Interactive Visual Analysis of miRNA Target Prediction Results

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Abstract—Integrated analysis of mRNA and miRNAs is essential to comprehend regulation of gene expression. In this paper, we present a case study with miRTarVis, a recently introduced visual analytics tool that supports effective visualizations of the miRNA target prediction results. In the case study, we evaluate the feasibility of miRTarVis by applying it to analyzing miRNA-mRNA expression profiles from TCGA (The Cancer Genome Atlas) breast cancer dataset. Our study results show that miRTarVis can be effective in confirming the previously reported miRNA-mRNA interactions, and it has potential to help researchers generate new hypotheses when it is applied to new dataset.

Keywords—miRNA Target Prediction; miRNA-mRNA Interaction; Graph Visualizations.

I. INTRODUCTION

Recent advancement of next generation sequencing (NGS) enabled researchers to acquire more accurate sequencing information with higher throughput. However, using NGS involves some challenges due to its large data size. There are billions of reads for whole-genome sequencing and ten millions of reads for transcriptomes and methylomes. According to Zhang et al. [1], NGS experiment generally generates terabytes of raw data. As a result, the importance of analysis tools for bioinformatics is increasing, since such tools are essential to achieve full benefit in large NGS data [2] [3].

NGS technologies enable researchers to measure important genomic factors in gene regulation. MicroRNA (miRNA) is one of the important genomic factors since it is an important gene expression regulator. In addition, regulatory RNAs contribute to epigenetic processes that control differentiation and development [4]. Therefore, integrated analysis of mRNA and miRNA (i.e., one of the well studied regulatory RNAs) is essential to comprehend the regulation of the gene expression.

Some analysis tools, such as MMIA [5], mirConnX [6], and MAGIA [7], were introduced to analyze miRNA-mRNA expression profile data using miRNA prediction algorithms. They integrated various sequence-based and miRNA-mRNA expression profile based prediction algorithms for more accurate miRNA target prediction. However, there still is a demand for more accurate miRNA target prediction with miRNA-mRNA expression data.

In addition, such tools help users to easily analyze miRNA-mRNA expression data by supporting user-friendly interfaces or visualizations for the miRNA-mRNA interactions. For example, mirConnX [8] and MAGIA2 [9] used a node-link diagram to visualize a miRNA-mRNA interaction network. However, the visualizations in such tools are limited in terms of a scalability and user interaction. For example, mirConnX and MAGIA are not proper to visualize large miRNA-mRNA interactions. In addition, it is difficult to explore the miRNA-mRNA interaction network in the current tools.

According to Keim [10], visual data exploration should follow Visual Information Seeking Mantra [11] for the scalable exploration: Overview first, zoom and filter, and details on demand. However, existing visualization tools cannot fully support the Visual Information Seeking Mantra due to the lack of user interactions.

One of the recent tools that is designed based on the Visual Information Seeking Mantra and support comprehensive target prediction algorithms is miRTarVis [12]. In this paper, we briefly introduce this tool and present the result of an additional case study using TCGA (The Cancer Genome Atlas) breast cancer dataset to further evaluate the feasibility of miRTarVis.

II. SYSTEM OVERVIEW

The visual analysis procedure in miRTarVis consists of four steps (Fig. 1): (1) load, (2) filter, (3) predict, and (4) visualize. Users first load miRNA-mRNA expression profiles in miRTarVis. Then, they filter the profile data to focus on the subset of miRNAs and mRNAs for the next steps. By using various miRNA target prediction algorithms, users can predict miRNA-mRNA interactions. Finally, users can see visualizations for the miRNA-mRNA interaction network to let the users grasp the structure of the network.

In miRTarVis, two novel visual representations for the miRNA-mRNA interaction networks are supported: enhanced node-link diagram and bipartite treemap. The enhanced node-link diagram (Fig. 1) intuitively shows overall structure of a miRNA-mRNA interaction network. To enhance the visual exploration of the network, users can select one of four graph layout algorithms (i.e., ISOM layout [13], KK layout [14], force-directed layout, and circular layout).
Since the node-link diagram has occlusion problem, miRTarVis also provides another visualization technique (i.e., bipartite treemap, Fig. 2) that expands a Treemap visualization [15]. In the bipartite treemap, the size of mRNA nodes represents the significance of the prediction that is calculated by the prediction step. In addition, the color of node represents the fold change values.

III. CASE STUDY

Using miRTarVis, we analyzed miRNA-mRNA expression profile data from TCGA (The Cancer Genome Atlas) breast cancer dataset. We downloaded miRNA-mRNA expression profile data from 60 cell lines. Among them, 50 samples are cancer cell lines while 10 samples are normal cell lines. We selected the miRNASeq and MiRNASeqV2 types for TCGA download data parameter.

In the load step of miRTarVis, we set the data type as unpaired two-sample data type because the number of cancer cells and normal cells are different. We set the t-test type as unequal variance since the variances of miRNAs and mRNAs are expected to be different, and we select the t-test mode as two-tailed t-test. When a user load miRNA-mRNA expression profile data, histograms appears to show the distribution of fold change of miRNAs and mRNAs. In filter step, a user can remain only the significant miRNAs and mRNAs.

In prediction step, we use correlation analysis (i.e., Pearson coefficient) with only negative correlation, mutual information, MINE, GenMiR++, TargetScan, and miRanda. In visualization step, the predicted miRNA-mRNA regulatory network is visualized by enhanced node-link diagram (Fig. 2) and bipartite treemap (Fig. 3).

As shown in the bipartite treemap (Fig. 3), the miRNA that has the most predicted target mRNA was hsa-miR-29b-3p. According to previous studies [16] [17], miR-29 plays an important role in development of cancer. In addition, Fig. 2 shows that CCND2 is an important mRNA that is predicted to be regulated by multiple miRNAs (i.e., hsa-let-7a-3p, hsa-let-7g-5p, has-miR-141-3p, and has-miR-29b-3p). We could verify that regulation of CCND2 gene by let-7a miRNA plays an important role in cancer development from a literature [18].

Using miRTarVis, we could effectively analyze the miRNA-mRNA expression profiles of TCGA breast cancer data. The visualizations generated by miRTarVis helped us to confirm previously reported miRNA-mRNA interactions from the literatures. This shows the possibility that miRTarVis might also enable users to find new insights from miRNA-mRNA interactions that can be further verified by a biological experiment.
In this paper, we demonstrate miRTarVis, a recently introduced visual analytics tool that supports various miRNA target prediction algorithms with effective visualizations. We conducted a case study to further evaluate the feasibility of miRTarVis using TCGA breast cancer dataset. The case study results demonstrated that miRTarVis can be effective in confirming the previously reported miRNA-mRNA interactions, and it has potential to help researchers generate new hypotheses when it is applied to new datasets by exploring two interactive visualizations (i.e., enhanced node-link diagram and bipartite treemap).

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REFERENCES


