easy-to-use consumables and efficient sample prep kits are now a focus area for all the major players in the market.

In India, DNA sequencing technology per se is well-adopted and employed in almost all the areas of life science research. Being the inventor of the first automated DNA Sequencer, Applied Biosystems (AB) dominates the Indian market with its market share thought to exceed 90 percent followed by other players like GE Amersham, Beckman and Licor.

Next generation DNA sequencers

Predictably, the entry of next generation sequencers will have a significant impact in the market. However, the ability of these platforms to enable novel sequencing applications apart from "de novo sequencing" remains to be seen. Therefore at least for the next few years, market dynamics in the context of technology development is much less predictable. Though it would appear that AB's traditional Sanger-based CE products will maintain their own in the DNA sequencing market at least for a few more years to come. It would be reasonable to expect further fragmentation of the market, with ultra high-throughput technologies competing to become the de facto sequencing standard. Roche/454's Pyrosequencing based GS 20, AB's much awaited solid platform based on sequencing by Oligos ligation and detection technique and Illumina/Solexa's Illumina genome analyzer platform are the three most highly anticipated products in this space in India. Additionally, the Indian scientific community has already expressed great interest in these technologies. Especially in the Indian context, these capital-intensive products would demand high quality informatics capabilities as well as application and service support and that would ultimately differentiate the true leader from others.

Thermal cyclers (PCR)

The Polymerase Chain Reaction (PCR) was invented in 1983 by Dr Kary Mullis. PCR is now the single most widely used method in the molecular biology space. PCR exponentially amplifies DNA via enzymatic replication, capable of producing

billions of copies of a DNA fragment from just a few copies, in less than two hours. There exists a large repertoire of modified PCR-based techniques that is used to perform a wide variety of genetic manipulations.

Market dynamics in India

PCR is used in medical and biological research labs for a variety of applications including basic gene sequencing, diagnosis of hereditary diseases, the identification of genetic fingerprints (used in forensics and paternity testing), the detection and diagnosis of infectious diseases, and the creation of transgenic organisms.

- The life science research in India has been on the rise, propelled by growth in analytical instrument market.
- For automated DNA sequencer, Applied Biosystems dominates with more than 90 percent market share.
- Applied Biosystems, Eppendorf, Bio-Rad, Stratagene, Techne, Corbett and Cepheid are the major players in PCR market.
- For Real Time PCR, the focus has gradually changed from hardware to complete end-to-end workflow solution .
- The major commercial players in the microarray space are Affymetrix, Perkin Elmer and Applied Biosystems.

At the core of the PCR technique, as it is practiced currently, lies the concept of repetitive thermal cycling. This required the development of a very accurate and highly reproducible automated temperature cycling system, known as the thermal cycler. Perkin-Elmer introduced the first commercially available thermal cycler. This platform was based on compressor driven refrigeration technology. Perkin-Elmer dominated the PCR market for almost a decade with their highly well-engineered and reliable products. Gradually, other players also started penetrating the market by introducing more user-friendly and flexible products. The introduction of Peltier-based temperature controlled blocks brought about a landmark change in the PCR market. This was followed by the introduction of interchangeable blocks, multiple blocks, low reaction volume blocks, blocks with high ramping rates all of which were also well received in the Indian market. The introduction of temperature gradient blocks was another key development in the thermal cycler market.

The use of molecular techniques in all segments of the clinical, diagnostic and testing markets has been growing by leaps and bounds over the last few years. This is the primary driver for the growth in the PCR market at present. Major players in PCR market in India include Applied Biosystems, Eppendorf, Bio-Rad, Stratagene, Techne, Corbett and Cepheid.

Real-Time PCR

In the post human genome project era, the wealth of information now available to the scientific community has spurred widespread use of complementary technologies such as real-time PCR, microarrays analysis.

The real-time PCR market in itself has come a long way, since the introduction of the first commercial real-time PCR platform by Applied Biosystems. The focus has gradually changed from hardware to "complete end-to-end workflow-based solution".

During the developmental stage of this product line, real-time PCR was perceived merely as an optical upgrade of conventional PCR. But as more sophisticated applications were enabled by the real-time PCR technique, instrument manufacturers also realized that the technique offered great potential and the need for rapid improvements in their platforms. As a result, hardware features including the light source, the detection systems etc. were rapidly upgraded to keep pace with the application development without diluting the cost to performance ratio. Innovative approaches such as virtual filters were also implemented to deconvolute complex fluorescent dye spectra thus achieving better signal to noise ratios. But soon the technology reached its peak and the chemistry became the bottleneck .

Even though, there are various real-time PCR chemistries available, two chemistries are widely used by the scientists all over the world. These are FRET-based TaqMan technology and SYBR Green chemistry which is dependent on SYBR Green's ability to bind any double-stranded nucleic acid molecule. TaqMan chemistry is extremely accurate and highly specific and considered to be the gold standard for real-time PCR experiments. However, with proper optimization SYBR green based methods can also work well.

Having sensed the need for speed and reliability, technology providers started offering "readymade off-the-shelf" assays, "customized" assays and optimized reagents enabling sample preparation from a wide range of specimens. As of today, the entire focus has shifted to provide complete "workflow solutions" to researchers. This has allowed scientists to focus on the science and discovery rather than the technique. This strategy has largely been successful as witnessed by the wide acceptance of AB's TaqMan assays-on-demand and similar products from other vendors.

The most recent and novel innovation in this area has been the adoption of the microarray format for running real-time PCR experiments. This format allows researchers to interrogate the expression level of hundreds of genes simultaneously. With increasing number of scientists wanting a bird's eye view of gene expression at the pathway and individual biological process level, which typically involves a few hundred genes, these real-time PCR based low density arrays have already become a very popular tool. These arrays are also becoming an incredibly powerful tool to analyze global gene expression changes in the entire miRNA gene set. Another significant advantage for scientists is the simple workflow and significantly lower dependence on bioinformatics.

Globally more than a dozen companies operate in this space in the Indian market, Applied Biosystems has the highest share

of the market with Bio-Rad, Stratagene, Eppendorf and Roche being the other major stake holders in the basic research market. Additionally, Corbett, Cepheid and Techne are also trying to make inroads into this market. As further innovation in instrument technology has been slowing down over the last few years, one can expect that further growth in this market will be mainly driven by innovative reagents and consumables at least for the next few years.

Globally there are three major players in the regulated clinical and in vitro diagnostics market-Roche, Abbott and Corbett. This critical market is growing by leaps and bounds but "per sample" cost is the major concern for most end users.

Microarray

Over the last few years, based on end-user specific application needs, the microarray market has been fragmented into multiple segments such as SNPs, alternative splicing, microRNA, whole transcriptome, ChIP-on-Chip etc. Microarrays are also being offered with increasing amounts of content on a single array. With all these developments taking place and even more in the pipeline, microarray technology in India still remains largely underutilized. The primary reason for this is the lack of sequence information for many of the plant and microorganism species, which are worked on in India. A microarray with appropriate content for these species is not available commercially. Further compounding this problem is the lack of proper training and experienced personnel and especially the lack of strong bioinformatics support. The latter is the major bottleneck for sub-optimal microarray usage in India even in laboratories which work on standard model organisms such as human, rat and mouse.

The microarray market can be divided either via end-user requirement into whole genome arrays and smaller customized arrays. It can also be segmented into pre-spotted arrays and custom-spotted arrays. Another way to segment the market is as closed system arrays and open system mix & match type arrays.

With the multitude of different platforms and product offerings available, it has become a real challenge to the Indian scientists to choose the right technology for their projects. By and large, Affymetrix is seen as the market leader in this market space in the world for expression arrays and Illumina for genotyping/SNP arrays.

As far as Indian market is concerned, flexibility to work with a wide range of species and a wide range of spots per array at a reasonable price are the major selection criterion. Thus, "mix & match" types of open platforms are most preferred in India.

The major commercial players in the microarray space in India are Affymetrix, Perkin-Elmer and Applied Biosystems.

Bioinformatics

Bioinformatics is an interdisciplinary field, which addresses biological problems using computational techniques, and makes the rapid organization and analysis of biological data possible. Bioinformatics plays a key role in various areas, such as functional genomics, structural genomics, and proteomics, and forms a key component in the biotechnology and pharmaceutical sectors.