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Gene Sequencing Fulfills Multiple Needs

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Sequencing technology has intensified the mapping of human genome and brings humanity closer to understand the molecular mechanisms of life. Years after the introduction of the first gene sequencer, gene sequencing technology has played a vital role in enhancing modern molecular research.

The completion of the Human Genome Project (HGP) marked the end of ‘the first half of genetics’. Armed with a reference sequence of 3.2 billion bases of DNA, the scientific community has at its fingertips a priceless resource that could change the face of biomedical research and medicine.

The free availability of reference sequence raised a host of crucial questions like, what genetic variations are associated with evolution of mankind? Which genes are associated with complex genetic diseases? What does genetic variation tells us about ethnic susceptibility to drugs and diseases? What is the function of the vast stretches of non-coding or junk DNA? The scientific community across the world quickly realized the need for a paradigm shift in DNA sequencing technology to address these and many other questions. After all, by most estimates, the HGP consumed 13 years and $2.7 billion to map the human genome. It was impossible to reproduce these efforts every time when scientists make an attempt to solve the most complex puzzles in medical science; unless it can be done much faster at really affordable cost without compromising the accuracy.

Next generation 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. 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 solid platform based on sequencing by oligos ligation and detection technique, and Illumina/Solexa's Illumina genome analyzer platform are the three most highly successful products in this space in India.
In India, DNA sequencing technology 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.

A mighty technology

The DNA and protein sequencing technology has revolutionized genomics by allowing rapid automated sequencing of genes. Development in DNA sequencing technology has provided unprecedented insight into the entire collection of genome transcribed sequences. Without this technology, the progress that led to the biotechnological production of enzymes, active agents as well as antigens for vaccines would not have been possible. The introduction of gene sequencer has extensively accelerated the pace of biological research and various discoveries. The quick pace of sequencing is achieved by employing sophisticated modern DNA sequencing technology. The technology has helped scientists to generate the complete DNA sequences of many plants, animals and microbial genomes across the globe. The success of the human genome project has led to rapid advances in the life science industry.
DNA sequencing technology has shown promising results in treating pathogenic infections such as HIV and hepatitis virus,as well as other ailments; and is also gaining prominence as it offers a ray of hope for those afflicted with genetic disorders. The extensive data from protein and DNA sequencing experiments have provided scientists with a wealth of information that forms the basis for the investigation of cellular processes. Towards the end of their research and development efforts, pharmaceutical companies seek to deliver safe and efficient molecules.
With tremendous technological developments happening in protein and DNA sequencing, pharmacogenomic approaches have benefited from the availability of the human protein sequence, which provides clues to describe genetic networks and may ultimately initiate new ways of developing compounds. The availability of the human protein sequence, together with the pharmacogenomic and pharmacogenetic approaches, is expected to contribute to a better selection with a faster development of safer and more effective drugs.

Genesis of technology

The genomics revolution that reached its peak point owes its very existence to two men. The first is Frederick Sanger, who in 1977 developed the method for DNA sequencing. The second is Leroy Hood, who with colleagues Michael Hunkapiller and Lloyd Smith, at the California Institute of Technology (Caltech) in 1986 developed the key technology behind the DNA sequencing machines and the reagents needed to run them. The DNA sequencing machines are now marketed by Applied BioSystems.
Sanger's enzymatic approach relies on specially modified reagents (2',3'-dideoxynucleotide triphosphates) whose incorporation into a growing DNA strand terminates the extension reaction. The method calls for extending a primer-template pair in the presence of a radioactive marker and, in four parallel reactions, either dideoxy-A, dideoxy-C, dideoxy-G, or dideoxy-T. The resulting products can then be resolved on a high-resolution polyacrylamide gel to produce a four-lane-wide ladder that reveals the template's sequence. Brilliantly inventive, the technique is also laborious, producing a few hundred or perhaps a thousand bases at a time, which then have to be read by hand.
Hood's invention, the automated DNA sequencer, simplified the process of sequencing developed by Sanger by replacingthe radioactive marker with safer fluorescent ones. That first system, marketed by Applied Biosystems could produce 4,800 bases of sequence per day. Today, some companies still market systems based on this design. But the polyacrylamide gel of Hood's first foray for the most part has been replaced by arrays of tiny capillaries, each of which acts as a lane from an old-style gel.

Technological development

The general methodology has changed relatively little since the introduction of the first protein sequencer. However the useof automated equipment to perform multiple cycles has greatly improved the efficacy of sequencing. Automated protein sequencing is considered as a major development in the field of biotechnology. Optimization has allowed the determination of extended sequences of very low abundance proteins. Much effort in recent years has been devoted to improve the sensitivity of protein sequencers by using new, highly sensitive methods for identifying amino acids. A large number of upgraded, automated and sensitive DNA sequencing machines continue to enter the market at a much cheaper cost.
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. The processes like filling the capillary with gel, sample injection, electrophoresis, real-time detection of labeled DNA strands and converting raw data into analyzed data 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. These advancements have 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 preparation kits are now a focus area for all the major players in the market.

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