NOVATEUR PUBLICATIONS
JournalNX- A Multidisciplinary Peer Reviewed Journal
ISSN No: 2581 - 4230
VOLUME 8, ISSUE 12, Dec. -2022

ADVANTAGES AND DISADVANTAGES OF THE TECHNOLOGY FOR DETERMINING THE NUCLEOTIDE SEQUENCE OF DNA

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Resume
This article discusses the main advantages and disadvantages of the technology of different generations of DNA sequencing. The main innovative ideas in the evolution of sequencing technology.

Keywords: sequencing, DNA, amplification, oligonucleotides, sequencers.

INTRODUCTION

DNA sequencing is an experimental method for determining the sequence of bases consisting of nucleic acids (A, T, G and C) in a polynucleotide encoding various proteins that function in a cell. The complete set of coding and non-coding nucleotides in the DNA of organisms is called the genome. The genome contains information about all the proteins that are important for the normal functioning of the body. There are similarities between biological sequences that can be determined by comparing them with each other. To do this, we need to know the complete genome sequence of the organism under study.

INITIAL DATA AND METHODS

The chemical degradation method proposed by Maxam and Gilbert, the deoxy chain termination method developed by Sanger and his team in 1977, and automated fluorescence-assisted sequencing technologies developed in the 1990s formed the first generation sequencing (FGS). Due to its simplicity, the Sanger method has become the preferred method in FGS. Sanger sequencing made it possible to read the complete genome of the bacteriophage PhiX 174, consisting of 5375 nucleotides. In 2003, within the framework of the international project of the consortium "Human Genome", a map of the complete human genome was sequenced and completed in the laboratories of the world.

Second generation sequencing (single genome sequencing - SGS) or next generation sequencing (NGS) are high throughput DNA sequencing technologies capable of sequencing millions or billions of strands of DNA. In doing so, the sequencing process allows multiple sequencing of target regions and high throughput properties. Third generation sequencing (TGS) is characterized by the addition of single nucleotides, which provides long and accurate sequencing results and does not use amplification technology. Single cell sequencing is also a TGS technology.

Each generation and sequencing platform has certain advantages and disadvantages in accordance with its methodological approach, and these features determine their use in a particular practical application. Thus, an assessment of these properties, limitations, and potential applications will help determine the future direction of research related to sequencing technologies.

FIRST GENERATION

The main convenience of Maxam-Gilbert sequencing is that the DNA template used in this method can be single-stranded or double-stranded. The Maxam-Gilbert method can be used for DNA-protein and epigenetic DNA modifications. The limitations of the Maxam-Gilbert sequencing method were the use of harmful chemicals, X-rays, and radioactive targets. The complexity of expanding and using these methods, as well as the use of a strong neurotoxin, hydrazine, made the method useless and almost irrelevant in the further development of technology.

Sanger sequencing has helped researchers identify the root cause of mutations and genetic diseases. This method is considered the most advanced for sequencing short tandem repeats and isolated genes. However, the biggest disadvantage is that it takes a long time due to the low conductivity. The method can only process short DNA sequences (300-1000 base pairs) at a time.

Automatic DNA sequencers are expensive and difficult to sequence repetitive portions of sequences. Despite the advent of next generation sequencers, automated Sanger sequencing is still considered the "gold standard" due to read length and accuracy. However, this sequencing method is slow and expensive for mass application.

The main advantage of **pyrosequencing** is that it saves time, so the process can be carried out in real time. The method is more economical than dideoxynucleotide chain termination sequencing and facilitates the separation of haplotypes and identification of the structure of genetic variations spanning tens of thousands of bases of the genomic template. However, the main disadvantage of the method is significant frameshift errors, which lead to systematic errors in the reading process. Only relatively short sections can be determined by the method.

SECOND GENERATION

The main advantage of **SBS (sequencing by synthesis)** technologies is that up to 96 samples can be sequenced in one run using standard reagents. In addition, SBS technology has a distinct advantage in homopolymer sequencing over 454 or Ion Torrent, as it allows one nucleotide to be added per reaction. Another advantage of the technology is that it can read DNA sequences with paired ends. The main limitation of SBS technology is the short read length. This is especially noticeable when reading de novo sequences. Switching errors due to increased background noise on each cycle also limit the capabilities of this technology. The high cost of this technology is one of its disadvantages.

The advantage of **ABI/SOLiD sequencing** technology is that it is the only NGS sequencing method in which each nucleotide is read twice, which improves sequencing accuracy. The main limitation of the ABI/SOLiD Sequencing technology is the complexity of sequencing palindromic sequences, the method records them as different random sequences.

The main advantage of **Ion Torrent sequencing** is that it is chemically simple and requires a small sample size for analysis. As a result, sequencing speed is fast and running costs are low. The disadvantage is the occurrence of insertions and deletions of single nucleotides during sequencing. To address this issue, Life Technologies has released an updated version of its Ion Reporter product.

Another disadvantage of the system is the brevity of the reads compared to Sanger sequencing or pyrosequencing.

THIRD GENERATION

Single molecule real time sequencing (SMRT) allows to obtain very long reads (on average from 20,000 to 60,000 nucleotides), which helps to solve a number of problems that arise when working with short fragments, facilitating further analysis. Free from initial DNA amplification, studied by PCR. This method provides very high sequencing speed (theoretically it is limited only by the speed of DNA polymerase). The method has a high level of sensitivity and specificity and allows to detect inclusions with a probability of 0.1% in mixed samples. The main disadvantage of SMRT sequencing is a high level of error, sometimes reaching 15%. The weak point of the technology is its dependence on the immobilization of DNA-polymerase/SMRTbell-matrix complexes, which leads to the predominance of short DNA fragments.

Nanopore sequencing. Among the known sequencing methods, this method is superior due to its low cost and ease of use, high sensitivity, long reading length (tens of thousands of base pairs), compactness, speed of analysis, and the ability to display results in real time. The disadvantages include the low quality of reading, the failure of biological probes over time. In addition, it was determined that the environment affects the speed and quality of reading.

RESULTS AND CONCLUSIONS

After the chemical chain termination method introduced by Maxam and Gilbert in 1977, the Sanger method, discovered in the same year, revolutionized biology. These methods led to the sequencing of larger genomes, culminating in the Human Genome Project. As a next step, large-scale sequencing projects can be used to study human variation. However, for such large-scale projects, the Sanger method was too expensive and time consuming. In 2004, the National Human Genome Research Institute (NHGRI) launched a program to reduce the cost of reading a complete genome to $1,000 over 10 years. This has led to the development of fast and inexpensive NGS technologies capable of multiplying many millions of reactions in a single run. The main advantage of NGS technologies was to avoid bacterial cloning of DNA fragments and electrophoretic separation of sequencing products. Illumina NGS technologies are currently leading the global market. Due to its low cost, NGS technology has allowed small laboratories to sequence the genome. Currently, NGS technologies are the backbone of biology and are widely used in clinical and agronomic research. Although NGS technologies are high throughput, their main disadvantage is their short read length. Because genomes contain many repetitive sequences that are slightly longer than the length read by NGS, misassembly and breaks are observed as a result. Because of this, many genomes are divided into hundreds and thousands of contigs. In addition, large structural variations (SVs) are difficult to find and characterize, while single nucleotide variations (SNVs) and short indices can be accurately detected with short reads. This is an important question since most medical specimens are inherently SV. Branches with extreme GC% are also inefficiently amplified by PCR. After NGS came TGS technologies. In 2014, Oxford Nanopore Technologies (ONT) proposed a nanopore sequencing method. PCR amplification is not used in this method. However, third-generation sequencing technologies have a number of disadvantages. An example is the high error rate of nanopore-based sequencing. To solve these problems, world laboratories and companies continue research.

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