**BIOINFORMATICS: AN EMERGING**

 **TOOL FOR BIOLOGICAL SCIENCE**

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**ABSTRACT**

Recent advances in technology have accelerated the understanding of the genetic basis of phenotypes. With these developments, genomics has altered the way that biological challenges are thought about on a genome-wide (genome-wide) scale, revealing a large amount of information and creating a myriad of opportunities. One of these recently developed fields is bioinformatics, which uses the concept of computer Science, molecular biology, mathematics, and statistics to store, retrieve, and analyze biological data. Even though it is still in its infancy, it has quickly emerged as one of the field with the quickest growth rates and established itself as a crucial part of any biological research program. It is becoming more well-known because of its capacity to quickly and affordably analyze vast amounts of biological data. A biologist can use a variety of web- and/or computer-based tools provided by bioinformatics to extract valuable information from biological data, the majority of which are free to use. This introductory chapter aims to provide overall picture on basics and advancement in the field of bioinformatics benefitting readers in various fields of Biological science.

**Keywords :** Genomics, Genome-wide, Bioinformatics, database, molecular biology

1. **INTRODUCTION**

Due to enormous advancements in the domains of molecular biology and genomics, the amount of biological information has greatly increased during the genomic era. Since its inception in the 1980s, the field of bioinformatics has expanded quickly in tandem with the expansion of genome sequence data. In order to develop methods for the storage, retrieval, and analysis of biological data, multiple diverse fields of study—including computer Science, molecular biology, mathematics, and statistics—were combined to form the interdisciplinary field of study known as bioinformatics [32]. The amount of molecular data collection from multiple levels of organization of an organism or environmental sample has significantly increased as a result of the quick adoption of omics techniques, their expanding power, and more affordable costs. With the recent development of Next-Generation Sequencing (NGS) technologies, the sequencing of nucleic acids underwent yet another revolution, ushering in a new era for omics techniques.

 Paulien Hogeweg is credited with creating the term "bioinformatics" (1979). Since the establishment of SWISS-MODEL server and the introduction of user-friendly interactive automated modeling about 18 years ago [37], this field has expanded tremendously. Since then, using databases and informatics at the backend to process biological data at a much faster rate has been crucial to the biological sciences. Large-scale biological data management, analysis, and manipulation fall under the purview of the field, which includes all computational tools and techniques [27]. To store, organize, and index the massive amount of sequence data generated by various sequencing techniques, electronic databases are required. The databases also require specific tools so that researchers may access, analyze, and add fresh or updated sequencing data. In order to identify structural quirks and interactions of molecular sequences that are essential for structural biology and the creation of pharmaceuticals, bioinformatics tools can be employed for restoration, pattern recognition, folding, simulation, and molecular modeling. [40]. It is difficult to manually examine all of these enormous, genome-derived, molecular sequence studies of raw "Big Data." [30].

1. **DEVELOPMENT OF BIOINFORMATICS**

 The networking of computers and the collection of data on genes and proteins marked the beginning of the development of bioinformatics. In 1956, 51 amino acid residues of bovine insulin were described as the first protein sequence. A few years after the first protein sequence became accessible; the first bioinformatics database was built. Physical chemist Margaret Dayhoff, who lived in America from 1925 to 1983, was a pioneer in the use of computational techniques in the field of bioinformatics. She gathered all the sequence data that was available and created the "Atlas of Protein Sequence and Structure," the first bioinformatics database. David J. Lipman, a former director of the National Center for Biotechnology Information (NCBI), referred to Dayhoff as "the mother and father of bioinformatics" because of her significance to this field [32]. This is because of her contribution to the creation of algorithms that can recognize and display structures for use in X-ray crystallography, as well as computational approaches for protein sequence comparison that allow us to deduce the evolutionary relationships between kingdoms [21,50]. Dayhoff also created the one-letter amino acid code that is still in use today, as well as three-letter abbreviations (e.g., Lys for lysine, Ser for serine) (Table 1). For the first time this one-letter code was used in the Dayhoff and Eck's ‘Atlas of Protein Sequence and Structure’ (1965) [9], the first biological sequence database

**Table 1: Symbols used to represent amino acid in Protein Sequences**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
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| --- | --- | --- |
| **Single letter code** | **Amino acid** | **Three letter code** |
| A | Alanine | Ala |
| B | Asparagine or Aaspartic acid | Asx |
| C | Cystine | Cys |
| D | Aspartic acid | Asp |
| E | Glutamic acid | Glu |
| F | Phenylalanine | Phe |
| G | Glycine | Gly |
| H | Histidine | His |
| I | Isoleucine | Lie |
| K | Lysine | Lys |
| L | Leucine | Leu |
| M | Methionine | Met |
| N | Asparagine | Asn |
| P | Proline | Pro |
| Q | Glutamine | Gln |
| R | Arginine | Arg |
| S | Serine | Ser |
| T | Threonine | Thr |
| V | Valine | Val |
| W | Tryptophan | Trp |
| X | Any amino acid | Xaa |
| Y | Tyrosine | Tyr |
| Z | Glutamine or Glutamic acid | Glx |

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 The foundation of the Indian Institute of Science in 1990 and the Bioinformatics Institute of India in 2002 helped the field of bioinformatics to expand in India during the 1980s. GN Ramachandran is considered as the god father of Indian bioinformatics.  The Department of Biotechnology published a plan in 2004 to make India a centre for bioinformatics worldwide.

 George Bell and associates began compiling DNA sequences into GenBank in 1974 in order to provide immunology research with a theoretical foundation. Between 1982 and 1992, Walter Goad's team [32] produced the first version of GenBank. As a result of their efforts, the most widely used DNA sequence databases GenBank [17], "The European Molecular Biology Laboratory (EMBL) [45], and DNA DataBank of Japan (DDBJ) [8] were made in 1979, 1980, and 1984, respectively. The most significant development in DNA sequence databases was the introduction of web-based search engines, which allow researchers to locate and evaluate the target DNA sequences. These pioneering inventions were made by David Benson, David Lipman, and associates, who also developed the software programs "GENEINFO" and "Entrez" [32]. Researchers may rapidly search database-indexed sequences and compare them to the sequence they were querying by utilizing this application. Software is now easily accessible through web-based interface of the National Center for Biotechnology Information (NCBI) database's web-based interface [46]. Comparison, analysis, and visualization of molecular sequences have become more sophisticated, and a variety of techniques have helped to advance bioinformatics in this field.

1. **Branches of Bioinformatics**

 Gene products have come into emphasis since the first draught of the human genome was finished [23, 49] instead of genes themselves. Genetic information is given a functional relevance in functional genomics. When analysing and interpreting biological data, information is taken into account at different levels, including the genome, proteome, and transcriptome. Transcriptomics is the study of the messenger RNA transcripts generated by a cell, whereas proteomics is the study of the total number of proteins (proteome) expressed by a cell (transcriptome).

**COMPLEXITY**

TRANSCRIPTOMICS

GENOMICS

PROTEOMICS

**Figure 1.Flow diagram representing complexity of genomic data processing (Source: Bayat A, 2002)**

 Gene is considered as the basic unit of heredity responsible for the transmission of traits from one generation to the next, and is stored in a genome as DNA molecules. Generating detailed genetic and physical maps of the genome in order to designate segments with ever higher resolution and sequentially organize the segments is the primary goal of genome sequencing.  (18). A method known as the direct shotgun methodology is also used for genome sequencing [48]. The goal of this method is to break the genome into overlapping, random fragments, and then use computer algorithms to sequence the fragments and put the sequences together. Analysis of genomic sequences reveals that each organism possesses an array of genes required for basic metabolic processes and also the genes whose products determine the specialized function of an organism. Complete genome sequencing confer better understanding of a particular gene and protein expression based on the information obtained by evaluating the genome sequences. Complete genome sequencing offers a foundation upon which to construct knowledge about the expression of genes and proteins [29], but it is not always adequate to describe all of the protein constituents of an organism. In proteomics, the amino acid sequence of a protein is analyzed to determine its three-dimensional structure and to link it to the protein's specific function. Applications of bioinformatics in the field of proteomics included the study of amino acid sequences, the discovery of protein binding partners, the detection of polymorphism, splice variants, and post-translational modifications. The major technologies in the field of proteomics include two-dimensional gel electrophoresis, mass spectrometry, and protein microarrays. Understanding and extracting information from the data generated by these instruments requires the use of bioinformatics techniques. The functional study entails metabolic pathway reconstruction and simulation, protein-protein interaction prediction, protein sub-cellular localization prediction, and gene expression profiling [42, 52]. These aspects of bioinformatics analysis are not isolated, but often interact to produce integrated results.

1. **Databases**

 Biological databases are collections of biological sciences gleaned from high throughput experimentation techniques, published literature, and computational analysis. Storage and management of biological data and information in computer accessible forms is the primary goal of biological databases [2]. An integrated collection of computer software known as a "database management system (DBMS)" allows access to the information in the databases. By using this software users get access to all of the data stored in the databases. The data that is stored can be used as primary source as well as for future use. As a result of the range of information that they store, databases are divided into three categories: *primary*, *secondary*, and *composite*.

1. **Primary Sequence Database(s)** are those that serve as repositories for raw sequence data and may be freely accessed via the Internet contain information on the sequences or structure alone (WWW). For example, the DNA Databank of Japan (DDBJ) for genome sequence, the Nucleotide Sequence Database operated by the European Molecular Biology Laboratory (EMBL), and GenBank, maintained by the National Center for Biotechnology Information (NCBI).

It gathers distinctive data from the lab and makes these data available to the users without any change. Each data when entered has their unique accession number through which data can be later retrieved.

1. **Secondary sequence database(s)** consists of information that was obtained via the study of data found in primary databases, such as conserved sequences, a protein family's active sites, or conserved secondary motifs [14,19]. The primary database is subjected to computational algorithms, and the secondary database contains useful and instructive data. Some databases, including SCOP made at Cambridge University, CATH created at University College London, eMOTIF created at Stanford, etc., are built and hosted by individual researchers in their own labs.
2. **Composite database(s)** contains a range of primary database sources, eliminating the need to look up information at several places. Nucleotide and protein databases are provided by the National Center for Biotechnology Information (NCBI), on its vast, highly accessible network of computer servers.

**Table 2: LIST OF IMPORTANT DATABASES**

|  |  |  |
| --- | --- | --- |
| **DATABASE** | **DESCRIPTION** | **REFERENCES** |
| **Nucleotide Databases** |  |
| DNA Databank of Japan (DDBJ) | It is one of the largest databases for nucleotide sequences and a member of the International Nucleotide Sequence Databases (INSD). | [8] |
| European MolecularBiology Laboratory(EMBL) | Repository of DNA and RNA sequences that is complementary to GenBank and DDBJ | [45] |
| GenBank | It belongs to the international nucleotide sequence databases (INSD). NCBI's primary nucleotide sequencing database in the USA | [17] |
| **Protein Databases** |  |
| Uniprot | One of the largest collection protein sequences | [47] |
| Protein DataBank | A significant source of information on proteins, giving details on the complex assemblages of nucleic acids, proteins, and their empirically confirmed structures |  [5] |
| Prosite  | Gives details on the active sites, conserved domains, and protein families. | [43] |
| SWISS-PROT | A section of the UniProt knowledge repository where protein sequences have been manually annotated. | [6] |
| InterPro | Resource that includes information on protein families, conserved domains, and active sites. | [41] |
| SCOP | Relationship between Familial and Structural Proteins | [16] |
| **Genome Database** |  |
| Ensemble Plants | A comprehensive database that provides genome-scale data for an increasing number of sequenced plant species. | [15] |
| Protein Information Resource ( PIR) | Non-redundant, comprehensive, and annotated protein sequence database | [51] |
| Phytozome  | A comparative hub for comparison and research of plant genome and gene family information. | [20] |
| **Miscellaneous databases** |  |
| TAIR | For the model plant Arabidopsis thaliana, The Arabidopsis Information Resource (TAIR) keeps a collection of genetic and molecular information. | [44] |
| KEGG | The Kyoto Encyclopedia of Genes and Genomes (KEGG) is a knowledge repository that connects genomic data with higher order functional data to analyse genes' activities systematically. | [25] |

1. **Gene identification and sequence analyses**

 Understanding the various characteristics of a biomolecule, such as a protein or nucleic acid that give it its particular function is referred to as a sequence analysis. The sequences of the associated compounds are first acquired from open databases. After refinement, if required, they are subjected to various tools that enable prediction of their more precise features. The analysis can be used to recognize a transit peptide, introns, exons, or an open reading frame (ORF), as well as to identify specific variable regions that can be used as signatures for diagnostic purposes. It can also be used to identify promoter, terminator, or un-translated regions involved in the expression regulations. There are many tools designed for this purpose, some of which are crucial (enlisted in Table 3 with function).

**Table 3: Tools for Primary Sequence Analysis**

|  |  |
| --- | --- |
| **Tools** | **Description** |
| BLAST (Local Sequence Alignment) | It is a search tool that is used to identify DNA or protein sequences. |
| Clustal Omega (Global Sequence Alignment) | This program can be used to conduct multiple sequence alignments. |
| HMMER  | With the use of this tool, homologous protein sequences can be searched in the relevant databases |
| Open Reading Frame (ORF) Finder | This tool can be used to find ORF for putative genes. |
| ProtParam | used to forecast proteins' physicochemical qualities |
| PPP | Prokaryotic Promoter Prediction tool used to determine the promoter sequences that are present upstream of the gene |
| JIGSAW | To find genes, and to predict the splicing sites in the selected sequences  |
| Genscan | makes use of genomic sequences to determine the intron-exon locations |
| Softberry Tools | Along with the structure and function prediction of RNA and proteins, some technologies are specialized in the annotation of animal, plant, and bacterial genomes. |

1. **Sequence Alignment**

 The increased accessibility of data produced by NGS technologies has processed alignment, which is widely utilized and crucial for biological sequence comparison [12]. Comparing two or more nucleotide sequences (DNA or RNA) or amino acid sequences (peptides or proteins) entails looking for specific features or patterns that are ordered in the sequences as well [24,28]. The identification of point mutations, the creation of evolutionary trees, the categorization of genes and proteins, biological function prediction, the classification of genes and proteins, and other activities all rely on sequence similarity. Indicators of how conserved a given section or sequence motif is throughout lineages can be made using the degree of similarity between amino acids at a specific place in a protein's sequence.

 Sequence alignment seeks to reduce mismatches and gaps while maximizing the number of matches. Given an alignment and a scoring system, the alignment with the highest alignment score is the best alignment. A scoring system includes two components. The first is a match/mismatch matrix that details how many points are added for matches and subtracted for mismatches. The second is gap penalty which specifies how gaps are penalized by deducting points. Three scores are given in the simplest scenario: (1) the cost of aligning a character in one sequence with a gap in the other sequence (2) The advantage of aligning a pair of sites that have the same character (state) in both sequences. (3) The cost of aligning a pair of sites that include different characters.

**Sequence Alignment Types**

|  |  |
| --- | --- |
| Based on Number | Based on Length |
|  | Pairwise Sequence Alignment | Global Sequence Alignment |
|  | Multiple Sequence Alignment | Local Sequence Alignment |

1. **Pairwise Sequence Alignment (PSA)**

 **Pairwise sequence alignment** is a form of sequence alignment, where we compare only two sequences. A type of sequence alignment called pairwise comparison compares just two sequences. This procedure entails determining the best alignment between the two sequences, scoring according to how similar or distinct they are, and determining the importance of this score. Each pair of sequences is aligned by PSA once. The rapid search for matches to a query sequence in large DNA and protein databases is one particular application of pairwise sequence alignment .Algorithms based on dynamic programming are substantially slower than well-known heuristic algorithms as those from the FASTA [36] or BLAST families. It is the most basic type of alignment and can be carried out using either a *global* or *local* sequence alignment approach.

1. **Global Sequence Alignment**

The ideal sequences for global alignment are those that are closely related and have the same length. Here, the alignment is carried out from the start of the sequence to the end in order to find the optimal alignment. Saul B. Needleman and Christian D. Wunsch created ‘The Needleman-Wunsch algorithm’, also referred to as dynamic programming for sequence alignment in 1970 (33). Global alignments are generally used to compare two proteins with similar functions or homologous genes with the same function. The global sequence alignment is described in the algorithm for aligning nucleotide or protein sequences.

TARGET SEQUENCE

5’ACTACTAGATTACTTACGGATCAGGTACTTTAGAGGCTTGCAACCA 3’

 5’ ACTACTAGATT­\_\_\_\_\_ACGGATC\_ \_ GTACTTTAGAGGCTAGCAACCA 3’

QUERY SEQUENCE

1. **Local Sequence Alignment**

 Smith and Waterman were the one who first proposed the fundamental local alignment method (1981b). Similar to the Needleman-Wunsch algorithm, this method is likewise based on dynamic programming, but with more options to start and terminate at any location (38). It identifies nearby areas with a high degree of resemblance. Any two sequences can be locally aligned because local alignment identifies sequence stretches with a high level of similarity without taking the alignment of the other sequence regions into account.

TARGET SEQUENCE

 5 ’ACTACTAGATTACTTACGGATCAGGTACTTTAGAGGCTTGCAACCA3’

 5’TACTCACGGATGAGGTACTTTAGAGGC 3’

QUERY SEQUENCE

1. **Multiple Sequence Alignment**

 Multiple sequence alignment, or MSA, is a technique used to align three or more biological sequences (protein or nucleic acid) of comparable length. The results allow us to study the evolutionary relationships between sequences and the inference of homology. A known phylogenetic tree was required for early alternate methods for multiple alignments. Progressive alignment is the method for multiple sequence alignment that eventually gained a lot of traction [12,13]. In progressive alignment, one typically begins by creating all feasible pairwise alignments (there are n (n-1)/2 pairs for n sequences). Using a distance-based procedure like the un-weighted pair group method with arithmetic mean (UPGMA) or neighbor joining, these pairwise alignments are utilized to estimate a phylogenetic tree. A pairwise approach is used to match the most comparable sequences to one another using the tree as a guide. On the basis of the phylogenetic tree's structure, one then gradually adds sequences to the alignment, one sequence at a time.

 Higgins created CLUSTAL series of programs, which employs a progressive algorithm, is one of the most effective MSA solutions because it uses heuristic methods with approximate approaches [12].

1. **DYNAMIC PROGRAMMING**

The application of dynamic programming results in the best alignment of two sequences. It discovers the alignment in a more quantitative way rather than just applying dots by awarding specific values for fits and mismatches (Scoring matrices). The greatest scores in the matrix can be used to precisely locate alignment.

1. **Substitution Matrices**

 Sequence alignment using pairwise and multiple sequence alignment techniques is scored using substitution matrices. Since all bases experience equal amounts of mutation, the score matrices used for nucleotide sequence alignment are quite simple. A match is given a positive or higher value, whereas a mismatch is given a negative or lower value. The matrices can be scored using these scores based on assumptions. Point Accepted Mutation (PAM - Dayhoff 1978) and Blocks Substitution Matrix are two common protein substitution matrix models (BLOSUM - Henikoff and Henikoff 1992).

1. **PAM Matrices:** Margaret Dayhoff invented the PAM matrix, also known as the Point Accepted Mutations matrix. PAM matrices are computed using differences in proteins that are closely related to one another. For every 100 amino acid residues, one PAM unit (PAM1) indicates one allowable point mutation, implying that only 1% of the original structure is changed.
2. **BLOSUM:**Henikoff and Henikoff's created BLOcks SUbstitution Matrix in 1992, which utilizes conserved regions. Actual percent identity values make up these matrices. Blosum 62 means there is 62 % similarity.
3. **Gap (-)** representing one or more nucleotide indel events.

The algorithm that was utilized can be categorized as either optimum or heuristic [38]. The best alignment is the ideal outcome, but the heuristic, while not delivering an optimal result, displays the best alignment within a specific time window of analysis.

1. **BLAST**

The Basic Local Alignment Search Tool (BLAST) is the most popular similarity search tool. Regions of similarity between sequences are discovered via BLAST. The software compares protein or nucleotide sequences and determines the statistical importance of matches. BLAST can be used to infer functional and evolutionary relationships between sequences in addition to identifying members of gene families.

 The Smith-Waterman method (1981) was the source of the specialized local alignment algorithm known as BLAST, which displays a maximum alignment score of two sequences [1]. To search the sequences in the database, BLAST uses a heuristic based on the *k*-tuple approach in addition to the dynamic programming resulting from the aforementioned algorithm [24]. The *k*-tuple method restricts the search to words that are more significant, which are words with a length of 3 or 11 characters for amino acids and nucleotides, respectively. BLAST is a group of software tools that can be used for a variety of tasks depending on the sequence type of interest and the database being searched [39]. Table 4 lists a few applications that are accessible by BLAST.

**Table 4: Description of BLAST family programs**

|  |  |  |
| --- | --- | --- |
| Program | Query | Subject |
| BLASTx | nt\* | aa |
| BLASTn | nt | nt |
| BLASTp | aa | aa |
| tBLASTn | aa | nt\* |
| tBLASTx | nt\* | nt\* |

nt: nucleotide, aa: amino acid, \*Translated for all possible sequences [1]

 The value of the score (Score bits) and the E-value are the two parameters through which the BLAST results are displayed. When the alignment score and database size are taken into account, the E-value is a statistical value that shows the likelihood that the alignment did not happen at random [39, 1]. However, the algorithm assigns the score based on the similarities and differences between the input sequences and the database [1].

1. **Phylogenetic analyses**

Due of the shared requirement of determining sequence similarity, phylogenetics and sequence alignment are closely related fields [[35]](https://en.wikipedia.org/wiki/Sequence_alignment#cite_note-ortet-25). Sequence alignments are frequently used in the study of phylogenetics to build and understand phylogenetic trees, which are used to categorize the evolutionary relationships between homologous genes found in the genomes of different species. Sequences' evolutionary separation from one another is qualitatively connected to how much they differ from one another. The simplest approaches use distance matrices, like un-weighted pair group method with arithmetic mean (UPGMA) or neighbor joining (NJ).

**Table 5: Description of Tools to study Phylogenetic Relationship**

|  |  |
| --- | --- |
| **Tools** | **Description** |
| MEGA (Molecular Evolutionary Genetics Analysis) | constructs phylogenetic trees to investigate evolutionary proximity |
| PAML | A collection of applications for phylogenetic analyses of DNA or protein sequences using maximum likelihood. |
| PHYLIP | A package for phylogenetic studies |
| TreeView  | Software that allows t switch between different views of the phylogenetic trees. |
| itol (Interactive Tree of Life) | An online tool for managing, displaying, and annotating phylogenetic trees. |

1. **Application of Bioinformatics**

**Figure 2 Basic bioinformatics tools of biological sciences. (Source: Mehmood et al 2014)**

**Table 6: Application of basics Bioinformatic tools in various areas of Biological Sciences**

|  |  |
| --- | --- |
| **DNA Sequence Analyses** | * BLAST
* Clustal X
* Promoter Analyses
* Gene Prediction
* Regulatory Elements
* Intron - Exon finding
* Primer Designing
* Codon Usage Optimization
* Virtual Translation
 |
| **Molecular Dynamic Simulations** | * Protein-DNA Simulations
* Drug-DNA Simulation
* Protein-Ligand Simulation
 |
| **Drug / Pesticide Designing** | * Target identification
* Target validation
* Lead identification
* Lead optimization
* ADMET prediction
 |
| **Protein Sequence Analyses** | * Molecular mass, pI, amino acid composition
* Domain and Motifs search
* Single peptide identification
* Secondary structure analyses
 |
| **Phylogenetic Analyses** | * Reconstruction of evolutionary history
* Tracking gene flow
* Identification of conserved regions
 |
| **Molecular Interactions** | * Protein-Protein docking
* Finding inhibitors and activators of protein
* Protein-DNA interactions
* Transcriptional factors identification
* Interaction between Protein and Ligand
 |

1. **Conclusion**

 The emerging discipline “Bioinformatics” is the solution for the current demand in the every field of plant research. Sequence analysis, data mining, gene discovery, the development of phylogenetic trees, the prediction of protein structure and function, interaction networks, and many more computational approaches are used in this field. The field of bioinformatics will play a significant role in plant research. If plant science could be summed up in one word, it would be "integration," barring any unforeseen circumstances. The link that will enable all of these forms of integration will come from bioinformatics. For a better understanding of functional and expression-related issues in a specific gene family, specific cellular process, or any specific plant disease, the increasing number of databases in combination with tools offering a targeted dataset and extensive annotation to the omics technology is highly helpful. The outcomes of genetic research will revolutionize the medical industry. As a result of genomic status, diagnostic methods will change quickly and may now concentrate on the association between genotypes and complicated phenotypes with the use of bioinformatics. This will advance the discipline of bioinformatics since the future generation of biologists will need to be equally at ease using a computer workstation as they are using laboratory benches.

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