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Article

NetRA: An Integrated Web Platform for Large-Scale Gene Regulatory Network Reconstruction and Analysis

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Abstract: Several effective online and offline inference tools offer an interactive platform for inference, visualization, and analysis of gene regulatory networks. However, a tool currently needs to offer a scalable, lightweight, integrated online platform for carrying out inference, visualization, benchmarking, and extensive network analysis in an integrated manner. We introduce NetRA (**Net**work **R**econstruction and **A**nalysis for Gene Regulatory Network), a comprehensive web tool for network analysis, visualization, and inference of large expression networks. Additionally, a platform for benchmarking and evaluation is provided. In order to deliver a highly scalable, lightweight, and rich user interface, the tool is created using the most recent technologies. We incorporate the original code of eleven (11) inference algorithms (not limited to) from Bioconductor in the current version. We also report a qualitative comparison of 11 candidate methods regarding prediction accuracy and network characteristics which will shed light on their performance against 4000 sizes synthetic DREAM network. We believe the tool will significantly aid biologists' downstream system biology research. NetRA tool can be extensible to different kinds of complex network analyses.

Keywords: interactive tool; gene regulatory network; inference; visualization; complex network; benchmarking

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1. Introduction

The advancement of high-throughput technologies has led to the availability of a massive amount of expression data (Guzzi and Roy 2020). When adequately analyzed, it could lead to a significant breakthrough in the field of medicine. It is possible when we can infer genome-scale large GRNs with many thousand genes and visualize the network effectively. It may help a system biologist to understand the underlying molecular dynamics properly. One gene's influence on another gene's activity is significant (de la Fuente 2010) but difficult to detect in a wet lab environment. As a result, computational techniques and approaches are crucial in inferring near-optimal network structures (Teji et al. 2022; Teji and Roy 2022), which may be confirmed by wet lab experiments. The analysis and interpretation of biological network relationships are becoming a key research focus in current computational biology, with implications for genomics medicine. Several challenges occur when dealing with large regulatory networks, including thousands of genes/protein interactions. As a result, the scientific community, computer engineers, statisticians, and biologists have joined forces to develop new techniques and algorithms to address these difficulties by creating open-source reconstruction and visualization tools (Bayat 2002).

Several similar tools have been developed and used for the last few decades. Table 1 lists a few of the presently available tools along with their available features and various information.

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Table 1. Available GRN inference and visualization tools and their feature

Tool	Description	Platform	URL	Exp.datasets	Benchmark	Network data	Visualization	Plugins	Web	Analysis
GeneNetWeaver (GNW) (Schaffter et al. 2011)	It is non-interactive benchmarking tool for rigorous testing of methods for gene network inference.	Java	http://gnw.sourceforge.net/	✓	✓	✓	✓	✗	✓	✗
SynTReN (Van den Bulcke et al. 2006)	It is a network generator from synthetic gene expression data for design and analysis of structure learning algorithm.	Java	http://bioinformatics.intec.ugent.be/kmarchal/SynTReN/index.html	✓	✗	✓	✗	✗	✗	✗
GeNeCK (Zhang et al. 2019)	It constructs gene networks from expression data and allows users to use ten different network constructing methods	Web-Based	http://lce.biohpc.swmed.edu/geneck	✓	✓	✓	✗	✗	✗	✗
SysGenSIM (Pinna et al. 2011)	It simulates Systems Genetics (SG) experiments in model organisms for the purpose of evaluating and comparing statistical and computational methods.	Matlab	http://sysgensim.sourceforge.net/index.html	✓	✗	✓	✗	✗	✗	✗
Netsim (Di Camillo et al. 2009)	It is gene network simulator to assess reverse engineering algorithms.	R	http://www.dei.unipd.it/dicamill/software/netsim	✓	✗	✓	✓	✗	✗	✗
ReTRN (Li et al. 2009)	It is a tool for extracting subnetworks from known transcription network and for generating corresponding gene expression data.	Matlab	http://www.sciencedirect.com/science/article/pii/S0888754309001992	✓	✗	✓	✓	✗	✗	✗
GenGe (Hache et al. 2009)	It is a tool for the generation and analysis of gene regulatory networks.	Web based	http://genge.molgen.mpg.de/GeNGe/welcome	✓	✗	✓	✗	✗	✓	✓

Most of the efforts to offer a web platform are limited to one or few inference methods (Schaffter et al. 2011; Hache et al. 2009). Some tools are built to provide benchmarking and synthetic data generation facilities (Schaffter et al. 2011; Zhang et al. 2019). Other than the inference of GRN, only some tools offer visualization of networks as an integral component (Schaffter et al. 2011; Di Camillo et al. 2009; Li et al. 2009) of the tool. There is a lacking of a suitable platform for performing inference, visualization, network analysis, and benchmarking of GRN inference methods in an integrated fashion. As tool developers try to code the inference methods from scratch to fit their platform, it always has limitations in accommodating many methods quickly. A plethora of inference methods is available for free access. They are primarily developed using R script or Python and archived in public platforms like *Bioconductor* (Gentleman et al. 2004) [1]. Such codes are bare scripts not understandable by the non-programmers. Moreover, they do not offer post-inference analysis on the same floor. Another interesting limitation of the available tools and methods is their scalability issue for inferring large-scale networks.

We developed a novel tool, **NetRA**, that offers an easy-to-use integrated web platform that uses original R scripts from Bioconductor and plugs into our proposed tool. Hence, state-of-the-art methods can be integrated with minimal effort into our tool with a similar input/output structure. Listed below are the critical contributions of our work.

- A lightweight tool built upon *NextJS*, *Python*, *R* and *Flask* that provides the user to infer, visualize, and network analysis of large networks with ease.
- Offered many complex network analysis facilities applicable to any network.
- Server-side rendering is used for interactive visualization of large networks to reduce client burden.
- A parallel inference engine has been integrated that can make any inference method handle large networks efficiently.
- A benchmarking facility has been integrated to assess the prediction quality of inference methods on user-given networks. Our tool can also assess and compare any newly developed inference method with 11 candidate methods.
- We evaluate the performance of eleven (11) candidate methods using our tool and compare their qualitative performance and the characteristics of the networks produced.

1 https://www.bioconductor.org/

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2. The Workflow of NetRA Tool

The NetRA tool is intended to provide four major independent functionalities, Inference, Visualization, Analysis, and Benchmarking. The user can independently use any of the functionalities. This feature makes the tool more generic and applicable for network analyses like Protein Interactions and Social Networks. The overall workflow of the tool is illustrated in Figure 1. The tool is composed of four independent engines. The respective screenshots of the four engines can be seen in Figure 6.

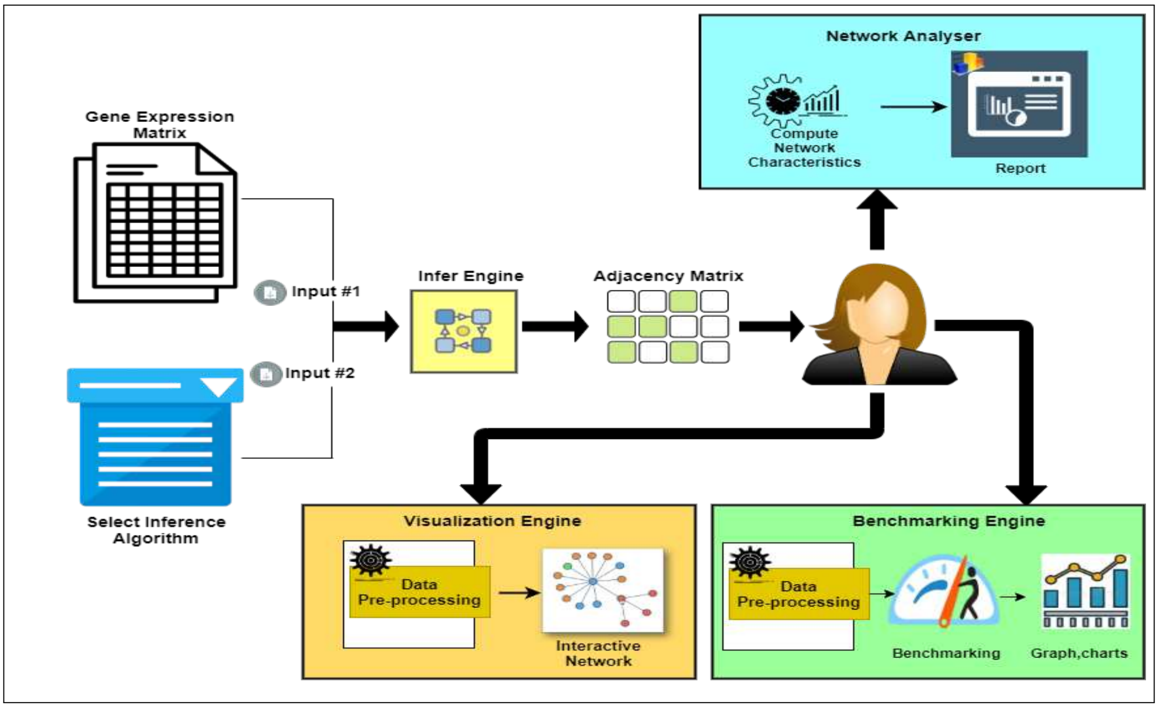

Figure 1. NetRA workflow showing four major activities of the tool.

2.1. *Inference Engine*

A dedicated inference engine has been designed to offer a user-friendly web platform for inferring gene networks from expression profiles. Instead of re-coding of any inference method, which may lead to implementation bias, we use readily available R scripts from Bio-conductor. We integrated 11 (CLR, ARACNE, MRNET, BC3NET, C3MTC, C3NET, MINE, MRNETB, PPCOR, RELNET, SPCOR) (Faith et al. 2007; Margolin et al. 2006; Meyer et al. 2007; de Matos Simoes and Emmert-Streib 2012 2011; Altay and Emmert-Streib 2010?; Meyer et al. 2010; Kim 2015?; Butte 2002) state-of-the-art algorithms and their parallel extensions to infer an extensive network. Depending on the varied size of the input network to be inferred, the inference engine automatically switches between serial and parallel execution modes for efficient and low-latency computation.

2.1.1. Parallel Framework for Large -Scale Inference

State-of-the-art network inference techniques can only reconstruct networks of a few hundred nodes. Thus, it is necessary to make use of parallel computing paradigms in order to build massive networks. We integrate, recently published, a generic parallel framework (Sebastian et al. 2022) that enables any existing approach to infer large networks in parallel, without re-engineering, and with high-quality output.

2.2. *Visualization Engine*

Any network in proper JSON format can be uploaded, or inferred data from the Inference engine can be used for interactive visualization. The robust D3.js framework provides an interactive

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visualization of the uploaded network. The visualizer offers the user to interact and inspect visually the various nodes and their immediately adjacent neighbors. We have used a technique for visualizing only hub nodes first and then on-demand clicking of its adjacent connected nodes, making the network rendering very light weighted for an extensive network dataset. We also offer a hub node list with a degree of each node from where the user may jump to the node of its interest.

2.3. Analysis Engine

We try to encompass most of the topological analysis measures in our tool. The degree distribution plot, network module detection, centrality analysis, and topological co-efficient are allowed in the analysis engine. This generic platform allows users to analyze any biological or social network. The input network data is restricted to an edge list with a tab-delimited format.

2.4. Assessment Engine

It is always challenging to assess the efficiency of any novel inference method with state-of-the-art contemporary methods. It involves extensive coding. We provide an integrated platform where users can assess the performance of their method with other methods available in the NetRA Tool. Users may assess the inferred network with the gold standard network for prediction accuracy.

A detailed description of the above four engines and their functionalities in-built within the tool is listed in Table 2 for quick reference. NetRA's extended functionalities make it different from other presently available tools.

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Table 2. Functionalities offered by Four Engines of NetRA tool.

Functionality	Description
Inference Engine	
Algorithm	User can select across the 11 algorithm for inferencing the network
Inference Statistics	User can find the resultant inferred Network and Inference Statistics which includes time taken by the algorithm, number of nodes and number of vertices.
Visualization Engine	
Visualize	Any inferred or social network can be interactively shown, with related nodes highlighted. The network is rendered using the lightweight library d3js, which draws a force-directed graph layout with its features of zooming, scrolling, and highlighting the connected nodes.
Gene list (with degree)	A list of Genes with their respective degrees is shown. The user can use the list to search for any gene, which on click, will highlight the node in the visualized network.
Visualization Stats	Information about the network, such as the number of nodes and edges, is provided.
Analysis Engine	
The network statistics	The network statistics viz. The diameter of the graph, vertex-id of the maximum degree, maximum degree, average degree, average-clustering, triadic-closure, is-connected, the density of the graph, number of nodes, and number of edges are provided in the table.
The degree histogram	A light weighted and interactive degree histogram chart is provided with features like zoom, pan, auto scale, lasso select, box select, and data on hover.
Centrality Analysis	
Centrality Betweeness	It is an indicator of a node's centrality in a network. It equals the shortest paths from all vertices to all others that pass through that node. Betweenness centrality quantifies the number of times a node acts as a bridge along the shortest path between two other nodes.
Centrality Pagerank	It is the way of measuring the node's importance by a value from the number of in-links in a node.
Centrality Closeness	It measures the speed with randomly walking messages reaching a vertex from elsewhere in the graph.
Eigen vector Centrality	All nodes in the network are given relative scores based on the idea that connections to high-scoring nodes contribute more to the node's score than equal connections to low-scoring nodes. A high eigenvector score means that a node is connected to many nodes that themselves have high scores.
Hubs and Authorities Analysis	
Hubs Score	The hub scores of the vertices are defined as the principal eigenvector of A*t(A), where A is the graph's adjacency matrix.
Authority Score	A good authority score represents a page linked by many different hubs. The authority scores of the vertices are defined as the principal eigenvector of t(A)*A, where A is the graph's adjacency matrix.
Clustering and Communities Analysis	
Cluster-infomap	The cluster info map finds a community structure that minimizes the expected description length of a random walker trajectory.
Cluster-fast-greedy	This function tries to find dense subgraphs, called communities in graphs, by directly optimizing a modularity score.
Cluster-walktrap	This function tries to find densely connected subgraphs, called communities, in a graph via random walks. The idea is that short random walks tend to stay in the same community.
Cluster-leading-eigen	This function tries to find densely connected subgraphs in a graph by calculating the leading non-negative eigenvector of the modularity matrix of the graph.
Cluster-label-prop	This is a fast, nearly linear time algorithm for detecting network community structure. In works by labeling the vertices with unique labels and then updating the labels by majority voting in the neighborhood of the vertex.
Topology	
Shortest path	The shortest path calculates one shortest path (the path itself, and not just its length) from or to the given vertex.
Assessment Engine	
Algorithm	User can upload their Network along with its Gold Standard Network to benchmark with more than one algorithm from the set of 11 algorithms provided.
Own Algorithm	We have provided a feature for uploading the inferred network of the user's algorithm in which the user will be able to compare the benchmark statistics with the present 11th algorithm in NetRA Tool.
Assessment Scores bar	A comparative bar chart with *Fscore*, AUROC score, *AUPR score* for each algorithm is shown in this menu. User can compare these values for multiple algorithms at a time.
AUROC Curve	The performance metrics of the area under Receiver Operating Characteristics for every algorithm is plotted in this tab.

3. Inner Engineering of NetRA Tool

NetRA's architecture is based on cutting-edge technologies such as *Next.js* in the front end and *Flask* at the back end. In addition, Python and R are used front and back-end scripting. The *React-redux* architecture is used for UI binding of the application. It is updated with API changes to ensure that the React components behave as expected. It implements performance optimization, allowing components to re-render only when needed. A middleware (thunk) is used for interacting with the API. A schematic diagram of the architecture and process flow of the tool is shown in Figure 2. The Flask framework is used on the back end, which accepts requests from APIs and passes the data to R scripts for performing different tasks.

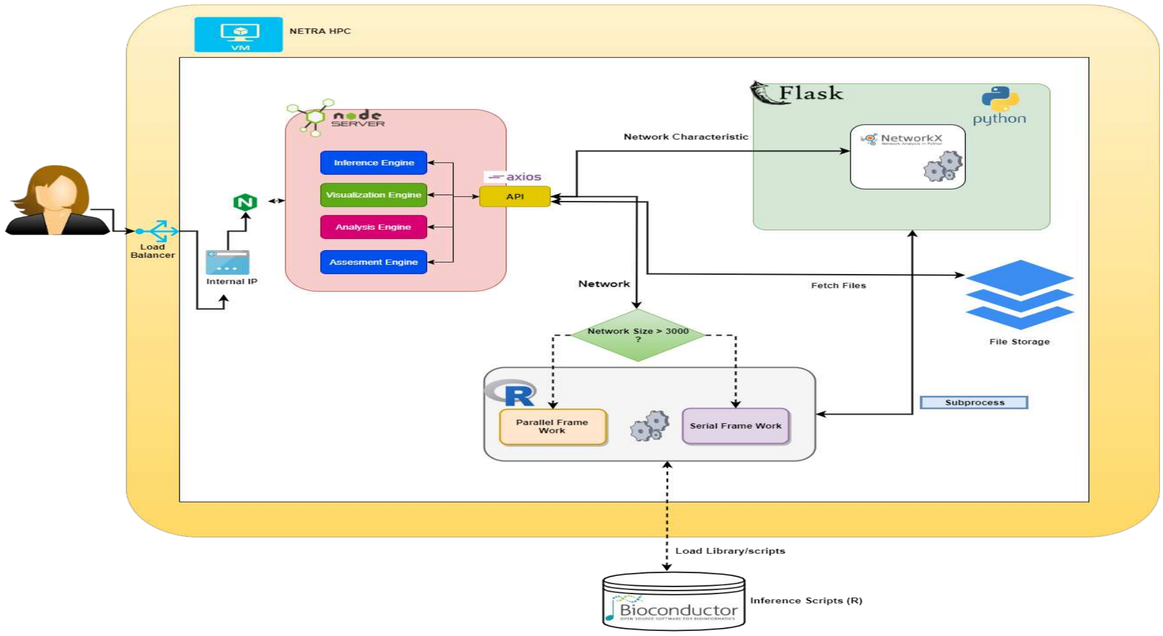

Figure 2. Client-Server Architecture of NetRA Tool

In order to infer a network from micro-array expression data matrix (input) using 11 candidate methods, original R scripts downloaded from *Bioconductor* are used during inference. NeTRA tool is capable of handling large-scale networks. Original inference methods are all limited to only inferring a network of size 4000 nodes. We integrated a generic parallel platform (Sebastian et al. 2021) that uses the original methods and runs in a multi-core environment. It smoothly transitions from serial to the parallel engine of network inference. The present version is restricted to offline access of the implementations from Bioconductor. In the future, online access will be available, where the user may use the methods directly from Bioconductor through the NetRA tool. Moreover, the parameter setting is also not provided for the optimized performance of the housed inference methods. The python script is used in various network analysis and visualization modules.

During visualization, the Flask server takes the inferred network as input and creates an event that calls the *d3js* [2] for generating the force-directed graph. The *d3js* creates an interactive network with a smooth transition and interaction from the inferred file and binds it to the *Document Object Model* (DOM) element in the front-end (Dutta and Roy 2022). It also calculates the degree of each node and dispatches it in the front end. Up to 1000 nodes, the visualizer can render the interactive graph directly. However, we adopted a bubble-busting concept to visualize large networks effectively. At first, high-degree nodes are visualized as isolated nodes. On clicking the nodes, it will expand to the sub-network of the clicked node. Subsequent clicking on each node will expand further.

[2] https://d3js.org

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For performing the calculation of the network properties, R based *igraph*(Csardi et al. 2006) package has been used, and plots are generated through R and *plotly*[3]. igraph is a collection of network analysis tools emphasizing efficiency, portability, and ease of use. R igraph comprises numerous classes and pre-defined methods for the calculation of the properties and statistics of a network. The list of statistical scores generated by these methods is then fed to the front end for user interaction.

The assessment is performed using *validate*[4] available in minet(Meyer et al. 2008) library that takes in the actual(gold-standard) network along with the predicted network as a parameter and calculates the *AUROC*, *AUPR*, *F-score* of the network. The *AUROC*, *AUPR*, and *F-score* values are written to an external CSV file, and the respective comparison bar graph is plotted in the front end using *d3js*.

4. Qualitative Assessment of Inference Methods

To demonstrate the usability of the NetRA tool, we decide to report a performance assessment of 11 candidate methods using the DREAM Challenge [5] benchmark network. We use GNW platform (Schaffter et al. 2011) to reverse engineer the expression data from the network dynamic. We use a network of 4000 *Yeast* genes with 210 expression values. We assess the outcome based on prediction correctness and network characteristics produced. Due to the present limits of the tool, we execute them with default parameters as in the original implementation.

4.1. Characteristics of Predicted Networks

We compute various network characteristics of the predicted network inferred from the candidate inference algorithms compared to the actual score achieved from the gold network. Figure 3 presents various sub-plots for each of these characteristics that span over 11 inferred network characteristics in the light of the actual network perspective. Such a discernment further paves the way to comprehend the topological network performance of the algorithms for a given network dataset.

We observe that the *average degree* characteristic does not reveal enough about the graph structure yet concerns the network's connectedness, thereby suggesting near the average degree of all nodes in the graph. The inferred networks generated from the list of inference algorithms, including $BC3NET$, $ARACNE$, $MINE$, $C3NET$, and $C3MTC$, do gain a significant average degree score concerning the target gold network score. However, for the *clustering coefficient* characteristic, which is also a degree measure groups high-density connection among network nodes. Amongst all the inferred networks $BC3NET$ network reaches a mark of 0.22 for the actual score of 0.09, whereas $ARACNE$, $C3MTC$, and $C3NET$ remain at 0. For, *graph density* characteristic represents the graph affinity to accommodate new links in addition to the existing links in the network. In other words, it describes how dense the network is regarding link connectivity. Most of the derived inferred networks from all the inference algorithms mark a significant count close to the actual score for graph density property. Another network topological characteristic which is *graph diameter* that calculates the shortest path length between the most distanced nodes in a network. The inferred networks viz. $RELNET$, CLR, $MRNET$, and $MRNETB$ reach closer graph diameter score in comparison to the actual score (06) of the gold network. Finally, the *triadic closure* property uses the existential mechanism of a network in alluding to the likelihood of missing links among the network nodes. From all the inferred networks, only the $B3CNET$ network reaches the true score value of 0.01.

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3 https://plotly.com/r/
4 https://rdrr.io/bioc/minet/src/R/validate.R
5 https://dreamchallenges.org/

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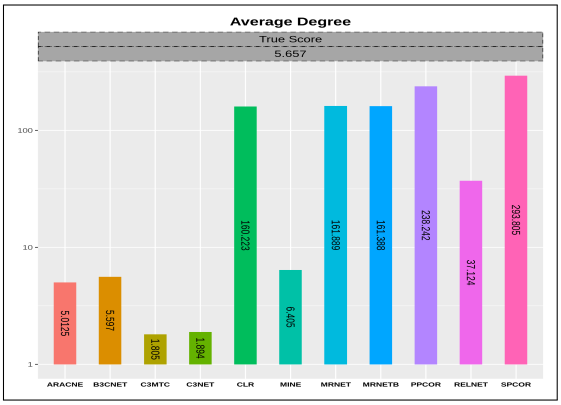
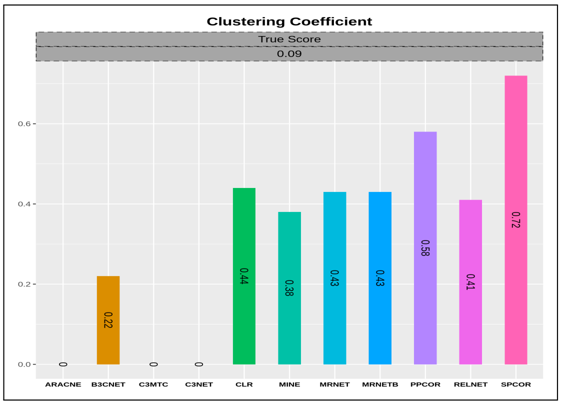
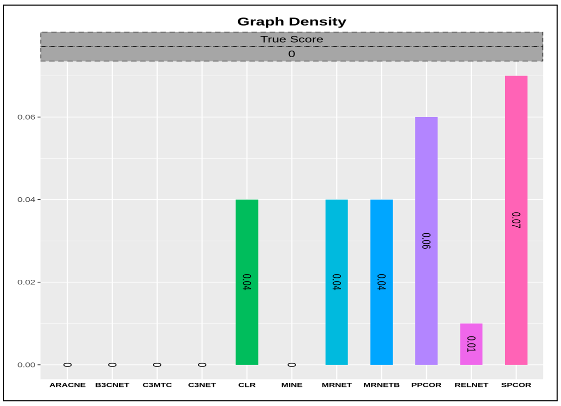


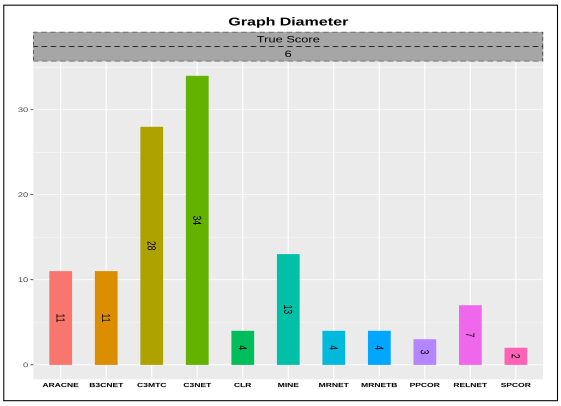
(a)



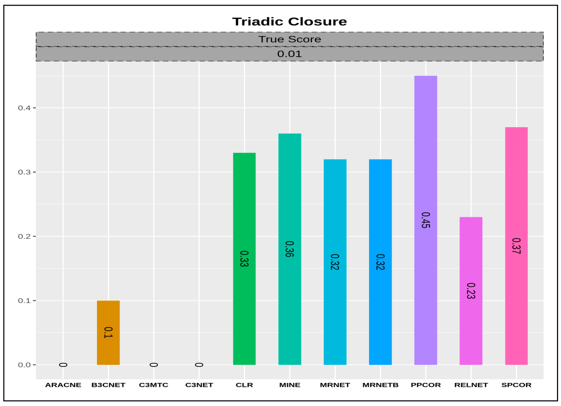
(b)



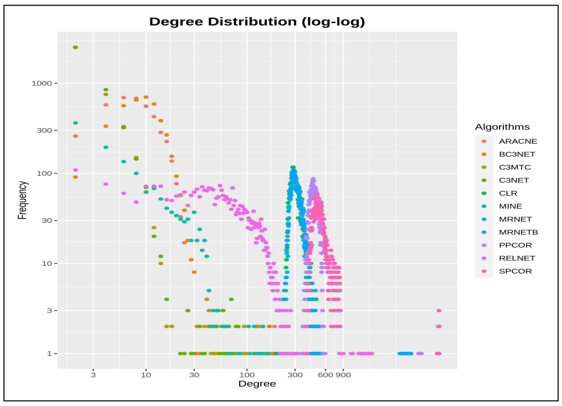
(c)



(d)



(e)



(f)

Figure 3. Different network characteristics of the predicted networks by various inference algorithms. *Fig. a) to e) are predicted network characteristics in comparison to the gold network characteristics termed as True Score with its corresponding value (attached at the top of each sub-figure). The x-axis describes the network characteristic of the respective inferred network with its predicted characteristic value labeled on each bar. Fig. f) shows the degree distribution plot of the inferred networks where x-axis describes the degree and y-axis describes the frequency of network nodes.*

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We further analyze the inferred network structure by examining the spread of the node degrees with their corresponding frequency distribution. Therefore, a particular fraction of network nodes will have the exact degree count. From the *degree distribution* plot, a significant cluster of nodes counting from 2 to 90, inferred from $RELNET$ algorithm, carry node degree range from $20 - 300$. At the same time, the network inferred from the $MRNETB$ algorithm possesses the node frequency range from 5 to 100 counts that share a significant degree range from $250 - 400$. However, the network derived from the $PPCOR$ algorithm majoritarily occupies a frequency distribution from 3 to 95, thereby splitting the degrees from $350 - 600$. Another vital spread of the network node degrees derived from the $SPCOR$ algorithm captures a dense plot from 2 to 70 node counts from $400 - 800$ degree share. From the inferred networks discussed above, we observe that only a few nodes from these networks are well connected as each carries a very high degree which is beyond 900.

As an additional analysis, we further evaluate the network characteristics of the 11 inferred networks concerning the gold network, thereby measuring the strength of the linear relationships between the predicted and the true values. We use the Pearson correlation coefficient by vectorizing the predicted and gold network characteristics scores in two separate lists and measure their relationship within the normalized range from -1 to $+1$. In Figure 4, we observe that the magnitude of the coefficient produced from $BC3NET$, $MINE$, and $ARACNE$ inferred networks are above 0.9, which represents high correlation, whereas, for other inferred networks, it is 0.6, which is still a significant mark of good association.

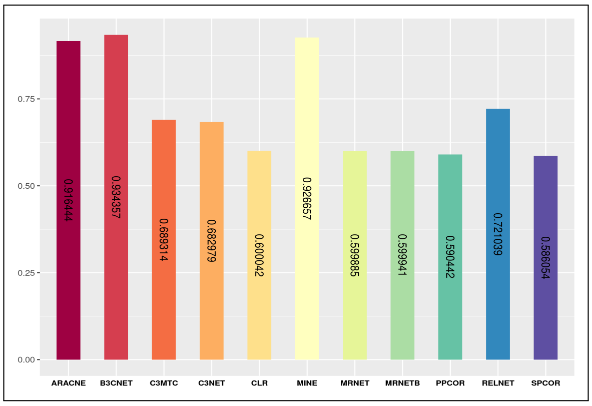

Figure 4. Pearson Correlation Coefficient (PCC) between inferred and gold network characteristics. *Each bar corresponds labeled PCC value between the inferred network characteristics and gold network characteristics.*

4.2. Comparative Analysis of Inference Quality

We use three assessment metrics viz. *area under the receiver operating characteristic* (AUROC), *area under the precision-recall curve* (AUPR), and *F-score* for evaluating the inferred quality of the derived networks obtained from the respective candidate inference algorithms with the gold network. Figure 5 presents the plot of the corresponding metrics with their respective score. We observe that the AUROC score for $ARACNE$, $B3CNET$, $C3MTC$, $C3NET$, and $MINE$ inferred networks obtain a range from $40 - 45\%$, hence representing the poor quality of the inferred networks. However, algorithms including $SPCOR$, $PPCOR$, $MRNETB$, $MRNET$, and CLR describe a slightly improved quality of the inferred networks as they mark the AUROC score ranging from $50 - 52\%$. Unlike AUROC, the AUPR and F-score remain close to 0% for all the candidate algorithms.

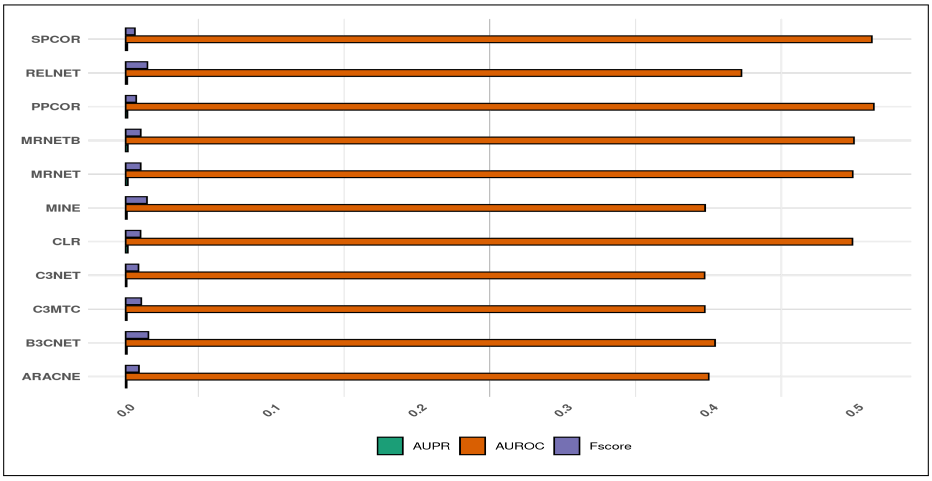

Figure 5. Predictive quality comparison of candidate methods using various metrics.

Therefore, the final remarks from the correlation and metric quality plot suggest that *BC3NET*, *MINE*, and *ARACNE* form a good correlation between the inferred and gold network characteristics. At the same time, these inferred network algorithms' predictive quality remains mediocre compared to *SPCOR*, *PPCOR*, *MRNETB*, *MRNET*, and *CLR*, which is relatively higher for the AUROC score.

5. Conclusion

We created a revolutionary integrated platform for inference, visualization, analysis, and evaluation of large-scale networks. We used their original implementations to incorporate eleven (11) well-known algorithms into the present version. We utilized a method for the seamless display and transition of massive networks using an interactive bubble-burst approach. We offered several topological, centrality, and community detection in a graph together with the network statistics and interactive degree distribution that can analyze any other complex graphs. The benchmarking tool gives future inference method developers an excellent platform to compare and evaluate performance. Our platform was designed to be as lightweight as possible so that smartphone users can utilize it without concern for the limits of their small devices.

The execution pipeline will be expanded further to prioritize the genes that cause diseases, followed by searching and designing small therapeutic molecules.

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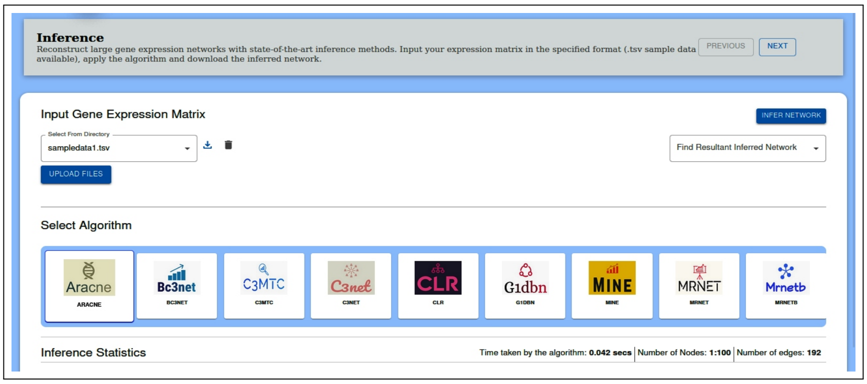

(a) Network Inference Engine

(b) Visualization Engine

(c) Network Analysis Engine

(d) Benchmarking Engine

Figure 6. Screenshots of four engines of the NetRA tool.

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Data Availability Statement: On request (sroy01@cus.ac.in

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