

## Data and text mining

## BicAT: a biclustering analysis toolbox

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## ABSTRACT

**Summary:** Besides classical clustering methods such as hierarchical clustering, in recent years biclustering has become a popular approach to analyze biological data sets, e.g. gene expression data. The Biclustering Analysis Toolbox (BicAT) is a software platform for clustering-based data analysis that integrates various biclustering and clustering techniques in terms of a common graphical user interface. Furthermore, BicAT provides different facilities for data preparation, inspection and postprocessing such as discretization, filtering of biclusters according to specific criteria or gene pair analysis for constructing gene interconnection graphs. The possibility to use different biclustering algorithms inside a single graphical tool allows the user to compare clustering results and choose the algorithm that best fits a specific biological scenario. The toolbox is described in the context of gene expression analysis, but is also applicable to other types of data, e.g. data from proteomics or synthetic lethal experiments.

**Availability:** The BicAT toolbox is freely available at <http://www.tik.ee.ethz.ch/sof/bicat> and runs on all operating systems. The Java source code of the program and a developer's guide is provided on the website as well. Therefore, users may modify the program and add further algorithms or extensions.

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Microarray technology has become a central tool in biological research, and the identification of gene groups with similar expression patterns represents a key step in the analysis of gene expression data. Traditional clustering algorithms partition an expression matrix into submatrices that extend over the whole set of conditions, giving all conditions equal weight. For specific biological questions, though, the assumption that all genes behave similarly in all conditions, may be too restrictive. To account for this, biclustering approaches carry out the grouping in both dimensions simultaneously: genes and conditions. This allows to find subgroups of genes that show the same response under a subset of conditions, e.g. if a cellular process is only active under these conditions. Furthermore, if a gene participates in multiple pathways that are differentially regulated, one would expect this gene to be included in more than one cluster; this cannot be achieved by traditional clustering.

Several biclustering algorithms have been proposed in the literature, each of which has strengths and weaknesses for the application in different biological scenarios (Madeira and Oliveira, 2004). A recent comparative study has shown that there are significant differences in performance among biclustering approaches, depending on the biological problem that is examined (Prelic *et al.*, 2006).

Since every algorithm is subject to a specific mathematical problem formulation, it cannot be expected that a single approach is well-suited for all scenarios. Accordingly, it can be useful in practice to try different approaches and to choose that algorithm that delivers the best results. Although implementations are available for some of the proposed biclustering algorithms, each program may be accompanied by a different user interface and use different input and output formats, which in turn makes the application of several methods a time-consuming task. Desirable is a software tool that offers different biclustering approaches within a common framework—to our best knowledge, such a tool has not been available so far. BicAT tries to fill this gap and provides the following functionality:

- **Data handling:** Tree-structured data handling that allows (1) access to all analysis steps and (2) data export of biclustering and filtering results.
- **Data preprocessing:** Normalization ( $\log_2$ , mean centric) and discretization.
- **Clustering:** Five biclustering algorithms and two traditional clustering algorithms.
- **Data visualization:** Heatmap and profile visualization of biclusters.
- **Postprocessing:** Analysis of gene pair occurrence to derive gene interconnection graphs.

In the following, the main characteristics of the tool will be described—for each of the above aspects separately.

**Data handling.** All data, be it entire gene expression matrices loaded from external files or sets of submatrices generated by specific biclustering algorithms, are organized in a tree structure that is depicted in the left panel of the graphical user interface, cf. Figure 1. The loaded datasets form the top hierarchy of the tree. The second hierarchy is built up by the clustering, search and filter procedures with the generated lists of biclusters. This structure allows to access every performed analysis step, which is particularly useful, e.g. for the comparison of different clustering runs. Every search and filter operation produces a new list of biclusters that can be further examined in the next analysis steps or exported to a file.

**Data preprocessing.** The input data file can be any tab-separated text file including annotations of genes and conditions. The loaded gene expression data can then be transformed by means of normalization and discretization. For normalization, the  $\log_2$  or the mean centric of the original values can be computed; discretization can be performed with regard to upregulated, downregulated or complementary expression patterns on the basis of a user-defined threshold.

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