TOOLS AND APPLICATIONS OF BIOINFORMATICS IN SERICULTURE: A REVIEW

ABSTRACT

Rapid advances in genomic and other molecular research tools, as well as advances in information technology, have resulted in a massive volume of data relevant to molecular biology during the last several decades. The term "bioinformatics" refers to the mathematical and computational methods used to get a better understanding of biological processes. Bioinformatics commonly uses genetic sequences, which are easier to manage with computers than by hand. Although genomic and proteomic techniques have advanced our understanding of how genes and proteins contribute to physiology, biochemistry, genetics, and evolution in insects, a complete picture of genomics and proteomics and their interactions remains difficult. Meanwhile, bioinformatics developments have discovered hidden omics features in other species, leaving insects with a substantial information gap. *Bombyx mori* has sparked research interest in countries all over the world due to its adaptability and status as the first Lepidopteran species to have its genome sequenced. The entire genome sequence of the silkworm was reported in 2004 and updated in 2008 based on its biological and industrial value. The genome of *B. mori* was the first in a lepidopteran to be sequenced, and it has served as a foundation for Lepidoptera research. Bioinformatics tools and techniques not only aided in the detection of proteomic and genomic variation among species/strains, but also led to the discovery of a gap in a silkworm genome sequence that diverged during domestication. Databases of Seri-bioinformatics are an important Seri-bioresource. The accessible internet resources on silkworms and associated organisms, such as databases and informational websites like SilkDB, MorusDB, WildSilkbase, KAIKObase, SilkPathDB etc., have aid in the improvement of silkworm health, disease resistance, and productivity. These databases contain information on gene, protein, disease sequences, and have evolved as a highly beneficial platform via which the scientific community may communicate molecular data across the globe with a single mouse click, not only minimizing the gap and time but also allowing information to be accessed. This review paper will cover all of these bioinformatics tools and methodologies in order to better understand their application in silkworms and host plants.

Keywords: molecular biology, bioinformatics tools, silkworm, genomic, databases

INTRODUCTION

The term "bioinformatics" refers to the mathematical and computer techniques that are used to better comprehend biological processes. Bioinformatics is a field of research in which biology, computer science, and information technology are combined into a unified discipline, according to the National Center for Biotechnology Information (NCBI 2001). Bioinformatics is defined by Fredj Tekaia of the Institute Pasteur as "mathematical, statistical, and computer methodologies aimed at solving biological problems using DNA and amino acid sequences and related information." Since the first full microbial genome of *Haemophilus influenzae* was sequenced in 1995, hundreds of microbial genomes have been sequenced and archived at Gen Bank for public research. It is the perfect combination of computer as well as biology. It is the use of computational methods to biological problems at the molecular level. Computational Microbiology is another name for it. In 1970, Paulien Hogeweg and Ben Hesper created the term "bioinformatics" to describe the study of informatic processes in biotic systems.

During the last several decades, rapid developments in genomic and other molecular research techniques, as well as advances in information technology, have resulted in a large volume of data pertinent to molecular biology. Genetic sequences are extensively used in bioinformatics, as they are easier to manipulate with computers than by hand. It is simply impossible to acquire, organise, process, analyse, and interpret the massive volumes of data accessible without the use of bioinformatics tools, especially following whole genome sequencing studies. The sericultural community will profit greatly from the sequencing of Host plant and silkworms.

Components of Bioinformatics

1. Technology
2. Database
3. Algorithm
4. Analysis tools
5. Computing power

Proteomics, genomics, and bioinformatics discoveries have resulted in an exponential increase in the amount of data stored in various databases (Punyavathi, 2013).

Types of Data

1. **Primary Database**
   DNA - AATGCCGCTATAGGC
   Amino acid – MDVMKGLSKAKE
2. **Secondary Database**
   Secondary protein structure – “motifs”: regular expressions, blocks, profiles, fingerprints e.g., alpha-helices, beta-strands
3. **Tertiary Database**
   Tertiary protein structure –domains, folding units

History of Bioinformatics:

- **1859:** Theory of genetic evolution was given by “Charles Darwin”
- **1953:** Watson and Crick double helix model of DNA based on X-ray obtained
- **1955:** 1st protein sequence, Bovine Insulin announced by F. Sanger
- **1958:** Advance research projects agency (ARPA) formed
- **1973:** Brookhaven Protein Data Bank (PDB) announced
- **1987:** PERL (practical extraction report language) released
- **1988:** NCBI (National center for biotechnology information) founded
- **1990:** Human Genome project, BLAST program introduced
- **1992:** TIGR (The Institute of genome research) formed
- **2001:** Human genome (3,000 Mbp) published

Importance of Bioinformatics:

Bioinformatics arose from the urge to comprehend the code of life (DNA). Massive DNA sequencing programs have evolved and contributed to the advancement of bioinformatics science. Bioinformatics’ ultimate goal is to find the abundance of biological information hidden inside the massive amounts of sequence, structure, literature and other biological data.

What is done in Bioinformatics?

1. Creation of novel algorithms and statistics for analyzing relationships between individuals in massive data sets.
2. Nucleotide and amino acid sequences, protein domains, and protein structures are all examples of data that may be analyzed and interpreted.
3. Creation and deployment of technologies that allow for the efficient access and administration of various forms of data.

Software and Tools

Software tools for bioinformatics range from simple command-line tools to more complex graphical programs. The computational biological tool best known among biologist is BLAST. It is an algorithm for determining the similarity of arbitrary sequences against other sequences. BLAST is one of the available programmes for doing sequence alignment. Other analytical tools are WEGO, GO browse, genome browser, etc.

FASTA:

First fast sequence searching algorithm for comparing a query sequence against database. It was first created by Pearson and Lipman in 1988. The method looks for exact matches between words in query and test sequence.

BLAST:

The BLAST (Basic Local Alignment Search Tool) program was designed by Eugene Myers, Stephen Altschul, Warren Gish, David J. Lipman and Webb Miller at the NIH and was published in *J. Mol. Biol.* in 1990. It is based on the assumption as FASTA that good alignments contain short lengths of exact matches. It is design specially for database searches.

Application of Bioinformatics in various fields:

- Insect Resistance
- Improve nutritional quality
- Development of drought resistance varieties
- Crop improvement
- Veterinary Science
- Evolutionary Studies

- Microbial genome applications
- Antibiotic resistance
- Drug development etc.

Bioinformatics in Sericulture:

“Bioinformatics is a rapidly evolving field that analyses and manages the massive amounts of data created by genomic and proteomic studies from bacteria to humans. Along with the fruit fly (*Drosophila melanogaster*), *Bombyx mori* L. is regarded a model insect for molecular studies and a fundamental model species for genome studies in moths and butterflies (the insect order Lepidoptera)” (Punyavathi and Manjunatha, 2013). The accessible internet resources on silkworms and associated organisms, such as databases and informational websites, aid in the improvement of silkworm health, disease resistance, and productivity (Singh *et al*., 2016). “In 1999, the Central Sericultural Research and Training Institute (CSRTI) in Mysore developed a bioinformatics Centre as a sub node of the BTISnet to facilitate biotechnological research in sericulture” (Wani *et al*., 2018).

Objectives of Seri bioinformatics:

1. Organize a database of silkworm and mulberry genotypes and breeds.
2. Develop and maintain databases containing structural information for mulberry and silkworm genomes.
3. Conduct training/workshops in the subject of bioinformatics in general, and Seri-bioinformatics in particular, to raise awareness and increase visibility.
4. To give sericulture-related assistance information via the internet.

IMPORTANCE IN SERICULTURE:

The entire genome sequence of the silkworm was reported in 2004 based on its biological and industrial value. This silkworm genome data was updated in 2008, and further data, like as microarray-based gene expression profiles, has subsequently become accessible. The genome of the *B. mori* was the first lepidopteran genome to be sequenced, and it has served as a foundation for Lepidoptera research.

Since 2004, there have been 7,024 relevant publications published in NCBI PubMed using the keywords "(*Bombyx mori*) OR (silkworm)." (Shoji *et al*., 2013) found a novel chromodomain-containing gene based on the SilkBase genome sequence, and later (Shoji *et al*., 2014) identified a number of genes whose expression can be boosted by heterochromatin protein 1. (Wang *et al*., 2015) mapped “their clean reads to the SilkDB reference genome to get the brain transcriptome profiles of BmNPV-infected and non-infected silkworm larvae”. (Li *et al*., 2016) studied “the transcriptome differences between susceptible and resistant *B. mori* strains following BmNPV infection in depth”. (Li *et al*., 2019) updated “the analysis of the different alternative splicing events using the same reference genome three years later”. (Sun Q. *et al*. 2020) recently downloaded “genome sequences and annotated files from the SilkDB website for transcriptome study of *B. mori* immune response after early bidensovirus infection”.

Application in Host Plant

“Transgenic mulberry plants overexpressing barley Hva1 driven by the actin1 promoter were shown to be drought and salt tolerant” (Lal *et al*., 2008). “In comparison to non-transgenic plants, transgenic plants demonstrated enhanced proline accumulation, cellular membrane integrity, and photosynthetic production under stress conditions. Transformation of mulberry with hva1 gene from barley for drought and salinity” (Lal *et al*., 2008; Checker *et al*., 2011).

Application in Silkworm

BmNPV is a significant silkworm pathogen that mostly infects silkworm larva. The most promising technique for improving resistance is to overexpress antiviral genes in silkworms. Endogenous Bmlipase-1 is a protein that is only found in the midgut of a silkworm. Transgenic silkworm lines with strong resistance to BmNPV were effectively produced by overexpressing an endogenous antiviral gene. The transgenic antiBmNPV line might be used in the sericulture business to reduce silkworm larval mortality.

An enzyme called UGT46A1 is an odor degrading enzyme that aids in the breakdown of odor molecules in the silkworm's olfactory system. The complete amino acid sequence of the silkworm UGT46A1 was utilized to search the NCBI database for homology. Bioinformatics analysis suggests that its function is linked to the silkworm's feeding patterns and UGT46A1 was discovered to be strongly expressed in the heads of silkworms. The study suggests that UGT46A1 may impact silkworm nutrition by changing the silkworm's olfactory system (Song *et al*., 2021).

DATABASE FOR SERICULTURE

“There are currently 61 databases which comprise of genome, proteome, transcriptome and other data of silkworms, host plants, pest and pathogens, *etc*. There are currently roughly 20 databases accessible that contain silkworm-specific data. These databases are classified as nucleotide (13 numbers), protein (04 numbers), genetic resource (02 numbers), and pathway (01 number) databases based on the data type" (Dey *et al*., 2016).

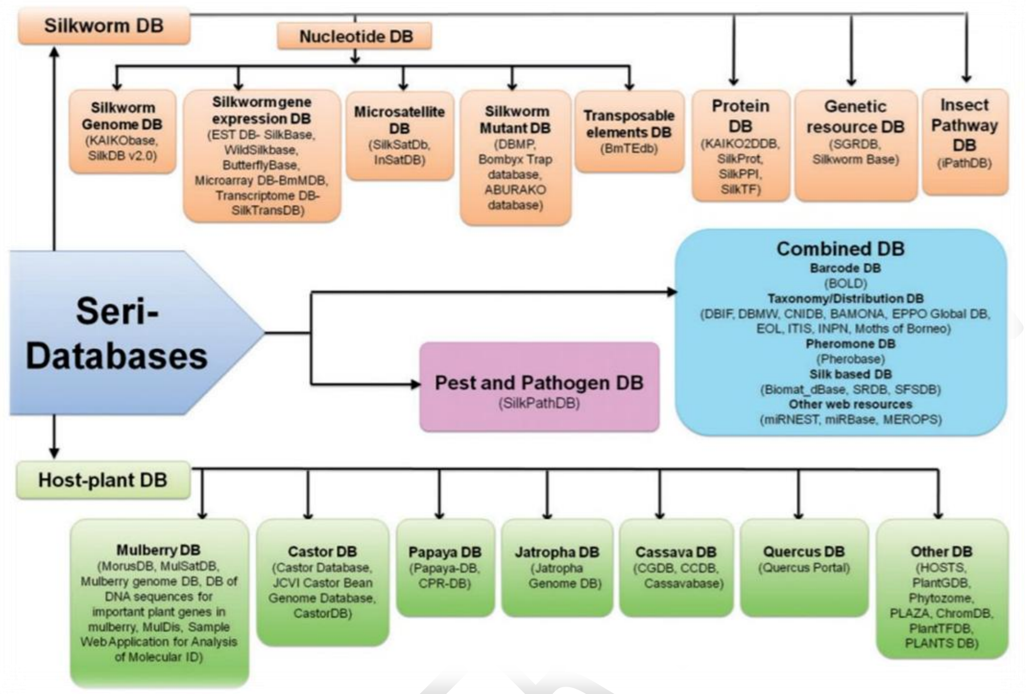

Fig.1. Flowchart of Seri-Database

A. Silkworm Databases

1. Nucleotide databases

a) Silkworm genome database

'SilkDB' also known as 'Silkworm Knowledgebase,' is Beijing Genomics Institute's (BGI) first comprehensive genomic database of *B. mori* (Lu *et al*., 2020). 'KAIKObase' and 'SilkDB v3.0' (an improved version of SilkDB) were published in 2009 and 2019, respectively, to accommodate the new integrated and complete genomic information. KAIKObase was developed by Japan's National Institute of Agrobiological Sciences (NIAS) as part of the Silkworm Genome Research Program (SGRP), while SilkDB v3.0 was developed by Southwest University's Institute of Sericulture and Systems Biology.

b) Silkworm gene expression database

"EST sequences of five lepidopteran insects can be found in SilkBase (*B. mori*, *B. mandarina*, *S. cynthia*, *Ernolatia moore* and *Triloca varians*). Users can BLAST searches for each against cDNAs. This silkBase was developed by Munetaka Kawamoto, University of Tokyo, Japan" (Mita *et al*., 2003).

"The WildSilkbase is a collection of ESTs derived from various tissues of three economically important saturniid silk moths at various developmental stages. There are currently 57,113 ESTs in the database, which have been clustered and assembled into 4,019 contigs. Wildsilkbase was developed by Centre for DNA Fingerprinting and Diagnostics (CDFD), India and Max Planck Institute for Chemical Ecology, Germany, published in 2008" (Arunkumar *et al*., 2008).

c) **Microsatellite database**

"SilkSatDb is a relational database of microsatellites derived from the *Bombyx mori*'s expressed sequence tags and whole genome shotgun sequences. A simple and comprehensive web-based search capability was constructed using PHP to render the database" (Prasad *et al*., 2005). InSatDb is an interactive database of insect microsatellites that allows users to query information about them. The results reveal some fascinating insights on the life cycle and genomic flow. (Archak *et al.*, 2007).

d) **Silkworm Mutant database**

'*Bombyx* Trap database' have been developed and maintained by National Institute of Agrobiological Sciences, Japan. "This database, which is integrated into the silkworm genome database, KAIKObase, contains information on reporter expressions and the sites of transposon vectors (mutators) in transposon insertion lines" (Shimomura *et al*., 2009).

e) **Transposable Elements databases**

"Transposable elements (TEs) constitute 40% of the silkworm genome. These TE families and their classification information were organized into a comprehensive and easy-to-use web-based database, BmTEdb. BmTEdb also included sequence analysis tools including BLAST, HMMER, and EMBOSS GetORF" (Xu *et al*., 2013).

2. Protein databases

KAIKObase was founded in 2009 as the domesticated silkworm *Bombyx mori* genome database. It contains many gene sets, genetic maps, and genome annotation provided from the International Silkworm Genome Consortium's sequencing project in 2008. They released a revised silkworm genome assembly in 2019, with improved gap closing and coverage of more and longer gene models - KAIKObase (ver.4.0.0) (Yang *et al.*, 2021). SilkProt, SilkTF and SilkPPI developed by Bioinformatics Centre, CSR&TI (Central Sericulture Research and Training Institute), Mysore, India is accessible at http://www.btismysore.in/silkprot/, http://www.btismysore.in/SilkTF/ and http://210.212.197.30/SilkPPI/, respectively.

SilkOrganPDB is an open-access database for silkworm organelle proteomics. The SilkOrganPDB uses Chado for genomic and proteomic data administration, React for the internet interface, and bioinformatics tools for data analysis such as NCBI BLAST+, HMMER, Muscle, and FastTree. The database includes not only organelle protein subcellular localizations, but also extensive sequencing, gene ontology, homlogy, and phylogeny information, as well as facilities for searching, browsing, and analyzing data (Li *et al*., 2021).

3. Genetic resource databases

"The National Academy of Agricultural Sciences of Korea created the Silkworm Gene Resource Database (SGRDB), which is a relational database. Variety searching, characterization viewing, general information, and a photo gallery are the four main function menus in the silkworm database. The database provides of 321 silkworm gene resources and 1,132 images regarding life cycle of various silkworm varieties" (Kim *et al*., 2010). With the help of the National Bioresource Project, which began in 2002, resources for mutants of *B. mori* have been concentrated at Kyushu University in Japan. Researchers may look for information on 560 silkworm strains (SilkwormBase, https://shigen.nig.ac.jp/silkwormbase/top.jsp), which covers the majority of known morphological alterations (Banno *et al*., 2010).

B. Host plant Databases

1. Mulberry database

"MorusDB is an integrated data source with easy access to mulberry large-scale genomic sequencing and assembly, predicted genes and functional annotations, expressed sequence tags (ESTs), transposable elements (TEs), Gene Ontology (GO) terms, horizontal gene transfers between mulberry and silkworm, ortholog and paralog groups, and horizontal gene transfers between mulberry and silkworm" (Li *et al*., 2014). The Mulberry Microsatellite Database (MulSatDB) is a web-based database with a user-friendly web interface. EST-SSRs and Whole genome-SSRs are the two types of SSRs in the database (Krishnan *et al*., 2014). MorusDB can be accessed at http://morus.swu.edu.cn/morusdb and MulSatDB' can be accessed at http://btismysore.in/mulsatdb respectively.

2. Castor database

"By combining information on the genome, transcriptome, and proteome of *R. communis*, a comprehensive database has been created to provide a useful resource. Castor bean plant sequence data was gathered from a variety of sources, including the National

Center for Biotechnology Information (NCBI) and JCVI Castor Bean Genome Database" (Thakur *et al*., 2011). One can access CastorDB database at - http://CastorDB.msubiotech.ac.in

3. **Jatropha database**

The 'Jatropha Genome Database' created by the Kazusa DNA Research Institute in Japan, contains genetic data and DNA markers for the Jatropha plant.

"It contains the complete genome sequence, amino acid sequences, and motif predictions via InterPro. BLAST homology searches, keywords searches, as well as data download is possible from this site" (Zhang *et al*., 2019).

C. **Pest and Pathogen Databases**

'SilkPathDB' was constructed as first pathogen database by State Key Laboratory of Silkworm Genome Biology (SKLSGB) at Southwest University, China. "The data includes genome sequences, gene annotation, proteomic and transcriptomic profile of silkworms under infected conditions, etc". (Li *et al*., 2017).

Case studies:

1. Title: Defense role of the cocoon in the silkworm *Bombyx mori* l.

Conducted by Pandiarajan *et al*., 2011

Objectives:

To figure out which antimicrobial proteins are found in the cocoon of the silk worm *Bombyx mori*

Materials and Methods:

The disc diffusion method was used to conduct a microbial susceptibility test against microorganisms using cocoon shell extract. It was then subjected to 7–15% sodium dodecyl sulfate/polyacrylamide gel electrophoresis (SDS-PAGE). It was extracted from the gel, trypsin digested, and analysed using matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS). MASCOT was used to examine the trypsin-digested peptide peaks, and the peptides were compared to the NCBI nr database.

Results:

- The presence of antimicrobial/immunogenic activity of the cocoon shell extract was established by the development of a zone of inhibition against the microorganisms.
- The protein profile of the cocoon extract revealed coomassie blue stained bands in the molecular range of 150 – 15 kDa. Interestingly, a polypeptide with a molecular mass

of roughly 29 kDa revealed significant expression variations throughout pupa development.

- The peptides were found to be extremely similar to the 18-wheeler protein, which is thought to be involved in innate immunity, belongs to the Toll family of proteins, and is involved in cellular mediated immunity in insects.

Inferences:

The main goal is to justify the existence of antimicrobial compounds in the cocoon shell, which protects the cocoon from external threats. A comprehensive result of the innate immune response in the cocoon shell was established. Preliminary evidence for the presence of innate immune proteins in the cocoon shell is also found; however, more research is needed to determine the mechanism of innate immunity polypeptides (29 kDa) and how they reach the cocoon to protect silk in *Bombyx mori*.

2. Title: Horizontal gene transfer in silkworm, *Bombyx mori*

Conducted by Zhu *et al*., 2011

Objectives:

To understand the HGTs in the evolution of *Bombyx mori* by whole genome analysis

Materials and Methods:

The 14,623 coding genes retrieved from SilkDB and were screened for gene candidates for HGT in *B. mori*. A team of researchers at Zhejiang University in China has produced a computer program that can build phylogenetic trees by analyzing protein sequences from 382 species representing a wide diversity of eukaryotes and prokaryote taxa. The program is powered by a local database containing predicted protein sequences (2,385,947 coding sequences in total) from more than 2.3 billion living organisms. BLAST was run against 14,623 predicted coding genes and phylogenetic analysis; EST analysis and transposon and re-transposon filter were used.

Results:

- Among 14,623 predicted coding genes only 107 candidate genes were found to be candidate genes when BLAST was run.
- 60 genes were excluded when phylogenetic analysis was done, 33 genes were removed when EST was checked and 4 genes were removed when transposon and re-transposon filter is done resulting into 10 putative HGT genes.

- In the phylogenetic trees, numerous bacterial species established basel branches within a bacterial clade. *B. mori* nested within a bacterial clade. This strongly supported the path of transmission of gene from prokaryote to *B. mori.*
- Expression analysis suggested that this gene was highly expressed in integument and fat body. Based on these results, we can infer that this gene may be associated with nutrient and energy metabolism in *B. mori.*

Inferences:

The findings of this study clearly showed that HGT happened in *B. mori* and that it may have offered beneficial gene activities that could improve disease resistance, food and energy metabolism, and toxin breakdown. Bioinformatics, a type of advanced computational technology, made this work possible.

Conclusion:

Rapid advances in genomic and other molecular research tools, as well as advances in information technology, have resulted in a massive volume of data relevant to molecular biology during the last several decades. The term "bioinformatics" refers to the mathematical and computational methods used to get a better understanding of biological processes.

Databases of Seri-bioinformatics are an important Seri-bioresource. The accessible internet resources on silkworms and associated organisms, such as databases and informational websites like SilkDB, MorusDB, WildSilkbase, KAIKObase, SilkPathDB etc., have aid in the improvement of silkworm health, disease resistance, and productivity.

These databases contain information on gene, protein, disease sequences, and have evolved as a highly beneficial platform via which the scientific community may communicate molecular data across the globe with a single mouse click, not only minimising the gap and time but also allowing information to be accessed.

Assam and rest of the India are particularly endowed with four types of Silkworms which offer a lot of scope for scientific research and their subsequent utilization for the welfare of sericulture industry. Sericulturists should focus on this component of next-generation sequencing-based research to better understand the silk microbiology. Therefore, it is high time to employ bioinformatics tools in sericulture research in order to increase silkworm and host plant performance.

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