A REVIEW ON ANALYSIS AND VISUALIZATION METHODS FOR BICLUSTERING

ABSTRACT

Recently, biclustering is one of the hot topics in bioinformatics and takes the attention of authors from several different disciplines. Hence, many different methodologies from a variety of disciplines are proposed as a solution to the biclustering problem. As a consequence of this issue, a variety of solutions makes it harder to evaluate the proposed methods. With this review paper, we are aimed to discuss both analysis and visualization of biclustering as a guide for the comparisons between brand new and existing biclustering algorithms. Additionally, we concentrate on the tools that provide visualizations with accompanied analysis techniques. Through the paper, we give several references that is also a short review of the state of the art for the ones who will pursue research on biclustering. The Paper outline is as follows; we first give the visualization and analysis methods, then we evaluate each proposed tools with the visualization contribution and analysis options, finally, we discuss future directions for biclustering and we propose standards for future work.

Keywords  Biclustering · Visualizations · Analysis

1 Introduction

The idea of biclustering is first introduced by Hartigan [1972], is also the specialized version of clustering problem. In essence, clustering refers to the process of organizing a set of input vectors into clusters based on specified similarity with respect to some predefined distance measure [Erten and Sözdinler 2009]. In some cases having the relaxed types of clusters that can group input vectors both horizontally and vertically or in other words, clustering both features and samples are more appreciated. This special instance of clustering, named as Biclustering. In general, clustering can have a resulting intuition that can be valuable in terms of a global perspective. The local perspectives and correlations are somehow disregarded by clustering algorithms unless the Principal Component Analysis or other dimensionality reduction methodologies are applied. Using biclustering, we can give both global and local perspectives by arranging the size of biclusters.

Biclustering is still a hot topic because of many opportunities to extend the problem and takes the attention from sub-disciplines of computer science, mathematics and statistics. This leads to several application areas such as data mining, pattern recognition, micro-array analysis, drug activity analysis, and motif detection [Ben-Dor et al. 2002], [Tanay et al. 2002], [Murali and Kasif 2003], [Kluger et al. 2003], [Bergmann et al. 2003], [Abdullah and Hussain 2006], [Prelic et al. 2006], [Madeira and Oliveira 2009], [Cheng and Church 2000], [Erten and Sözdinler 2009], [Bryan and Cunningham 2008], [Liu et al. 2009], [Gyenesi et al. 2007], [Gu and Liu 2008], [Cheng et al. 2008], [Dharan and Nair 2009], [Carmona-Saez et al. 2006], [Gan et al. 2008], [Li et al. 2009]. Particularly, biclustering problem turns into the optimization problem in several different types of research, concentrate on solving the specified optimization problem. In most cases, the problem is NP-Hard and heuristic solutions are needed. Many heuristic opportunities make

*Melih Sözdinler is supported by The Scientific and Technological Research Council of Turkey(TUBITAK)[BIDEB-2211].
We also suggest that existing specialized visualization methods could also be beneficial as a supporting evidence of biclustering. At Streit et al. [2014], the Furby is another interactive visualization technique for analyzing biclustering results. They propose tools and their pros and cons briefly. Since biclustering is important for both finding local and global perspective of applied biological data, we should be able to verify the success of biclustering on applied data using both computational analyses, visualizations, and biological validations. In the literature, we see the congestion that there is already an algorithm explosion in 10 years starting with Cheng and Church [Cheng and Church, 2000], but still there is a lack of unique comparison methodologies rather than scoring comparisons like $P$-value and $H$-value. In some cases, the proposed method can be application-specific such as applying on different paradigms of bioinformatics. We distinguish these methods. In the case when it is just another algorithm for biclustering on gene expression data, we believe that a fair sophisticated comparison methodologies for validation using both existing biological data and metrics are vital. We also suggest that existing specialized visualization methods could also be beneficial as a supporting evidence of the quality of biclusters. For this purpose, we will discuss the main analysis and visualization methods throughout the paper. We expect that this review should be useful for the forthcoming studies.

Recently, several tools for biclustering that have embedded supports for the visualization models and analysis methods. The main visualization models are Heatmap Representation [Barkow et al., 2006; Goncalves et al., 2009; Grothaus et al., 2006; Santamaria et al., 2008a] and Parallel Coordinate Plots [Barkow et al., 2006; Goncalves et al., 2009; Grothaus et al., 2006; Santamaria et al., 2008a; Cheng et al., 2007]. Rather than these, there are also specialized visualization models. These are Force Directed Layout Model [Santamaria et al., 2008a], Bubble Map Model [Santamaria et al., 2008a], Mountain Map Model [Rasmussen and Karypis, 2004], Enrichment Tree Visualization [Goncalves et al., 2009], Integrated Visualization of Biclusters Verifying with Protein-Protein Interactions [Aladağ et al., 2010], Advanced Heatmap Representation [Grothaus et al., 2009] and Modified Parallel Coordinate Visualizations [Goncalves et al., 2009; Cheng et al., 2007; Santamaria et al., 2008a]. BiCluster Viewers [Heinrich et al., 2011] is also being applied to highlight detected biclusters generated from the original data set by using heatmaps and parallel coordinate plots as visualization methods. BiCFIows [Steinbock et al., 2013] also provided a novel approach to the visualization of bipartite graphs where well fits into bicluster visualization too. The tool allows for multi-scale exploration through the hierarchical aggregation of nodes and edges using biclustering in the linked lists. Different than all these visualization methods, Forestogram [Ghaemi et al., 2017] specifically considers Hierarchical Biclusters and they provide a 3D method inspired by dendrograms to visualize biclusters.

At Streit et al. [2014], the Furby is another interactive visualization technique for analyzing biclustering results. They have twofold contribution claims. The first one is a high-level view of the overall results. And, that shows bicluster shared rows and columns with visualization. The second contribution is to provide heatmaps and bar charts and enable analysts to interactively set the thresholds that transform the fuzzy (soft) clustering into hard clusters.

Furthermore, several analysis methods are also used in literature. These are Significantly Enriched Gene Ontology Categories Analysis (FuncAssociate) or Enrichment Analysis or P-Value [Berriz et al., 2003; Boyle et al., 2004; Bryan and Cunningham, 2006; Erten and Sözdinler, 2009], H-value Scoring or Mean Squared Residue Score (MSRS) [Cheng and Church, 2000], Hv-value Scoring Bryan and Cunningham [2008], Average Correlation Value (ACV) [Teng and Chan, 2006], Pearson Correlation Coefficient Bhattacharya and De [2009], validation with previously known results [Liu and Wang, 2007; Murali and Kasif, 2003], and validation using biological networks [Prelic et al., 2006; Erten and Sözdinler, 2009].

In this review paper, we first discuss the methodology of each visualization and analysis method. Then, we overview proposed tools and their pros and cons. Finally, we talk about future directions and discussions.

## 2 Visualization and Analysis Methods

In the introduction, we review the recent literature of the visualization and analysis methods. In terms of visualization methodologies, there are several different approaches. We divide these into traditional ones and specialized ones. Traditional ones have their own root as an application of existing models to the visualization of biclusters. On the other hand, specialized ones have different properties that are the extensions of existing models, or completely new models. Furthermore, for some visualization approaches, we observe that there are efforts to give the resulting picture as a whole system in one layout and supporting sub-layouts with some interactivity. On the other hand, the remaining approaches consider one by one approach which means that for each bicluster, they give the corresponding visualizations and there are no such high-level visuals. Similarly, we can make a different classification for analysis methods; analysis with computation and analysis with biological validation. In several recent studies, analysis of biclusters conveys the results
of the validation using a scoring function. Also, there are biological validation methods using supplementary biological networks, existing natural groupings, and experimental data.

In this section, we first mention visualization methods, and then we review analysis methods.

2.1 Visualization Methods

We now review the visualization methods in two different titles. First, we will show traditional approaches, next we will demonstrate specialized ones.

2.1.1 Traditional Approaches

Heatmap Representation and Parallel Coordinate Visualization are assumed as traditional hence they introduced before the biclustering essentially for data visualization. In general, they are useful because you can obtain basic knowledge about the biclusters by looking at the resulting pictures of these approaches.

Heatmaps show us the selected parts of the dimensions and values corresponding to these selected dimensions of the dataset, also referred to as biclusters. The main contribution of heatmaps is their contribution to infer information about the bicluster structure. By looking at the resulting heatmap, we see the structure of a bicluster and we can predict the type of a bicluster such as all constant, constant row, constant column, coherent... Particularly, the structure of the bicluster in heatmap depends on the optimization criteria and scoring metric of the algorithm. Therefore, heatmaps are one of the basic validation of the results. A Colouring scheme is vital for heatmaps. Mainly, variations of colors (green-red) are used and each color represents the interval of values. Additionally, choosing an appropriate interval is necessary as well in order to evenly distribute the colors. Heatmaps are included in several tools Goncalves et al. [2009], Barkow et al. [2006], Sharan et al. [2003], Carmona-Saez et al. [2006], Santamaria et al. [2008a], Grothaus et al. [2006], Alada˘g et al. [2010] and each tools have some different modifications. Parallel Coordinates(PC) plots are another useful visualization of biclusters. PC plots mainly introduce visuals for one dimension of data with respect to other dimensions. From the perspective of gene expression data, the PC plots represent the genes under the subset of conditions. Using PC plots, one can easily detect the bicluster structure and it is easier to see coherent biclusters than heatmaps. In PC plots, if the overall picture has simultaneous increasing and decreasing plots, this means that the corresponding bicluster has a correlation in itself. Furthermore, PC plots need to have an appropriate coloring scheme and scaling of plots. Some approaches also add fuzzy effects on each plot to simplify the complicated drawings. Also, scaling is vital to show peak points, intervals of values. Parallel Coordinates are supported in several tools, makes it fundamental for biclustering tools Goncalves et al. [2009], Sharan et al. [2003], Barkow et al. [2006], Cheng et al. [2007, 2008], Santamaria et al. [2008a], Alada˘g et al. [2010]. Note that, some of these tools provide PC plots as Gene Expression Profiles Barkow et al. [2006], Goncalves et al. [2009] which is the non-scaled version of PC plots. We will not distinguish these similar approaches through the review.

Indeed, these two approaches are simple but not enough to see the whole picture and overall quality in both computationally and biologically. Overall, they are useful but more specialized approaches are required.

2.1.2 Specialized Approaches

The general property of specialized approaches is to show the biological relevance of biclusters and to give the general picture of the results while proposing a new idea or extending the existing methods. We review these methodologies in this subsection.

The first visualization approach is based on Force Directed Layout Santamaria et al. [2008a]. The authors’ claim is to unravel trends and to highlight relevant genes and conditions using both visual approaches and complementing biological and statistical analysis. Hence, end-users may have a chance to explore the results quickly and interactively. The visualization technique obtains its root from force-directed layouts that is represented as flexible overlapped groups of genes and conditions. The model is integrated with Heatmaps and Parallel Coordinate Plots and its advantage is the availability of the extension of its visualization methodology with biological relevance using transcriptional modules. Moreover, their proposed model can show several biclusters at once that also combines the overall view with the traditional approaches. Additionally, in their model, if the nodes are connected, a spring force keeps the nodes closer. Also, there is an expansion force that pushes every pair of nodes whether connected or not Kamada and Kawai [1989]. Their claim is that nodes in the same biclusters are closer and the remaining nodes belonging to different biclusters are separated. To represent the bicluster as a graph, they form a complete graph for each bicluster. For overall visibility, they do not show all the edges and nodes. Instead, they show the hull of each bicluster with some transparency. The transparency of this hull is useful to show overlapping biclusters and to increase visibility.
The second approach is a tree-based visualization method that gives biological relevance to biclusters. The method makes a connection between functional categories of an organism in Gene Ontology [Reference Genome Group of the Gene Ontology Consortium] and the corresponding biclusters. It is proposed by Goncalves et al. [2009]. In their method, they form a Gene Ontology (GO) category tree for each bicluster. The tree is in hierarchical layout and specification increases at each lower level of the layout. Next, they calculate Bonferroni corrected P-value overall category nodes of the constructed tree. They color the GO categories on the behalf of lower P-values. In addition to that, they have also different colors to show GO main categories: cellular component, molecular function and biological process. The intensity of each color changes according to the calculated P-value. The main contribution of this approach is to integrate the biclustering concept with the fair scoring of P-values. Rather than this approach, FuncAssociate [Berriz et al. 2003] and several other tools have to support to the calculation of P-values. With Goncalves et al. [2009] approach, we observe these results with a well-readable picture rather than text and we are able to see the hierarchy of GO categories inside the visual. The origin of the approach depends on the hierarchical layout using a well-known graph drawing tool named graphviz [Ellson et al. 2003]. Since graphviz provides nice visualizations, the picture of the layout is well readable and useful to detect enriched categories. Additionally, a similar approach is proposed as in the histogram format [Sharan et al. 2003]. Each histogram shows both the significant transcription factors and GO functional enrichment analysis of bicluster genes. Users can easily detect the most common transcription factor or most common category according to the calculated P-value using the histogram.

Recently, an integrated model for visualizing biclusters from gene expression data and PPI networks (IntegratedViz) tool is introduced [Aladag et al. 2010]. They proposed an approach that integrates Protein-Protein Interaction (PPI) networks and biclusters. Their method has one central graph that represents each bicluster as a node and each node in the main graph has a peripheral graph that corresponds to the sub-network formed by genes of the bicluster. The biological relevance is maintained by using these sub-networks of each bicluster and the edges between nodes of central graph. The Layout is based on Weighted Hierarchical Layout. Authors propose this layout as an extension to Unweighted Hierarchical Layouts as a new graph drawing approach. Introducing weights into graphs give more options to enrich the layout to demonstrate extra weight information of edges. Furthermore, comprising the peripheral graphs are done such that genes of the corresponding biclusters are extracted from the PPI network and eventually, using weighted hierarchical layout algorithm the final layout is obtained. Peripheral graph edges between genes show the reliability of the interactions. At the central graph, scores of each bicluster are calculated and nodes or biclusters in the main graph have a size proportional to these scoring functions. They use three scoring functions; H-value [Cheng and Church 2000], Hv-value [Bryan and Cunningham 2008] and Enrichment Ratio similar to P-value. Finally, edges in the central graph also show either the common genes or interacting edges between two biclusters. The advantage of IntegratedViz is its integration of PPI networks and biclusters, to show the biological relevance of each set of genes of biclusters in global and local views. With this idea, correlated biclusters tend to have more interactions in their corresponding PPI networks.

Another approach in [Grothaus et al. 2006], extends the traditional heatmap visualization. The proposed idea shows all biclusters on a special type of heatmap. The methodology extends the heatmap layout by including multiple labels of genes and conditions in the resulting heatmap. So, they are able to show each bicluster while maintaining the minimum number of repetitions of labels. They propose a novel algorithm, based on PQ-Tree. The algorithm is based on finding an ordering such that the binary formation of 1’s at each bicluster is consecutive. This is called Consecutive One’s Property (COP). In the beginning, discretization of bicluster data is needed in the form of 0’s and 1’s. Then, they set-up PQ-Trees from each discretized bicluster M and next, its rows are stored in list L. Using REDUCE operation, they perform hierarchical clustering to maintain COP property. Next, using the MERGE operation, they form resulting PQ-Trees as a new list, L’ by looking at the similarity score of column lists \( C_T \) and \( C_{T^*} \) where \( T \) and \( T^* \) are separate PQ-Trees. The similarity score is as follows.

\[
\sigma(T, T^*) = \frac{C_T \cap C_{T^*}}{C_T \cup C_{T^*}}
\]

\( \sigma(T, T^*) \) is a function to decide merge operation and each \( \sigma \) function results for all pairs are calculated at the beginning and sorted. Then, they perform REDUCE operation between the pairs with the highest \( \sigma \). If it fails, MERGE operation does not occur. In REDUCE operation, basically, they are checking that the restrictions defined by PQ-Tree, \( T \) holds for \( T^* \). If it holds, MERGE operation occurs. \( T \) and \( T^* \) are deleted from \( L \). Merged tree \( T_m \) is added to list by upgrading \( \sigma \) values. Finally, when all \( \sigma \) values are processed, they give the final layout as it appears on the set of columns of PQ-Trees. This method provides a combinatorial algorithm that holds for the minimum number of repetitions of labels where they are part of the original data in the resulting heatmap. Their method works better in overlapping biclusters and makes it available to show several biclusters in one heatmap. In several overlapping bicluster cases, their problem, as they mentioned, is the number of biclusters. To avoid this problem, they develop a web-based interface that allows execution and navigation through the web. There is also another specialized methodology on heatmap visualization
In [Rajaram and Oono [2010]. Although they mainly discuss the clustering point of view, their proposed toolbox should be applicable to biclustering. In that approach, they extend the view of heatmaps into the third dimension using dendrograms and it is more desirable in such a case to see all biclusters in one visualization.

In addition to all these mentioned approaches, in [Cheng et al. [2007], they propose an extended parallel coordinate visualization. Their approach is to give parallel coordinate plots of a bicluster by simultaneously drawing with the real data plots and the bicluster plots of the same conditions. They are colored with different colors and bicluster gene plots are more visible to emphasize. According to this claim, the global view of the parallel plots is not hidden. This provides a better understanding of gene plots over a subset of conditions. Furthermore, in [Goncalves et al. [2009], it is not a brand new method, but they have one screen that includes all plots. They provide all bicluster plots together to speed up the plots extraction process and this gives us to look at several results to investigate both local and global patterns of biclusters.

Finally, in [Santamaria et al. [2008a], they propose bubble map representation as a projection of 3D mountains in 2D as bubble maps. The conclusion of this section, visualization methods provide us with both local and global perspectives of biclusters. In recent trends, integrating biclusters with biological analysis and data becomes more popular and next-generation visualization tools should include this integration. We now discuss the existing Analysis Methods.

2.2 Analysis Methods

There are several scoring schemes for analysis and we assume that scoring is a good metric for the computational quality of biclusters. On the other hand, it is also important to analyze biclusters with biological knowledge and natural groupings. Therefore, we divide this subsection into two parts; Analysis with Computation and Analysis with Biological Validation.

2.2.1 Analysis with Computation

We have several scoring functions in order to analyze the resulting biclusters. For this purpose, we are mainly interested in the extracted submatrix \( A \) of original data using biclustering. The first scoring method, H-value [Cheng and Church [2000] is found by calculating residues for each entry in submatrix \( A \). Assuming each bicluster as a submatrix that consist of \( I \) rows and \( J \) columns, the residue \( R \) of an entry \((i, j)\) is

\[
R_{i, j}(i, j) = A_{i, j} - A_{Ij} - A_{iJ} + A_{IJ}
\]

where \( A_{i, j} \) is the mean of row \( i \), \( A_{Ij} \) is the mean of column \( j \) and \( A_{iJ} \) is the mean of the all \((i, j)\) pairs. Then, H-value is defined as,

\[
H_{I, J}(i, j) = \frac{1}{IJ} \sum_{i=0,j=0}^{I,J} (RS_{I, j}(i, j))^2
\]

\(H\)-value is a good measure and in many research papers and is used for comparisons and it is also assigned as optimization goal [Cheng and Church [2000], Cano et al. [2007], Liu et al. [2009], Cheng et al. [2008], Erten and Sözdinler [2009]. Furthermore, in [Gremalschi and Altun [2008], they changed this optimization goal by adding multiplication of \( W(i, j)\times\theta \) where \( W(i, j) \) is 1 if \( i \)th row and \( j \)th column is selected, otherwise, it is 0, and \( \theta \) is the overlap cost. With this extension, they claim that overlapping biclusters would occur with less probability due to the defined multiplication as an overlap penalty.

In addition, rather than \( H\)-value, it is possible to use another metric called as \( Hv\)-value [Bryan and Cunningham [2008]. \( Hv\)-value is similar to \( H\)-value and they claim that biclusters with similar row averages should get similar score values rather than \( H\)-values of the same biclusters. So they defined the \( Hv\)-value equation as,

\[
Hv_{I, J}(i, j) = \frac{\sum_{i=0,j=0}^{I,J}((A_{i, j} - A_{Ij} - A_{iJ} + A_{IJ})^2)}{\sum_{i=0,j=0}^{I,J}((A_{i, j} - A_{iJ}))^2}
\]

\(Hv\)-value is only used in its original paper, but it may be an alternative of \( H\)-value comparisons.
Average Correlation Value (ACV) \[\text{Teng and Chan}[2006]\] is another variant of \(H\)-value. According to the authors, it gives more desirable values for both additive and multiplicative biclusters and in their setup for comparison with \(H\)-value shows that ACV is more appropriate. The equation of ACV score is,

\[
ACV = \max \left\{ \frac{\left( \sum_i^n \sum_j^n (R(i,j) - n) \right) / (n^2 - n)}{\left( \sum_k^m \sum_l^m (C(k,l) - m) \right) / (m^2 - m)} \right\}
\]

where \(R\) is the function of the correlation coefficient between given two pair indexes of rows and \(C\) is the function of the correlation coefficient between given two pair indexes of columns.

\(P\)-value is another metric for comparisons of biclusters. It is a scoring function for enrichment measure that also implies the quality of bicluster in terms of biological validation. Gene Ontology Consortium Reference Genome Group of the Gene Ontology Consortium [2009] defined the naming convention for each organism and genes of each organism are appended to these categories. \(P\)-value maintains us to determine the significance of genes of biclusters with respect to each participated GO category. FuncAssociate [Berriz et al. [2003], GOTermFinder [Boyle et al. [2004] and several other tools are available for automated calculation of \(p\)-values and these tools are not only available for biclustering analysis but also available for other analyses [Tuncbag et al. [2009]. Rather than using GO categories and complicated tools, in [Bryan and Cunningham [2006], Erten and Sözdinler [2009] they calculate their own enrichment while using available datasets where the general categories of each gene of the specific organisms are determined. Using these datasets, they can calculate their own enrichment ratios by looking at the highest representative biclusters of each general category. This also refers to the enrichment and is an alternative to \(P\)-value.

Additionally, Pearson Correlation Coefficient (PCC) Scoring, that is pairwise function and it is similar to the calculation of \(H\)-value and varies between \([-1, 1]\). PCC provides a linear correlation between a selected pair of genes when the scores are approaching 1 or \(-1\). In the case of 0 PPC score, the correlation is not linear. In [Bhattacharya and De [2009], they use PPC to collect correlated genes while maintaining good correlation. Also, in [Gyenesi et al. [2007], they test with PPC to evaluate the performance of their biclusters.

Finally, it is also meaningful to compare row means, columns means, variance, and some other basic scoring schemes for each biclustering result. Several biclustering papers provide these comparisons as a supplement to the above scoring metrics.

In this section, we provide the definition of several scoring functions that are used for the analysis of biclusters. In general, \(H\)-value gives larger intervals. \(H\)-value gives narrow boundaries and in some cases, the difference may not be significant. ACV and PCC are good alternatives to \(H\)-value. \(P\)-value is also one of the main comparison metrics. Among these, rather than \(P\)-value, none of them gives biological validation, hence these scoring functions will not indicate the best biclusters in terms of their biological value although they have the quality in scoring, this does not mean that resulting biclusters are invaluable.

### 2.2.2 Analysis with Biological Validation

We review the computational analysis methodologies for biclusters. In this subsection, we partially give biological validation methodologies. Integrating the biclustering algorithms with biological validation or testing the resulting biclusters by referring to biological data is important since we can show the biological importance of biclusters rather than scoring as a metric. Last subsection, we mention about \(P\)-value. It provides scores but these scores have also biological meaning. \(P\)-value relies on GO categories with a set of genes. GO does the naming for categories and has a predetermined set of genes for each category. For a bicluster consisting of a set of genes and conditions, we consider genes such that in which categories these genes are represented more, in other words, what portion of bicluster has a predetermined set of genes for each category. You can also write your own evaluation, by downloading GO files from [http://www.geneontology.org/]. Therefore, \(P\)-value is used in several research papers for comparisons due to availability [Liu et al. [2009], Bryan and Cunningham [2008], Gyenesi et al. [2007], Prelic et al. [2006], Gu and Liu [2008], Cheng et al. [2008], Dharan and Nair [2009], Carmona-Saez et al. [2006], Gan et al. [2008], Li et al. [2009].

We have also another biological metric that is used for the validation of biclusters. In [Prelic et al. [2006], Liu and Wang [2007], Erten and Sözdinler [2009], they provide similar experiments to validate their biclustering methods. This validation is based on Protein-Protein Interaction (PPI) Networks. Their claim is the correlation between genes tends to have more interacting PPI subnetworks. This claim leads to some comparison metrics. You can use the reliability values of interactions to measure the total reliability. You can also measure the average distance between genes of biclusters in the original PPI network [Prelic et al. [2006], Liu and Wang [2007]. In addition, you can form a complete graph between
Table 1: Overview of existing tools

| Tool          | Heatmap | PC | Specialized Approach | Algorithm Support          | Biological Evaluation | Bicluster Analysis |
|---------------|---------|----|----------------------|---------------------------|-----------------------|--------------------|
| Expander 2003 | Yes     | No | No                   | SAMBA, Bimax, CC, ISA     | Yes                   | Yes                |
| BicAT 2006    | Yes     | Yes| No                   | OPSM, Bimax, CC, ISA      | No                    | No                 |
| BiVoc 2006    | Yes     | No | New Heatmap to visualize all biclusters | Import interface for existing results | No | No |
| BiVisu 2007   | Yes | Yes | Modified PC plots | Own Algorithm | No | Yes |
| Bicoverlapper 2008 | Yes | Yes | Force Directed Layouts | Import interface for existing results | Yes | Yes |
| BiGGEsTS 2009 | Yes | Yes | Functional Category Tree View | Integrated Visualization with PPI networks | ECC | Yes |
| IntegratedViz 2010 | No | No | Integrated Visualization with PPI networks | Import interface for existing results, REAL, Bimax, CC | Yes | Yes |
| Robinviz 2011  | Yes | Yes | A Graph Based, Reliability Measurement Criteria added upon IntegratedVis and Gene Ontology categories integrated to the results of biclustering algorithms | REAL, Bimax, CC | Yes | Yes |

genes of biclusters and check that for each gene pair is there any interaction in the original PPI network [Erten and Sözdinler 2009].

Finally, if we obtain some pre-knowledge about our input, we can integrate this knowledge to validate biclusters. For instance, Colon Cancer Dataset from [Alon et al. 1999] is used in [Murali and Kasif 2003, Liu and Wang 2007]. It has 40 colon samples with tumor and 22 healthy colon samples, and approximately 6500 genes. In [Murali and Kasif 2003, Liu and Wang 2007], they tested their algorithm such that how many samples from each bicluster have the cancer samples, with respect to set of genes. This experiment detects a clue for colon cancer if a bicluster has a high ratio of tumor samples and the resulting genes of this bicluster may be effective on colon cancer. That is surely one of the important analyses of biclustering results and with more available instances for other datasets, it would be good validation of the biclusters.

We finish our review on visualization techniques and analysis methods. Now, we give the related tools for biclustering that include at least one of the mentioned visualization techniques.

3 Survey of Existing Tools

In this section, we aim to review features of the existing tools and the visualization and the analysis methods are outlined here.

In Table 1 we give an overview of visualization tools. Table 1 supports our claim that there is fresh interest in the topic. Several tools with different properties are in the literature. Rather than visualization tools, there are also tools proposed for the self-execution of some algorithms [Carmona-Saez et al. 2006, Liu and Wang 2007, Shabalin et al. 2009, Kaiser and Leisch 2008]. Indeed, we go over specified tools in Table 1 and we give the pros and cons of each tool and available options.

3.1 Expander

Expander [Sharan et al. 2003, Tanay et al. 2002] is the eldest tool in our review. Expander is a complete tool with its support for heatmap and PC visualizations, analysis, and execution of algorithms. The tool supports the execution of their own biclustering algorithm SAMBA and clustering algorithm CLICK. Expander also provides the visualization of heatmaps, the resulting bitmaps can be saved easily, and biological evaluation in terms of functional categories in GO using corrected P-value is available. Obtained histogram of biclusters gives the specific encountered categories. Hence this property supports the biclustering results. It has other options such as Principal Component Analysis and viewing.
Box Plots. Additionally, Expander allows saving sessions which is also useful to continue at the point saved. It is coded in JAVA and available at

### 3.2 Biclustering Analysis Toolbox (BicAT)

BicAT [Barkow et al., 2006] is one of the early integrated tools for both execution, analyzing, and visualization of biclusters. It supports heatmap and PC visualizations. The main contribution of the tool is to provide a framework for the execution of well-cited algorithms CC Cheng and Church [2000], OPSM Ben-Dor et al. [2002], ISA Bergmann et al. [2003] and XMOTIF Murali and Kasif [2003] and Bimax Prelic et al. [2006]. On the other hand, the tool has no biological supported visualizations and narrow analysis support. In general, it is one of the earliest tools for bicluster visualization and it is famous because of its variety of supported algorithms and simple GUI. BicAT is coded in JAVA and it is free and downloadable at

### 3.3 BiVoc

BiVoc [Grothaus et al., 2006] specializes in the heatmap representation by extending the representation as multiple biclusters over the input matrix. The algorithm based on PQ-Trees is explained in the previous section. It is innovative since there is no such work to show overlapping biclusters as one heatmap for biclusters. The support of tools is limited due to specialization. They are supporting a defined input format for submitting biclusters and navigation via a web-based interface. Their main concern is to visualize the overlapping biclusters. The methodology of BiVoc does not concentrate on having a unique label. One label in the resulting heatmap could be represented several times but they claim that this repetition is minimized with the guaranteed algorithm. Therefore, for less number of biclusters, their method gives fine results in terms of the total number of rows and columns on the layout. Vice versa, despite the minimization, when the number of biclusters is high, their method gives several rows and columns that may disturb the overall view. Their solution to this problem is providing a web-based interface to follow and track the results. The program is coded in C++ and freely available at

### 3.4 BiVisu

BiVisu [Cheng et al., 2007] is proposed with the algorithm called PM. Their contribution is mainly on the PC plot drawing. Their approach draws parallel coordinate plots by giving plots of bicluster genes within plots of all genes inside the data. The color plots correspond to genes of bicluster with a different color. This enables the user to see the global view of the parallel gene plots for the corresponding bicluster with respect to a set of conditions in the bicluster. The tool also provides a heatmap view. Further analysis of biclusters are available in its GUI such as H-value and Average Correlation Value. Although they propose an extension to PC plots, the view has some problems of scaling as shown in Santamaria et al. [2008b]. Their program is implemented in MATLAB and available at

### 3.5 Bicoverlapper

Bicoverlapper [Santamaria et al., 2008a,b] is one of the sophisticated tools that mainly concentrates on the visualization techniques that exist before. They also propose a brand new method. In this new method, they use the force-directed layout of a graph of corresponding biclusters. The detail of the method is given in the previous section. Since it provides visualization for several biclusters, their method differs from other visualization methods except BiVoc and IntegratedViz do. Their main contribution is handling several overlapping and nonoverlapping biclusters with given biological relevance with respect to Transcriptional Regulatory Networks (TRN). They also support their main layout with heatmaps and PC plots as evidence of their integrated visualization, and they propose the 2D Bubble Map method by applying from 3D version named Mountain Map visualization. Moreover, they do not have implemented algorithms inside their tool, however, they provide the import interface for the results of biclustering algorithms. Their main concern is the execution time of force-directed layouts. These layouts are simple and easy to apply when the graph has a countable number of nodes. In the case of biclustering results with higher dimensions, meaning that many nodes, force-directed graph may slow the execution and meaning of the main layout may be intervened. Their tool is available at and they provided some example biological analysis in Santamaria et al. [2008b].

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1. Expander: [http://acgt.cs.tau.ac.il/expander/](http://acgt.cs.tau.ac.il/expander/)
2. BicAT: [https://sop.tik.ee.ethz.ch/bicat/](https://sop.tik.ee.ethz.ch/bicat/)
3. BiVoc: [https://bioinformatics.cs.vt.edu/~murali/software/biorithm/bivoc.html](https://bioinformatics.cs.vt.edu/~murali/software/biorithm/bivoc.html)
4. BiVisu: [http://www.eie.polyu.edu.hk/~nflaw/Biclustering/](http://www.eie.polyu.edu.hk/~nflaw/Biclustering/)
5. Bicoverlapper: [http://carpex.usal.es/~visusal/bicoverlapper/](http://carpex.usal.es/~visusal/bicoverlapper/)
3.6 BiGGEsTS

BiGGEsTS [Goncalves et al., 2009] is a recently proposed tool that supports both several visualizations and analysis methods for biclusters. The tool also maintains the execution of their algorithm [Madeira and Oliveira, 2009]. Its GUI is similar to BicAT and thus user-friendly. They provide embedded visualization methods which are heatmap, PC, multiple PCs, and enrichment tree visualization based on the method described in the last section. BiGGEsTS maintains an integrated environment. You can obtain both heatmaps and PCs. Also, their innovative enrichment tree visualization methodology gives the biological significance of biclusters. Furthermore, in their multiple PC plots, they also give the expression patterns that simplify the congested plots. These simplified plots show the general trend of PC plots and the pattern of bicluster as well. Additionally, BiGGEsTS use the Graphviz tool to support their enrichment tree visualization. The whole procedure except the production of graphs is executed using Graphviz’s dot program. BiGGEsTS supports sessions to save all the work that is done during the session and also allows execution of their own algorithm eCCC. Finally, BiGGEsTS is implemented using JAVA and it is under GPL license available at [6].

3.7 IntegratedViz and Robinviz

IntegratedViz is an integrated visualization tool and proposes an innovative approach of evaluation and validation of biclustering results using biological data. IntegratedViz also supports Heatmap and PC plots visualizations. Particularly, IntegratedViz concentrates on both global and local visualization of biclusters. Global view shows each bicluster as a node of weighted hierarchical layout and peripheral graphs corresponding to these graphs are accessible via clicking. The details of the methodology are described in the previous section. Due to the nature of the proposed methodology, IntegratedViz also provides some pieces of evidence for analysis such as scoring and enrichment value of biclusters. Furthermore, their visualization method is also supported with visual clues such as coloring of categories at peripheral graphs which shows the main category of genes among pre-determined ones, edge thickness, and node sizes. The main graph shows the H-values of each bicluster by arranging the size of nodes. They also allow importing the results of algorithms and execution of given algorithms in Table 1. The one disadvantage of the tool is again the problem of several biclusters as it happens in BicOverlapper and BiVoc. To prevent visualization disturbance, they added some scaling and hiding methods. IntegratedViz is written in C++ and freely available at [7]. They also extended this tool and renamed as Robinviz (Reliability Oriented Bioinformatics Network Visualization) [Aladag et al., 2011][8].

4 Future Directions and Conclusion

Indeed, we give the review of existing visualization and analysis methods providing a short explanation to each approach. We explain the common and recently proposed tools, mainly specialized in visualization, and have support for the described analysis options.

The problem of the biclustering area is the lack of fair analyzing tools and specialized visualizations. Inevitably, there are many algorithms based on a variety of disciplines due to the attraction of the topic but the dilemma is how to analyze and show the abstract results to the end-users such as biologists. Validating the visualizations with other biological data such as Functional Categories, PPIs and TRNs surely be important in next-generation bicluster visualizations and analyses. Heatmaps and Parallel Coordinate Plots are helpful but they are not able to demonstrate the quality due to biological relevance. Since gene expression data are the main input of biclustering algorithms, the validation of the existing algorithms is surely done with the biological relevance of genes. In that case, visualization methods should be able to show some clues about these relevance to inform end-users. In [Merico et al., 2009], they have a claim that networks in biology can appear complex and difficult to decipher. They provide a concept in order to analyze these networks using frequently employed visualization and analysis patterns. This approach supports our claim for the bicluster visualization. The increasing amount of data in subtopics of bioinformatics may result in relation to the biclustering problem. As a result, the visualization approaches from these topics can be integrated to decipher these relations.

We will also need to mention some standards. By now, we have some standards for gene expression data and each tool or algorithm can easily adopt these data, but we do not have the standard for importing the results of biclusters. This is important since the proposed tools are based on the assumption of having determined input. Tools have no chance to follow many different formats so indeed the proposers of algorithms should provide a stable format. This may be a new mark-up language format that is easier to parse. Also, it is possible to use simple notation as shown inside Figure 1.

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6BiGGEsTS: http://kdbio.inesc-id.pt/software/biggests/
7IntegratedViz: http://webprs.khas.edu.tr/~cesim/
8Robinviz: https://github.com/aladagemre/robinviz
This notation provides the name of the algorithm, number of biclusters, size of genes and conditions at each bicluster, and the labels of genes and conditions in a bicluster. After these vital entities, in the end, algorithm proposers may extend their file by adding their scores if it is used and other information related to the proposed algorithm.

Furthermore, providing an open-source codes or self-executable programs for the proposed biclustering algorithms should be beneficial. Therefore, it is possible to look at the other proposed method without reimplementation. Especially in biclustering, it is more desirable to have open-source codes or self-executable programs to help the prospective authors for their comparisons.

In a conclusion, we believe visualization and analysis of biclusters are still hot topics. With this review paper, we imply the analysis and visualization methods and we give the future directions. Understanding and analyzing biclustering results, setting up bridges to other related topics and providing a visualization approaches by integration with other topics would be soon more important. Hence extending the topic to the other applications would be easier.

Acknowledgements

Melih Sözdinler is paid by The Scientific and Technological Research Council of Turkey(TUBITAK)[BIDEB-2211]. Additional thanks to my PhD advisors; Can Özturan, Turkan Haliloglu, Arzucan Özgür and Cesim Erten

Conflict of Interest: None declared.

References

J. A. Hartigan. Direct clustering of a data matrix. *Journal of the American Statistical Association*, 67(337):123–129, 1972.

Cesim Erten and Melih Sözdinler. Biclustering expression data based on expanding localized substructures. In Sanguthevar Rajasekaran, editor, *Bioinformatics and Computational Biology*, pages 224–235, Berlin, Heidelberg, 2009. Springer Berlin Heidelberg. ISBN 978-3-642-00727-9.

A. Ben-Dor, B. Chor, R. Karp, and Z. Yakhini. Discovering local structure in gene expression data: the order-preserving submatrix problem. In *RECOMB ’02: Proceedings of the sixth annual international conference on Computational biology*, pages 49–57, New York, NY, USA, 2002. ACM. ISBN 1581134983. doi:http://dx.doi.org/10.1145/565196.565203. URL http://dx.doi.org/10.1145/565196.565203.

A. Tanay, R. Sharan, and R. Shamir. Discovering statistically significant biclusters in gene expression data. *Bioinformatics*, 18 Suppl 1, 2002. ISSN 1367-4803. URL http://view.ncbi.nlm.nih.gov/pubmed/12169541.

T. M. Murali and Simon Kasif. Extracting conserved gene expression motifs from gene expression data. In *Pacific Symposium on Biocomputing*, pages 77–88, 2003. URL http://helix-web.stanford.edu/psb03/murali.pdf.

Y. Kluger, R. Basri, J. T. Chang, and M. Gerstein. Spectral biclustering of microarray data: coclustering genes and conditions. *Journal Genome Res PMID J2671006*, 13:703–16, 2003. URL http://bioinfo.mbb.yale.edu/genome/expression.

S. Bergmann, J. Ihmels, and N. Barkai. Iterative signature algorithm for the analysis of large-scale gene expression data. *Physical review. E, Statistical, nonlinear, and soft matter physics*, 67(3 Pt 1), March 2003. ISSN 1539-3755. URL http://view.ncbi.nlm.nih.gov/pubmed/12889096.
A Review on Analysis and Visualization Methods for Biclustering

Ahsan Abdullah and Amir Hussain. A new biclustering technique based on crossing minimization. *Neurocomputing*, 69(16-18):1882–1896, 2006. URL http://dx.doi.org/10.1016/j.neucom.2006.02.018

A. Prelic, S. Bleuler, P. Zimmermann, A. Wille, P. Buhlmann, W. Gruissem, L. Hennig, L. Thiele, and E. Zitzler. A systematic comparison and evaluation of biclustering methods for gene expression data. April 2006. URL http://bioinformatics.oxfordjournals.org/cgi/content/short/22/9/1122?rss=1

Sara Madeira and Arlindo Oliveira. A polynomial time biclustering algorithm for finding approximate expression patterns in gene expression time series. *Algorithms for Molecular Biology*, 4(1):8, 2009. ISSN 1748-7188. doi:10.1186/1471-2105-9-S4-S9. URL http://www.biomedcentral.com/1471-2105/9/210

Smitha Dharan and Achuthsankar Nair. Biclustering of gene expression data using reactive greedy randomized adaptive search procedure. *BMC Bioinformatics*, 10(Suppl 1):S27, 2009. ISSN 1471-2105. doi:10.1186/1471-2105-10-S1-S27. URL http://www.biomedcentral.com/1471-2105/10/S1/S27

Pedro Carmona-Saez, Roberto Pascual-Marqui, F Tirado, Jose Carazo, and Alberto Pascual-Montano. Biclustering of gene expression data by non-smooth non-negative matrix factorization. *BMC Bioinformatics*, 7(1):78, 2006. ISSN 1471-2105. doi:10.1186/1471-2105-7-78. URL http://www.biomedcentral.com/1471-2105/7/78

Xiangchao Gan, Alan Liew, and Hong Yan. Discovering biclusters in gene expression data based on high-dimensional linear geometries. *BMC Bioinformatics*, 9(1):209+, April 2008. ISSN 1471-2105. doi:10.1186/1471-2105-9-209. URL http://dx.doi.org/10.1093/bmcinformatics/btn491

Guojun Li, Qin Ma, Haibao Tang, Andrew H. Paterson, and Ying Xu. Qubic: a qualitative biclustering algorithm for analyses of gene expression data. *Nucleic acids research*, 37(15):e101+, August 2009. ISSN 1362-4962. doi:10.1093/nar/gkp491. URL http://dx.doi.org/10.1093/nar/gkp491

S. C. Madeira and A. L. Oliveira. Biclustering algorithms for biological data analysis: A survey. *IEEE/ACM Trans. on Comp. Biol. and Bioinformatics (TCBB)*, 1(1):24–45, 2004.

A. Tanay, R. Sharan, and R. Shamir. Biclustering algorithms: A survey. *Handbook of Computational Molecular Biology*, 2004. URL http://en.wikipedia.org/wiki/Biclustering

Stanislav Busygin, Oleg Prokopyev, and Panos M. Pardalos. Biclustering in data mining. *Comput. Oper. Res.*, 35(9):2964–2987, September 2008. ISSN 0305-0548. doi:10.1016/j.cor.2007.01.005. URL http://dx.doi.org/10.1016/j.cor.2007.01.005

S. Barkow, S. Bleuler, A. Prelic, P. Zimmermann, and E. Zitzler. Bicat: a biclustering analysis toolbox. *Bioinformatics (Oxford, England)*, 22(10):1282–1283, May 2006. ISSN 1367-4803. URL http://view.ncbi.nlm.nih.gov/pubmed/16551664

Joana Goncalves, Sara Madeira, and Arlindo Oliveira. Biggests: integrated environment for biclustering analysis of time series gene expression data. *BMC Research Notes*, 2(1):124, 2009. ISSN 1756-0500. doi:10.1186/1756-0500-2-124. URL http://www.biomedcentral.com/1756-0500/2/124
Gregory Grothaus, Adeel Mufti, and T. M. Murali. Automatic layout and visualization of biclusters. *Algorithms for Molecular Biology*, 1(1):15+, September 2006. ISSN 1748-7188. doi:10.1186/1748-7188-1-15. URL http://dx.doi.org/10.1186/1748-7188-1-15

Rodrigo Santamaria, Roberto Theron, and Luis Quintales. BiOverlapper: A tool for bicluster visualization. *Bioinformatics*, 24(9):1212–1213, 2008a. doi:10.1093/bioinformatics/btn076. URL http://bioinformatics.oxfordjournals.org/cgi/content/abstract/24/9/1212

Kin-On Cheng, Ngai-Fong Law, Wan-Chi Siu, and Alan Liew. Bivisu: software tool for bicluster detection and visualization. *Bioinformatics (Oxford, England)*, 23(17):2342–2344, September 2007. ISSN 1367-4811. doi:10.1093/bioinformatics/btm338. URL http://dx.doi.org/10.1093/bioinformatics/btm338

Matt Rasmussen and George Karypis. gcluto - an interactive clustering, visualization, and analysis system. Technical report, 2004.

Ahmet Emre Aladağ, Cesim Erten, and Melih Sözdinler. An integrated model for visualizing biclusters from gene expression data and ppi networks. In *ISB '10: Proceedings of the 1th international symposium on Biocomputing*, Calcut,Kerala,India, 2010. ACM. doi: accepted.

Julian Heinrich, Robert Seifert, Michael Burch, and Daniel Weiskopf. Bicluster viewer: A visualization tool for analyzing gene expression data. In George Bebis, Richard Boyle, Bahram Parvin, Darko Koracin, Song Wang, Kim Kyungnam, Bedrich Benes, Kenneth Moreland, Christoph Borst, Stephen DiVerdi, Chiang Yi-Jen, and Jiang Ming, editors, *Advances in Visual Computing*, pages 641–652, Berlin, Heidelberg, 2011. Springer Berlin Heidelberg. ISBN 978-3-642-24028-7.

Daniel Steinbock, Eduard Groller, and Manuela Waldner. Casual visual exploration of large bipartite graphs using hierarchical aggregation and filtering. In *2018 International Symposium on Big Data Visual and Immersive Analytics (BDVA)*, pages 1–10, 2018. doi:10.1109/BDVA.2018.8533894

Mohammad Sajjad Ghaemi, Vahid Partovi Nia, and Bruno Agard. Forestogram: A visualization framework for hierarchical biclustering. pages 1–16, May 2017. URL https://www.gerad.ca/en/papers/G-2017-40

E. I. Boyle, S. Weng, J. Gollub, H. Jin, D. Botstein, J. M. Cherry, and G. Sherlock. Go::termfinder–open source software for accessing gene ontology information and finding significantly enriched gene ontology terms associated with a list of genes. *Bioinformatics*, 20(18):3710–3715, December 2004. ISSN 1367-4803. URL http://view.ncbi.nlm.nih.gov/pubmed/15297299

K. Bryan and P. Cunningham. Bottom-up biclustering of expression data. *Proceedings of the 2006 IEEE Symposium on Computational Intelligence in Bioinformatics and Computational Biology, CIBCB’06*, (4133177):232–239, 2006.

Li Teng and Lai-Wan Chan. Biclustering gene expression profiles by alternately sorting with weighted correlated coefficient. In *Machine Learning for Signal Processing, 2006. Proceedings of the 2006 16th IEEE Signal Processing Society Workshop on*, pages 289–294, 2006. doi:10.1109/MLSP.2006.275563. URL http://dx.doi.org/10.1109/MLSP.2006.275563

Anindya Bhattacharya and Rajat K. De. Bi-correlation clustering algorithm for determining a set of co-regulated genes. *Bioinformatics*, 25(21):2795–2801, November 2009. ISSN 1367-4811. doi:10.1093/bioinformatics/btp526. URL http://dx.doi.org/10.1093/bioinformatics/btp526

Xiaowen Liu and Lusheng Wang. Computing the maximum similarity bi-clusters of gene expression data. *Bioinformatics*, 23(1):50–56, 2007. doi:10.1093/bioinformatics/btl560. URL http://bioinformatics.oxfordjournals.org/cgi/content/abstract/23/1/50

Roded Sharan, Adi Maron-katz, and Ron Shamir. Click and expander: A system for clustering and visualizing gene expression data. *Bioinformatics*, 19:1787–1799, 2003.

T. Kamada and S. Kawai. An algorithm for drawing general undirected graphs. *Inf. Process. Lett.*, 31(1):7–15, 1989. ISSN 0020-0190. doi:http://dx.doi.org/10.1016/0020-0190(89)90102-6

Reference Genome Group of the Gene Ontology Consortium. The gene ontology’s reference genome project: a unified framework for functional annotation across species. *PLoS computational biology*, 5(7):e1000431+, July 2009. ISSN 1553-7358. doi:10.1371/journal.pcbi.1000431. URL http://dx.doi.org/10.1371/journal.pcbi.1000431
J. Ellson, E.R. Gansner, E. Koutsofios, S.C. North, and G. Woodhull. Graphviz and dynagraph – static and dynamic graph drawing tools. In M. Junger and P. Mutzel, editors, Graph Drawing Software, pages 127–148. Springer-Verlag, 2003.

Satwik Rajaram and Yoshi Oono. Neatmap - non-clustering heat map alternatives in r. BMC Bioinformatics, 11(1):45, 2010. ISSN 1471-2105. doi:10.1186/1471-2105-11-45 URL http://www.biomedcentral.com/1471-2105/11/45

C. Cano, L. Adarve, J. López, and A. Blanco. Possibilistic approach for biclustering microarray data. Computers in biology and medicine, 37(10):1426–1436, October 2007. ISSN 0010-4825. doi:10.1016/j.compbiomed.2007.01.005 URL http://dx.doi.org/10.1016/j.compbiomed.2007.01.005

Stefan Gremalschi and Gulsah Altun. Mean squared residue based biclustering algorithms. In Bioinformatics Research and Applications, pages 232–243. 2008. doi:10.1007/978-3-540-79450-9_22 URL http://dx.doi.org/10.1007/978-3-540-79450-9_22

Nurcan Tuncbag, Gozde Kar, Ozlem Keskin, Attila Gursoy, and Ruth Nussinov. A survey of available tools and web servers for analysis of protein-protein interactions and interfaces. Brief Bioinform, 10(3):217–232, May 2009. ISSN 1477-4054. doi:10.1093/bib/bbp001 URL http://dx.doi.org/10.1093/bib/bbp001

U. Alon, N. Barkai, D. A. Notterman, K. Gish, S. Ybarra, D. Mack, and A. J. Levine. Broad patterns of gene expression revealed by clustering analysis of tumor and normal colon tissues probed by oligonucleotide arrays. Proceedings of the National Academy of Sciences of the United States of America, 96(12):6745–6750, June 1999. ISSN 0027-8424. doi:10.1073/pnas.96.12.6745 URL http://dx.doi.org/10.1073/pnas.96.12.6745

Andrey A. Shabalin, Victor J. Weigman, Charles M. Perou, and Andrew B. Nobel. Finding large average submatrices in high dimensional data. ANNALS OF APPLIED STATISTICS, 3:985, 2009. doi:10.1214/09-AOAS239

Sebastian Kaiser and Friedrich Leisch. A toolbox for bicluster analysis in r, 2008. URL http://epub.ub.uni-muenchen.de/3293/

Rodrigo Santamaria, Roberto Theron, and Luis Quintales. A visual analytics approach for understanding biclustering results from microarray data. BMC Bioinformatics, 9(1):247+, May 2008b. ISSN 1471-2105. doi:10.1186/1471-2105-9-247 URL http://dx.doi.org/10.1186/1471-2105-9-247

Ahmet Emre Aladağ, Cesim Erten, and Melih Sözdinler. Reliability-Oriented bioinformatic networks visualization. Bioinformatics, 27(11):1583–1584, 04 2011. ISSN 1367-4803. doi:10.1093/bioinformatics/btr178 URL https://doi.org/10.1093/bioinformatics/btr178

Daniele Merico, David Gieller, and Gary D. Bader. How to visually interpret biological data using networks. Nature biotechnology, 27(10):921–924, October 2009. ISSN 1546-1696. doi:10.1038/nbt.1567 URL http://dx.doi.org/10.1038/nbt.1567