Biological databases and tools for neurological disorders

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Computational approaches to study of neuronal impairment is rapidly evolving, as experiments and intuition alone do not explain the complexity of the brain system. An overwhelming increase in the amount of new data from both theory and computational modeling necessitate the development of databases and tools for analysis, visualization and interpretation of neuroscience data. To ensure the sustainability of this development, consistent update and training of young professionals is imperative. For this purpose, relevant articles, chapters, and modules are essential to keep abreast of developments. This review seeks to outline the biological databases and analytical tools along with their applications. It is envisaged that such knowledge could provide a "training recipe" for young scientists and a guide for professionals and researchers in neuroscience.

Keywords

Neurological disorders (NDs); Database; Tools; Neuroinformatics; NeuroDNet; PubMed; Cytoscape
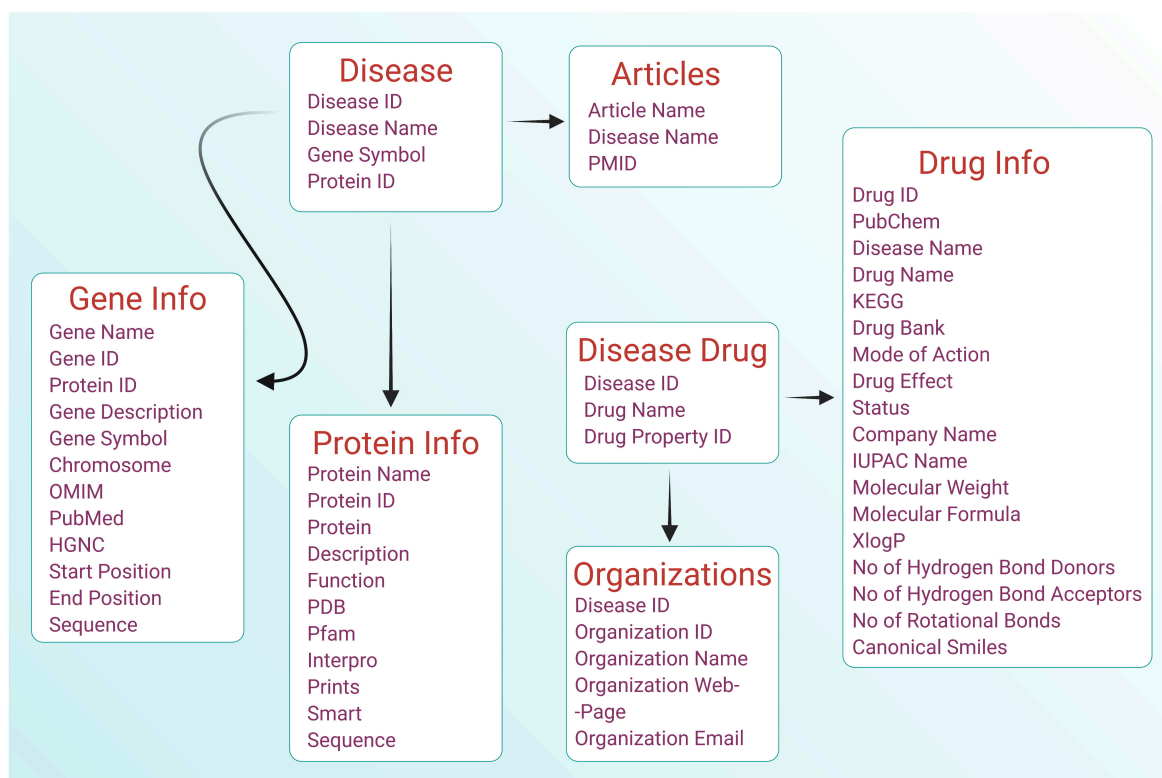
Fig. 1. Schematic representation of various NDs-associated informations which can be extracted using biological database.

1. Introduction

Neuronal impairments or neurological disorders (NDs) continue to attract much research attention owing to both their unknown etiology and the interwoven complexities of their underlying molecular and signaling pathways that often make the identification of practical classifications and therapeutic targets difficult. However, with recent advancement in computational methods, investigators are able to employ several databases and tools to demystify these complex networks for the identification of better therapeutic or mechanistic targets [1, 2]. These resources are not only useful for the study of bio-molecular interaction networks, but also help in network analysis, visualization and the establishment of relationships at the level of their genes and protein products. Databases serve as repositories for the retrieval of gene or protein interaction data, while the computational tools help withn data visualization, the establishment of interaction networks and data analysis. The various forms of, edical interaction networks being analyzed include: gene interaction (GI), protein-protein interaction (PPI), protein-DNA interactions, and protein-RNA interactions [3, 4]. Computational analysis of these interactions has revolutionized the modern understanding of NDs and provides better prospects for drug discovery.

Use of computational a approach to the study of NDs constitutes the field of Neuroinformatics. Recently, research in Neuroinformatics has gained ground, as it appears to be more promising in providing understanding of neural networks and disease. Research in Neuroinformatics extends to theory and methodology, including analytical tools, database design, meta-analysis, data sharing and discussions on computational modeling. The pool of data is vast and heterogeneous in the field of experimental neuroscience and the integration and analysis of these increasingly large-volume, high-dimensional data sets require Neuroinformatics to further understanding of the nervous system [5–8]. Neuroinformatics is at the crossroads of neuroscience and information science [9–11]. It involves the study of the nervous system, its structure, function and diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), Amyotrophic lateral sclerosis (ALS), Prion disease amongst others. Research in neuroscience contains many different sub-disciplines that analyze data from multiple levels of the brain and information science is concerned with the collection, classification, and dissemination of information [12–14]. To solve increasingly complex problems, clinicians and research scientists use computational tools, mathematical models and Neuroinformatic databases provided by neuroinformaticians to collaborate, share information and quantitatively support working theories [15].

2. The link between computational neuroscience and Neuroinformatics

Computational neuroscience employs theoretical analysis, mathematical models and abstractions of the brain to un-
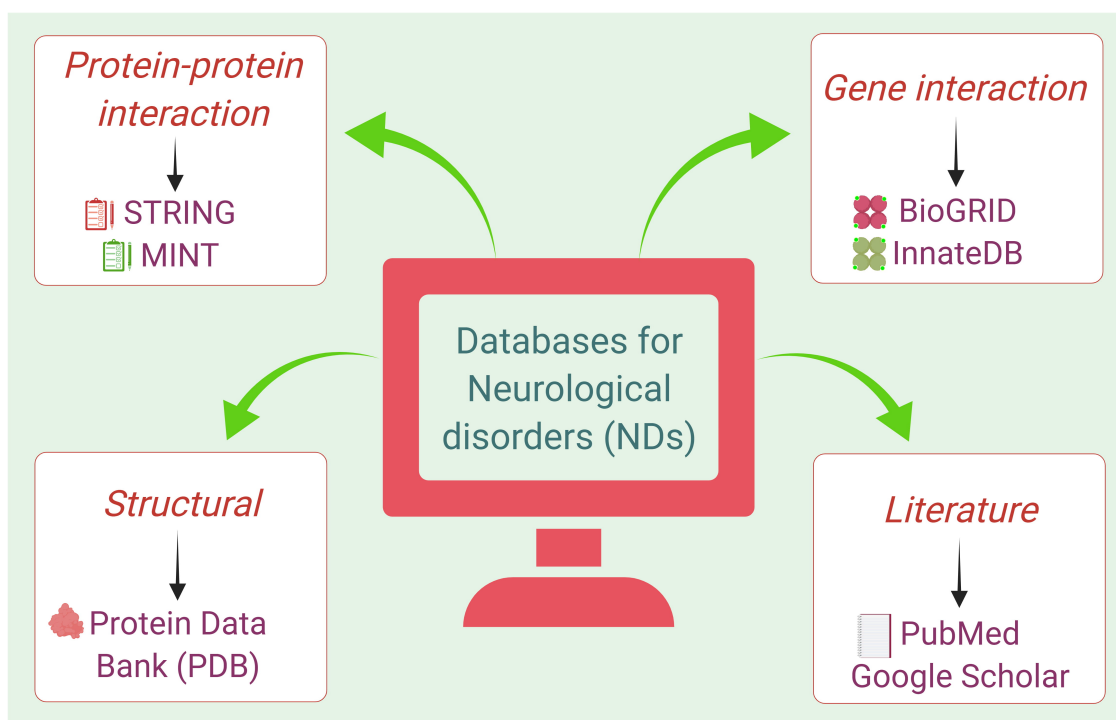
Fig. 2. Schematic classification of *in-silico* databases for NDs.

derstand the principles that govern the development, structure, physiology, information processing and cognitive abilities of the nervous system. Computational neuroscientists employ mathematical and computational approaches to understand how the brain processes information and informatics helps accelerate this neuroscientific discovery. Neuroinformatics tools such as image analysis, computer simulation and database integration help facilitate neural modeling and collaboration in the field of computational neuroscience. The nature of this sub-discipline of neuroscience is primarily quantitative, so Neuroinformatics is beneficial in the organization and analysis of data derived from computational research. Computational neuroscience differs in more qualitative experiments such as finding the optimal design of nervous systems or exploring various neural connectivity schemes in model networks [16, 17].

3. Fields related to Neuroinformatics

Neuroinformatics is rapidly evolving due to manifold ways of applying information technology to demystify complex problems related to neuroscience. These ways include development of databases and tools necessary for the analysis, modeling, management, and sharing of neuroscience data (Fig. 1). Thus, Neuroinformatics is multidisciplinary, with each discipline having a reasonable contributory role. Hence, fields related to Neuroinformatics are summarized as; (a) Psychology: Cognitive development and information processing theory, (b) Computer Science: Natural and Bio-inspired computation, (c) Philosophy: Computational theory of mind, (d) Engineering: Brain-Computer Interface technology, (e) Medicine: Aging and mental diseases like depression and anxiety, (f) Physical Sciences: Physical processes within neural cells and neuronal networks, (g) Mathematics: Statistical algorithms and Quantifying neuronal differentiation, (h) Chemistry: Molecular structures and their interactions in nervous system, and (i) Biology: Chemical processes and molecular structure.

4. *In silico* databases for neurological disorders

With an increasing number of large databases, data sharing in neuroscience may gradually become as common and useful as it is in genomics, where the existence of very large bodies of data is leading to increased knowledge as well as products and services linked to the improvement of human health. Numerous databases are being employed to study NDs; these databases can be open source (freely accessible) or proprietary (commercially available). Regardless of the source, databases for the study of NDs can be broadly divided into four as shown in Fig. 2.

Further, some of these databases along with their roles in the study of neuronal impairment are enumerated in Table 1 (Ref. [3, 4, 18–37]), while the commonly used ones are discussed below.

4.1 Google scholar

Google scholar is a web-based platform that enables the search of scholarly literature such as books, reports, and articles present in online libraries or databases. The powerful search engine indexes full-text journal articles, selected web

pages and other documents. Moreover, it avails users of opportunity to search across various disciplines and establish personal collection of articles via the save button. Interestingly, Google scholar can now efficiently be used to identify the highly-cited paper [38]. Thus, articles pertinent to NDs may also be searched, sorted, and pooled to make a collection for reasonable analysis [39].

4.2 Protein data bank

Protein Data Bank (PDB) is a freely available structural database that gives the 3D shape of macromolecules (such as proteins and nucleic acids). It's a primary database whose results are derived from experimental data obtained through X-ray crystallography and NMR spectroscopy. PDB is managed by Worldwide Protein Data Bank (wwPDB) and the current entries are 165,117. It affords users the opportunity of searching and downloading 3D structures and their visualization. PDB helps in the study of NDs by providing 3D shapes of several proteins involved, their molecular bonds, fragments, and domains which enable researchers to study the protein for modeling, ligand interactions, and drug design [31–33].

4.3 PubMed

PubMed is an open-source literature database being overseen by the US National Library of Medicine. PubMed as a gateway to MEDLINE database, contains freely available research papers, abstracts, older and recent references, PubMed Central (PMC) citations among others. As of June 2021, PubMed database has over 32 million citations and abstract of biomedical research. In the study of NDs, PubMed is utilized for the construction of datasets through literature search, effective searching is achieved by using keywords relevant to the NDs and related articles are collected. The database can also be used to confirm data extracted from other sources [22].

4.4 Universal protein resource

Universal Protein Resource (UniProt) is a freely accessible repository for annotated protein sequences; with unique protein ID, gene name, and gene symbols. UniProt is a combination of Swiss-Prot, Translated European Molecular Biology Laboratory (TrEMBL) and International Protein Sequence Database (PIR-PSD). UniProt has over 564,638 sequence entries, consisting of about 204 million amino acids from 278,054 references as of April 2020. Researchers make use of UniProt in studying neuronal impairments through retrieval of unique protein ID, gene names and symbols for construction and analysis of NDs complex networks, and extraction of specific protein sequence for further analysis [4, 24, 29].

4.5 Search tool for the retrieval of interacting genes/proteins

Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) is an open-source web-based repository of over 2,000 million predicted and known protein interactions. STRING database contains PPI networks based on functional associations and allows users to establish

a relationship between interacting proteins/genes through the confidence score. PPI in the STRING database is obtained from literature curation of experimentally determined interactions. Users can search for a gene/protein in the database through a Uniprot ID, single or multiple protein names, amino acid sequence (single or multiple). Nodes represent proteins or genes, while edges in different colors indicate the method used in detecting the relationship, confidence score is used for predicted functional associations [40]. In studying NDs, STRING is employed for the establishment of PPI networks, determination of confidence or evidence level for each interaction, gene ontology analysis, Reactome pathways, among others [3, 26].

4.6 Biological general repository for interaction datasets

Biological General Repository for Interaction Datasets (BioGRID) is a freely accessible database of genetic and PPI networks. It also contains post-translational modifications and chemical interaction data. In the current version 3.5.186, detailed information includes 1,871,024 protein and genetic interactions, 28,093 chemical associations, and 874,796 post-translational modifications obtained from humans and major model organisms. BioGRID provides gene and PPI data necessary for the study of neuronal impairment, the data extracted is used to construct datasets for network analysis in NDs [30].

4.7 Other databases

Web of science: it is a subscription-based website published by Thompson Reuters. Web of science, being an interdisciplinary database, offers access to various databases with comprehensive citation record such as Social Sciences Citation Index (SSCI) and Science Citation Index Expanded (SCI-EXPANDED). The SSCI contains record from Psychiatry, Psychology, and public health, while SCI-EXPANDED covers the area of medical discipline [41]. The website may be used to access various articles relevant to NDs.

In addition to the above databases, several others have been reported. For instance, the Database of Neurodegenerative Disorders (DND) provides a user-friendly interface and is designed as a source to improve research on NDs. It is developed as an open-source software system using Mysql-5.0.18-Win32 and PHP-5.2.0 and uses the relational data model (Gowthaman *et al.*, 2007 [42]). Further, a schematic diagram addressing the DND is shown in Fig. 1.

Similarly, another database known as NeuroGeM has recently been developed. NeuroGeM integrates a comprehensive collection of literature data on genetic modifiers of NDs and associated genetic information from an array of databases. To give complete information on genetic modifiers, NeuroGeM also integrates information from genome databases (SGD, FlyBase, EBML, WormBase, HGNC, and MGI), the homologous gene databases (HomoloGene and InParanoid), protein interaction database (STRING), and Gene Ontology [43]. Likewise, NDDVD, an integrated and manually curated Neurodegenerative Diseases Variation Database
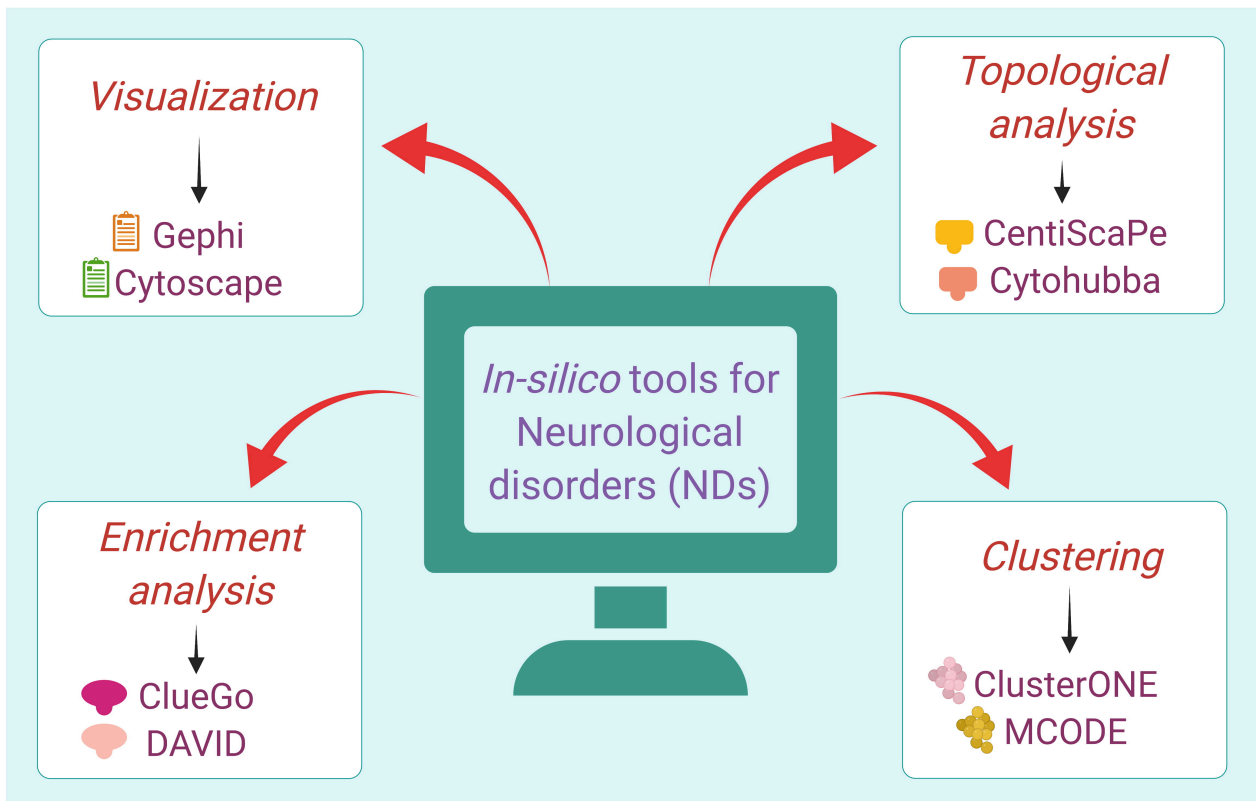
Fig. 3. Schematic classification of *in-silico* tools for NDs.

has recently been developed. NDDVD can provide data for the identification of common variation spectrum within Neurodegenerative disease (NDDs) and for developing universal biomarkers or drugs for NDDs as well. It can also serve as a research platform for further discovering relationships between diseases and genetic variations. The integrated database will act as a precious tool for quickly querying the NDD-related variations and systematically analyzing the relationships between diseases and variations [1].

5. *In silico* tools/software for neurological disorders

Many tools have been developed to study NDs; these can be freely accessible or commercially available.

Some Neuroinformatics tools are meant for analysis, modelling, and visualization of neural systems such as Cytoscape, Gephi and EEGNET. Others are simply plug-ins that provide interface for various analysis such as ClusterONE and Cyto-Hubba, while others were developed for structuring data to create consistent terminology and formats for the sharing of data such as BIRN (Biomedical Informatics |Research Network). *In silico* tools for the study of NDs can be divided into four broad categories as shown in Fig. 3, while Table 2 (Ref. [3, 23, 24, 26, 34, 44–54]) summarizes some of them. Further, the commonly used tools are discussed below.

5.1 Cytoscape

It is an open-source software developed by the Institute for Systems Biology for visualization and analysis of biomolecular interaction networks. Cytoscape works with almost all operating systems and provides a platform for data integration, gene and PPI analysis, and visualization. The presence of several layout algorithms makes the software robust for network construction, while several plug-ins (which are freely available in the Cytoscape App store) enhances its usability in several processes such as network and molecular profiling analyses, connection with databases, different layout, and scripting [40]. Moreover, many other analyses are possible through the Cytoscape App such as topological analysis, functional enrichment analysis, clustering, etc. Cytoscape is a very important software for the study of NDs owing to its versatility in modeling, visualization, and analysis. Through this great software, complex networks in NDs are visualized and analyzed for several purposes such as overlapping of pathways in NDs, molecular interactions, functional enrichment, and topological analysis [34, 44].

5.2 EEGNET (Electroencephalography NET)

Is a recently developed flexible and user-friendly tool. The open source *in silico* tool, running under MATLAB, allows the visualization and analysis of connectome from Magneto/Electroencephalography (M/EEG) recordings.

Table 1. List of *in silico* databases for NDs.

Database	Description	Use in NDs	Reference
NeuroDNet	Database for analysis and construction of ND networks	Retrieval of gene and proteins related to NDs and their interactions for analysis	[18]
Alzheimer's Disease Neuroimaging Initiative (ADNI)	ADNI database has information on AD for monitoring of research and treatments	Mining of data relevant to AD for further research	[19]
National Alzheimer's Coordinating Center (NACC)	NACC database contains collection of information on AD patients from various AD centers	Extraction of data of AD for analysis, monitoring and research	[20]
Online Mendelian Inheritance in Man (OMIM)	OMIM is a database of human genes and genetic disorders	Acquisition of data for disease genes in NDs	[21]
PubMed	Free online database for literature search	Construction of dataset for NDs through literature search	[22]
Interologous Interaction Database (I2d)	I2d contains protein interaction networks data	Construction of ND protein interaction networks	[23]
Universal protein resource (Uniprot)	Uniprot database is a collection of proteins with their unique IDs, gene name, gene symbol and sequences	Retrieval of unique protein ID, symbols or sequence for ND proteins	[4, 24]
Kyoto Encyclopedia of Gene & Genome (KEGG) pathway	Open source database for pathway mapping	Collection and mapping of ND pathways	[22, 25]
Search Tool for the Retrieval of Interacting Genes/Proteins (STRING)	STRING is a database of PPI network and gene ontology analysis	Establishment and growing of PPI networks for NDs and also for gene ontology	[3, 26]
Online Predicted Human Interaction Database (OPHID)	OPHID is a web-based database of human predicted PPI	For making interaction dataset of NDs	[27]
IntAct	Molecular interaction database	Data mining and retrieval of molecular interactions data for NDs	[25]
Human Protein Reference Database (HPRD)	HPRD is PPI database with disease associated to each protein	Text mining of PPI data and disease related to each protein in NDs	[22]
Molecular INTeraction Database (MINT)	MINT is a repository of molecular interactions which are experimentally verified	For collection of molecular interaction data related to proteins of NDs	[28]
Database of Interacting Protein (DIP)	DIP is a collection of experimentally determined PPI	Text mining and acquisition molecular interactions of ND proteins	[26]
InnateDB	Integration of signal pathways and gene interactions of innate immune responses	Retrieval of gene interactions of innate immune responses related to NDs	[29]
Biological General Repository for Interaction Datasets (BioGRID)	BioGRID contains genetic and PPI data	Data mining for PPI and genetic networks of NDs	[30]
Protein Data Bank (PDB)	PDB contains proteins in 3D format	Retrieval of 3D protein structures of NDs	[31–33]
Genetic Home Reference	Open source website that contains information on human genetic variations	Retrieval of genetic variations data related to NDs	[34]
NCBI Gene Expression Omnibus (GEO)	A repository of gene expressions data	Extraction and construction of ND gene expression datasets	[25]
Human Gene Mutation Database (HGMD)	Repository of human inherited gene mutations	Extraction of mutated or inherited genes related to NDs	[30]
ALSOD	Provides more detailed information's about various factors of ALS including, genetic, proteomic, and bioinformatics information associated with the disease	Helps in providing information about ALS	[35]

Table 2. List of *in silico* tools for NDs.

Tool	Description	Use in NDs	Reference
BioCyc Database Colletion	Consists of 17832 Pathway/Genome Databases (PGDBs) for model eukaryotes, thousands of microbes, and tools for analysis	Pathway analysis of various NDs	[36]
Reactome	Open access, manually curated pathway database that contains intuitive tools for visualization, modelling, interpretation, and analysis of genome and pathways	Pathway analysis and gene ontology analysis of NDs	[37]
Cytoscape	Open source tool for analysis and visualization of complex networks	Visualization and analysis of complex gene and PPI networks in NDs	[34, 44]
DAVID	It is a functional analysis enrichment tool that gives annotation in tabular form	Provide functional annotation of ND genes and their gene ontology analysis	[26, 45]
MATLAB	Tool for topological analysis and measurement of centrality	For characterization of ND networks and assessment of centrality	[3]
ClueGO	A Cytoscape plug-in for analysis of biological enrichment pathways	Analysis of ND pathways with respect to their gene ontology terms	[23]
Pathway Linker	A Cytoscape tool that links proteins to signal pathways	Categorization, visualization and connection of ND proteins to signal pathways	[46]
BLAST	NCBI tool for aligning biological sequences	Comparing gene/protein sequences in NDs	[24]
FatiGo	Web-based tool for finding gene ontology terms for group of genes	Extraction of gene ontology terms for ND genes in association with other genes	[47]
Gephi	Open source tool for network visualization and analysis	Construction of ND networks, visualization and their analysis	[48]
ClusterONE	It's a standalone App or Cytoscape plug-in that clusters proteins and find overlapping ones in a complex network	For identification and clustering of proteins in ND networks	[49]
Cytohubba	It's a java Cytoscape plug-in for several topological analyses	For topological analysis of various ND networks	[48]
CluePedia	Another tool for clustering networks and analysis of enrichment pathways	Analyzing ND enrichment pathways and clustering networks	[49]
Binom	A plug-in of Cytoscape that enhances the manipulation of biological networks	Facilitates manipulation of ND networks	[44]
CentiScaPe	A plug-in of Cytoscape that helps in topological analysis such as centrality measurements	Enhances the topological analysis of PPI in ND network	[50]
MetaCore	Commercially available tool for functional analysis of experimental data	For functional analysis of ND data	[51]
NetworkAnalyzer	Multi-functional tool in Cytoscape for analyzing topological parameters	Helps in analyzing wide range of topological parameters in ND networks	[50]
Molecular Complex Detection (MCODE)	A Cytoscape App that identifies highly connecting nodes (clusters) in complex PPI network	Facilitates the Identification of clusters with high quality in PPI networks of NDs	[51]
CytoCluster	A platform-independent App for visualization and analysis of biological network clusters	ND networks are visualized and their network clusters can be analyzed with this tool	[52]
BisoGenet	Another Cytoscape plug-in for gene network construction and topological analysis	For ND network construction and topological analysis	[53]
ToppFun	Open source functional enrichment analysis tool that provide annotation features like gene ontology terms, microRNAs, PPI etc.	To annotate the function of microRNAs, PPI, pathways etc. in NDs	[54]

The neural networks being analyzed could either be at reconstructed cortical sources level or even at the level of scalp [55].

5.3 ClusterONE (Clustering with overlapping neighborhood expansion)

ClusterONE is a graph clustering algorithm that exists as a standalone App or a plug-in in Cytoscape or ProCope. ClusterONE helps in identifying overlapping protein complexes in the PPI network and also generates the desirable clusters. In the study of NDs, it facilitates the finding of protein in interwoven networks and the construction of PPI network clusters [49].

5.4 Database for annotation, visualization & integrated discovery (DAVID)

DAVID is an internet-based functional enrichment analysis tool that gives holistic functional annotations for a large list of genes. The various forms of annotations included are interacting proteins, protein functional domains and motifs, the association between genes and disease, gene ontology terms, and literature. Other features include visualization of pathway maps and inter-conversion of gene identifiers. DAVID is used to provide a list of functional annotations for complex ND genes in tabular form as well as visualization of their pathway maps [26, 45].

5.5 Cytohubba

Cytohubba is a java plug-in of Cytoscape that provides a user-friendly interface for topological analysis of PPI networks. Cytohubba provides analysis through eleven topological scoring methods to identify essential nodes in the network, it allows the construction of sub-network (or subgraph) for the essential nodes to enhance the further analysis of direct interaction with top-ranked nodes, this facilitated node retrieval function and extraction of user interesting network make Cytohubba better option than other tools like CentiScaPe [56]. Consequently, Cytohubba is used by researchers for topological analysis of various PPI networks in NDs [48].

5.6 Basic Local Alignment Search Tool (BLAST)

BLAST is an algorithm for comparing biological sequences developed by National Center for Biotechnology and Information (NCBI). BLAST is an open-source web-based domain, that is compatible with different operating systems and allows researchers to align unknown (or query) sequences of proteins or nucleic acids with reference sequences in target databases to identify regions of similarities and conserved domains. BLAST helps in comparing various unknown protein or gene sequences of NDs with reference sequences to identify conserved domains. It is also used in modeling for unveiling regions of targets by ligands in NDs [24].

6. Future trends in Neuroinformatics/computational neuroscience

Advancements and successes made in the field of Neuroinformatics unveil more challenging perspectives. This challenge combines two tasks; development of new tools for understanding of neural networks and diseases on one side, and effective use of those computational tools and approaches on the other. Firstly, brain consists of large number of neurons with high complexity of structural connectivity that changes with experience. In the recent years, there is rapid increase in an overwhelming amount of new data from both theory and computational modeling to further understand the complex dynamic system. The new accruing data cover the area of brain connectomics, transcriptomics and neurophysiology, effective data analysis and interpretation are key to understanding of brain diseases. This challenge does not only necessitate collaborative efforts across the related fields, but also increase the demand for development of novel analysis tools [57].

Secondly, experiments and intuition alone could not explain the complexity of brain system, consequently, modern computational neuroscience is expanding synergistically with experimental research. One of the major benefits of this synergy is the increased use of artificial intelligence (AI) and machine learning (ML) for computational modeling and data analysis in neuroscience [58]. However, the current limitation of ML in recognizing higher cognitive functions and complex network visualization will continue to put pressure on Neuroinfromatics to develop more dynamic tools and methodologies. With the continues influx of an overwhelming amount of computational databases and tools, development of infrastructure, methodologies, and trainings for effective handling of the heterogeneous datasets will constitute the future challenge in Neuroinformatics and neuroscience [2].

Considering the successes recorded in Neuroinformatics, more attention needs to be given to infrastructural development, funding, and training to ensure the sustainability of brain research. Training opportunities would attract young talents that will drive the future development of computational algorithms and analytical tools. It's through regular training that professionals and young talents will be kept abreast of recent development. Therefore, having articles and chapters – like the present one - that summarize recent advances in analytical tools and databases would be a "training recipe".

7. Conclusions

Computational approach to study of NDs is rapidly evolving. The increase in synergistic relationship between computational and experimental neuroscience leads to the emergence of more analytical tools and databases. For sustainability of research in neuroscience, development of infrastructure, methodologies, and trainings are necessary. Frequent update and review of the emerging databases and tools along with their functionalities would be a training recipe for young professionals and guide for researchers. This is in a bid to further understand the fundamentals of NDs, their unknown etiology, interwoven complex molecular and signaling path-

ways. Additionally, it will also help in the development of the drug and further improves the neurotherapeutics. Further study is recommended to explore more of such databases and tools for their pertinent role in Neurological studies.

Author contributions

NKJ, MBU and AA conceptualized, wrote, and edited the manuscript. SKJ, DKC, GG, SKS, SR, NK, FAK, HD and VU performed the literature survey, drafted and edited the manuscript. NKJ ideated the scheme, performed artwork. PP, KKK, GMA, SO, KD, FZ helped in revision and edited the manuscript. All authors contributed to the article and approved the submitted version.

Ethics approval and consent to participate

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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