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Performance Evaluation and Enhancement of Biclustering Algorithms

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Abstract: In gene expression data analysis, biclustering has proven to be an effective method of finding local patterns among subsets of genes and conditions. The task of evaluating the quality of a bicluster when ground truth is not known is challenging. In this analysis, we empirically evaluate and compare the performance of eight popular biclustering algorithms across 119 synthetic datasets that span a wide range of possible bicluster structures and patterns. We also present a method of enhancing performance (relevance score) of the biclustering algorithms to increase confidence in the significance of the biclusters returned based on four internal validation measures. The experimental results demonstrate that the Average Spearman's Rho evaluation measure is the most effective criteria to improve bicluster relevance with the proposed performance enhancement method, while maintaining a relatively low loss in recovery scores.

1 INTRODUCTION

Biclustering is an effective unsupervised learning tool for discovering patterns of co-regulated/co-expressed genes across a subset of samples in gene expression data analysis (Madeira and Oliveira, 2004; Pontes et al., 2015a). As the name implies, clustering is performed simultaneously on both the row and column dimensions to discover biclusters, which are defined as submatrices in which the group of rows behave similarly across the subset of columns contained in the submatrix. Biclustering is a special case of pattern-based clustering algorithms (Kriegel et al., 2009).

In traditional clustering methods, the objective is to subdivide the entire data matrix into subgroups, or clusters, which consist of rows (examples) that exhibit more homogeneous patterns across *all* columns (features). In biclustering, these homogeneous subgroups, or biclusters, do not necessarily span all the columns. This makes biclustering useful for identifying possible relevant subspaces in the data. There are two underlying assumptions in biclustering: (i) the presence of irrelevant features, or of correlations among subsets of features, may significantly bias the representation of clusters in the full-dimensional space. By relaxing the constraint of global feature space, we could discover more meaningful subgroups; and (ii) different subsets of features may be relevant for different clusters which implies that objects cluster in subspaces of the data, rather than across an entire dimension.

In gene expression data analysis, such a problem formulation is particularly useful because according to the general understanding of cellular processes, only a subset of genes is involved with a specific cellular process, which becomes active only under some experimental conditions (Xu and Wunsch II, 2011). Usually, the expression levels of many genes are measured across a relatively small set of conditions or samples, and the obtained gene expression data are organized as a data matrix with rows corresponding to genes and columns corresponding to samples or conditions. However, such a practice is inherently limited due to the existence of many uncorrelated genes with respect to sample or condition clustering, or many unrelated samples or conditions with respect to gene clustering. Biclustering offers a solution to such problems by performing simultaneous clustering on both dimensions as well as automatically integrating feature selection with clustering without any prior information, so that the relations of clusters of genes (generally, features) and clusters of samples or conditions (data objects) are established.

Note that the usefulness of biclustering methods in discovering local patterns that exist among a subset of rows and columns are also applicable to domains beyond the context of gene expression data

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analysis such analysis of voting data (Hartigan, 1972) or more recently, collaborative filtering recommendation systems (Elnabarawy et al., 2016). In the past two decades, there has been an influx of multiple biclustering algorithms proposed, as reviewed in (Prelić et al., 2006; Eren et al., 2012; Oghabian et al., 2014; Pontes et al., 2015a; Roy et al., 2016). A recent review by Pontes et al. (Pontes et al., 2015a) classifies 30 different biclustering algorithms (which is still not an exhaustive list of all methods proposed in literature) by their inherent method of determining optimal biclusters. It separated the algorithms into two main categories: those based on evaluation measures vs. those non metric-based. Given that biclustering is an unsupervised machine learning technique, a key issue is how to evaluate/rank the goodness of the biclusters returned by varied algorithms, especially in the situations where the algorithm return a large number of biclusters. This task becomes particularly challenging in absence of ground truth.

The development of effective heuristic and suitable evaluation measures is of particular interest to the biclustering research community (Cheng and Church, 2000; Pontes et al., 2007; Mukhopadhyay et al., 2009; Ayadi et al., 2009; Pontes et al., 2010). These measures are based on inherent assumptions about possible bicluster patterns for gene expression data such as shifting, scaling or a combination of both. Several evaluation measures have been proposed for biclustering algorithms (Pontes et al., 2015b). These evaluation measures, also referred to as quality measures, attempt to quantify the goodness of the biclusters. They can be regarded as internal validation measures as they are evaluating the biclusters based on certain desired properties of possible patterns (shifting, scaling, and combined). Pontes et al. in (Pontes et al., 2015b) conducted a comparison analysis of 14 measures known in literature to assess their ability to identify optimal biclusters based on shifting, scaling or combined patterns. Their work identified two of these measures, average Spearman's rho (ASR) and transposed virtual error (VE^T) as been proficient in identifying all three types of biclusters.

In this work, we conduct a comparative empirical analysis of the performance of a subset of the 30 algorithms recently identified in (Pontes et al., 2015a), along with two improved algorithms that were not included in the review, using a state of the art benchmark synthetic dataset (Wang et al., 2016). We propose an enhancement framework based on application of two best-performing validation measures (ASR and VE^T) to enhance the performance of biclustering methods specifically in terms of identifying the optimal set of relevant biclusters returned by the algorithms. In addition, we present a comparative performance analysis of the proposed method using two other commonly used measures: mean squared residue (MSR) and scaling mean squared residue (SMSR). We also apply a statistical measure (Friedman's test statistic (Conover and Iman, 1981)) to quantify the significance of the improvements obtained. The objective of this study is to provide empirical evidence that can guide practical applications of biclustering methods along with these measures in discovering significant and relevant biclusters. The remainder of this paper is organized as follows. In section 2, we present an overview of the algorithms analyzed in this paper. Section 3 presents a description of the performance evaluation framework utilized in this paper. The experimental results obtained is illustrated and discussed in section 4 while the conclusion is drawn in section 5.

2 BACKGROUND

2.1 Motivation

Our overall goal in this paper is twofold. The first is to evaluate empirically the performance of eight commonly used biclustering algorithms using benchmark synthetic dataset that differ from previous surveys to provide an insight into the overall performance of the algorithms and an understanding of what types of applications it's best suited for. Secondly, we are interested in improving the overall performance of these algorithms using evaluation measures that have been proposed in literature. In the context of this work, an algorithm performs well if majority of the biclusters returned by the method are relevant and if it discovers (or retrieves) majority of the actual biclusters present in the data. We formally quantify performance based on relevance and recovery scores, as defined in section 3.1. Our hypothesis is that ASR and VE^T will result in the most significant improvement given that they have been demonstrated to successfully identify biclusters of shifting, scaling and combined patterns (known pattern concepts for gene expression data (Pontes et al., 2010)). We compare their effect on the enhancement of these algorithms to MSR and SMSR which have been demonstrated in literature as been effective internal validation measures for only one class of bicluster patters, shifting and scaling respectively.

It is commonly known that finding biclusters is an NP-hard problem (Pontes et al., 2015b). Each algorithm usually has its own internal method of guiding its search for the optimal set of biclusters. Some are

based on using a heuristic search guided by evaluation measures i.e. metric-based, of which MSR is the most commonly used, while others are non-metric based (Pontes et al., 2015a). Given that our goal is to improve the outcome of these algorithms using evaluation measures, we evaluate algorithms that belong to both categories and analyze the effect of our proposed method.

To ensure an unbiased systematic evaluation of these methods, we selected algorithms that had freely available implementations and have been readily cited/used among the biclustering community. Two of the methods described in this work were an extension/improvement of a prior method reviewed among the 30 biclustering algorithms in (Pontes et al., 2015a). In this work, we focused on the most recent improved method (as in the case of UniBic and BicPAMS described below). Table 1 presents an overview of the 8 algorithms empirically evaluated and analyzed in this work including the implementation source. They include both metric-based and non-metric based approaches and span two decades. To provide a context for the comparative analysis presented in this paper, we briefly describe each biclustering algorithm in a chronological order.

2.2 Review of Biclustering Algorithms

Cheng and Church (CC)

The Cheng and Church algorithm (Cheng and Church, 2000) was the first application of biclustering to finding local similarity patterns in gene expression data. CC is a deterministic greedy algorithm that finds biclusters by minimizing the Mean Squared Residue (MSR) score of a discovered submatrix. MSR is an evaluation measure that is a measure of bicluster homogeneity, as defined in the next section. As a heuristic-based method, it outputs a desired number of biclusters k based on user defined parameters k and δ, which is the maximum acceptable MSR score.

Iterative Signature Algorithm (ISA)

The iterative signature algorithm (Bergmann et al., 2003) is a non-deterministic method that discovers biclusters even in the presence of noise and overlapping biclusters. It defines the biclusters as transcription modules (TM): a set of co-regulated genes (rows) with relevant experimental conditions (columns). Starting from a set of randomly selected genes (or conditions), it iteratively refines the genes and conditions until they match the definition of TM. In the context of this work, we evaluate ISA as a non-heuristic based method (Pontes et al., 2015a) though in some others reviews (Prelić et al., 2006; Eren et al., 2012), it has been evaluated as a heuristic based method due to its iterative greedy search approach.

Order-Preserving Submatrices Algorithm (OPSM)

The Order-Preserving Submatrices Algorithm (Ben-Dor et al., 2003) is a deterministic method for finding biclusters that are defined as order-preserving submatrices i.e. a set of rows and columns in the data matrix in which all the values in the rows for the given set of columns are strictly increasing (or similarly ordered in the relaxed case). Using a probabilistic model describing biclusters hidden in otherwise random matrices and statistical strategies, OPSM algorithm can efficiently find multiple, potentially overlapping biclusters.

FLexible Overlapped biClustering (FLOC)

The Flexible Overlapped Biclustering algorithm (Yang et al., 2005) is a stochastic iterative based method for finding biclusters, particularly overlapping ones using a probabilistic model. It is an evaluation-based approach that assesses the quality of the biclusters using the mean residue function, similar to the CC algorithm. It consists of two steps. In the first step, crude initial biclusters are constructed on a probabilistic basis. The second step centers around iteratively refining these biclusters. This process involves greedily removing rows or columns from the bicluster in an effort to reduce the mean squared residue score of the bicluster.

Factor Analysis for Bicluster Acquisition (FABIA)

The Factor Analysis for Bicluster Acquisition method (Hochreiter et al., 2010) is a generative multiplicative model for discovering biclusters in expression data by assuming a non-Gaussian signal distributions with heavy tails. (This method was not included in the review presented in (Pontes et al., 2015a).) In FABIA, a bicluster is modeled as an outer product of two sparse vectors. It is a fuzzy like clustering method that returns probability of memberships. However, it can be set to return crisp biclusters by setting user-defined threshold parameters.

Table 1: Biclustering Algorithm Summary.

Algorithm (Year)	Algorithm Type	Deterministic / Metric based	Implementation Source
CC (2000)	Greedy Search	Yes / Yes (MSR)	Python (Eren, 2013)
ISA (2003)	Linear Algebra	Yes / No	R package `isa2` (Csárdi et al., 2010)
OPSM (2003)	Optimal Reordering	Yes / No	BicAT (Barkow et al., 2006)
FLOC (2005)	Stochastic Greedy Search	No / Yes (MSR)	R Package `BicARE` (Gestraud, 2008)
FABIA (2010)	Generative Biclustering	No / No	Bioconductor `fabia` (Hochreiter et al., 2010)
PPM[3] (2015)	Probabilistic	No / No	Java (Chekouo and Murua, 2015)
UniBic[2] (2016)	Graph-Based	No / No	C (Wang et al., 2016)[4]
BicPAMS[1] (2017)	Pattern-based	No / No	bicpams.com (Henriques et al., 2017)

[1] Most recent pattern mining approach. [2]Improvement on the QUBIC algorithm. [3]Extension of Bayesian Biclustering Model. [4]sourceforge.net/projects/unibic/

Penalized Plaid Model (PPM)

The Penalized Plaid Model biclustering technique (Chekouo and Murua, 2015) models biclusters using a Bayesian framework. It is a modified extended version of the Bayesian plaid model. The PPM method fully accounts for a general overlapping structure, which differs from other models that account for only one dimensional overlapping such as in the Bayesian Biclustering Model (Gu and Liu, 2008). Instead of using the sequential algorithm defined in (Zhang, 2010), the parameters in the Penalized Plaid model are found all at once by a dedicated Markov chain Monte Carlo sampler. It is a non-heuristic based approach.

UniBic

UniBic is an extension/improvement of the graph-based biclustering method: QUBIC (Li et al., 2009). In this work, we evaluate UniBic, which was not reviewed in (Pontes et al., 2015a) since it's an improved algorithm of QUBIC that was included in (Pontes et al., 2015a). In QUBIC, the input data matrix is initially transformed to a discrete integer rank matrix prior to subsequent operations. A graph G is constructed based on this matrix in which nodes represent the rows (genes) and the edge weights are number of corresponding conditions (columns) between two genes (rows). The biclustering problem is translated to finding heavy subgraphs in G.

UniBic (Wang et al., 2016) is very similar to QUBIC with the exception of edge weight calculation. UniBic applies the longest common subsequence (LCS) algorithm to translate the input data matrix to a rank matrix in which the rows are discretized as rank vectors. The n^{th} smallest value in each row is replaced with the integer n, with priority in ties given to the leftmost value. Edge weight in the graph is calculated as the magnitude of the maximal LCS between nodes. UniBic demonstrates a strong resilience to noise and can detect biclusters of both shifting and scaling patterns.

Biclustering based on PAttern Mining Software (BicPAMS)

BicPAMS (Henriques et al., 2017) is an aggregate of state-of-the-art pattern mining approaches to the biclustering problem. BicPAMS is the most recent pattern mining algorithms, an improved version of prior pattern mining biclustering algorithms since the initial publication of BicPAM (Henriques and Madeira, 2014a). Other prior versions of pattern-mining biclustering algorithms that it extends include BicSPAM (Henriques and Madeira, 2014b) (reviewed in (Pontes et al., 2015a)), BiP (Henriques and Madeira, 2015), and BicNET (Henriques and Madeira, 2016). BicPAMS is a highly parametrized algorithm including parameters relating to coherence of biclusters, structure of biclusters, quality of biclusters, and efficiency of the program. BicPAMS was not reviewed in (Pontes et al., 2015a). It is a non-heuristic based algorithm.

3 METHODS

3.1 Evaluation Framework

To effectively evaluate the biclustering algorithms, we utilize the benchmark synthetic data introduced in (Wang et al., 2016) and generated with the BiBench framework (Eren et al., 2012). The advantage of utilizing synthetic data in evaluation of algorithm performance is that there is readily available ground-truth. However, there is always the concern of whether the synthetic data generation captures the complexity of real applications. The benchmark data consist of 6 groups of square bicluster

structures (trend-preserving, column-constant, row-constant, shift-scale (combined), shift, scale) as well as 3 overlapping datasets and 3 narrow datasets: a total of 119 datasets. Square biclusters have the same number of genes and conditions in each bicluster while overlapping biclusters are biclusters that share one or more genes or conditions. Narrow biclusters contain many more genes than conditions. A comprehensive description of these bicluster types is presented in (Mukhopadhyay et al., 2010).

Given a bicluster $\mathcal{B}$, let I denote a set of row vectors in $\mathcal{B}$ and J, the corresponding set of column vectors. Then, the element in the i^{th} and j^{th} column of $\mathcal{B}$ is denoted by $\mathcal{B}_{ij}$. We index specific gene vectors or condition vectors using capital letters. For example, the gene corresponding to the i^{th} row of $\mathcal{B}$ across all conditions is denoted $\mathcal{B}_{iJ}$, while the condition corresponding to the j^{th} column of $\mathcal{B}$ across all genes is denoted $\mathcal{B}_{Ij}$.

To evaluate the performance of the algorithms, we utilize the recovery and relevance scores, derived from match score (Prelić et al., 2006). Match Score (MS) between two sets of biclusters $\mathcal{S}_1$ and $\mathcal{S}_2$ is defined as:

$$MS(\mathcal{S}_1,\mathcal{S}_2) = \frac{1}{|\mathcal{S}_1|}\sum_{\mathcal{B}_1\in\mathcal{S}_1}\max_{\mathcal{B}_2\in\mathcal{S}_2}\frac{|\mathcal{B}_1\cap\mathcal{B}_2|}{|\mathcal{B}_1\cup\mathcal{B}_2|} \quad (1)$$

which reflects the average of the maximum similarity for all biclusters B_1 in S_1 with respect to the biclusters B_2 in S_2. The intersection of two biclusters $\mathcal{B}_1 \in \mathcal{S}_1$ and $\mathcal{B}_2 \in \mathcal{S}_2$ denotes the set of rows common to both $\mathcal{B}_1$ and $\mathcal{B}_2$. Similarly, the union of two biclusters is the set of rows that exist in either $\mathcal{B}_1$ or $\mathcal{B}_2$ or both. The match score takes on values between 0 and 1, inclusive. In the case that no rows of any bicluster in $\mathcal{S}_1$ are found in any bicluster in $\mathcal{S}_2$, $|\mathcal{B}_1 \cap \mathcal{B}_2| = 0$ for all possible $\mathcal{B}_1 \in \mathcal{S}_1$, $\mathcal{B}_2 \in \mathcal{S}_2$. Subsequently, MS = 0 (equation (1). Similarly, if the sets of biclusters $\mathcal{S}_1$ and $\mathcal{S}_2$ are identical, then both $|\mathcal{B}_1 \cap \mathcal{B}_2| = |\mathcal{S}_1|$ and $|\mathcal{B}_1 \cup \mathcal{B}_2| = |\mathcal{S}_1|$, yielding a match score of one. The match score is also referred to as similarity score (Wang et al., 2016).

For a given dataset D, let $S(A_i)$ denote the set of biclusters returned by applying a specific biclustering algorithm A_i on D, while G denotes the corresponding set of known ground truth biclusters for D. The **relevance score**, $MS(S,G)$, is a measure of the extent to which the generated biclusters $S(A_i)$ are similar to the ground truth biclusters in the gene (row) dimension. The **recovery score**, given by $MS(G,S)$, quantifies the proportion of the subset of G that were retrieved by A_i. A high relevance score implies that a large percentage of the biclusters discovered by the algorithm are significant, while a high recovery score indicates that a large percentage of the actual ground truth biclusters are very similar to the ones returned by the algorithm.

3.2 Internal Validation Measures

Relevance and recovery scores are both external validation measures, as the computation is dependent on prior knowledge of ground truth data. Internal validation measures provide a means of evaluating quality of biclusters obtained without the knowledge of ground truth; which is very useful for real datasets for which ground truth is unknown. In this section, We formally describe the two evaluation measures that are used in our performance enhancement method: ASR and VE^T. We also discuss two other common internal validation measures that we utilize for comparison analysis: MSR and SMSR.

Average Spearman's Rho. The Average Spearman's Rho (ASR) (Ayadi et al., 2009) measure is an adaptation of the Spearman's Rho (Lehmann and D'abrera, 1975) correlation coefficient to assess bicluster quality. Spearman's Rho is defined as

$$\rho(x,y) = 1 - \frac{6}{m(m^2-1)}\sum_{k=1}^{m}\left(r(x_k) - r(y_k)\right)^2 \quad (2)$$

for two vectors x and y of equal length m, where $r(x_k)$ and $r(y_k)$ are the ranks of x_k and y_k, respectively. Let

$$\rho_{gene} = \frac{\sum_{i\in I}\sum_{j\in I, j>i}\rho(i,j)}{|I|\cdot(|I|-1)} \quad (3)$$

$$\rho_{condition} = \frac{\sum_{i\in J}\sum_{j\in J, j>i}\rho(i,j)}{|J|\cdot(|J|-1)} \quad (4)$$

ASR is defined as

$$ASR(\mathcal{B}) = 2\cdot\max\{\rho_{gene},\rho_{condition}\} \quad (5)$$

The ASR's value is in the range $[-1,1]$, where both -1 and 1 represent a perfect trend-preserving bicluster. ASR is one of the few bicluster quality measures that can detect both shifting and scaling patterns of biclusters, as well as shift-scale (combined pattern) biclusters (Pontes et al., 2015b).

Transposed Virtual Error. Transposed Virtual Error (VE^T) (Pontes et al., 2010) is another bicluster quality measure that correctly identifies shift, scale, and shift-scale biclusters. Transposed Virtual Error is an improvement on Virtual Error (VE) (Pontes et al., 2007), which does not identify shift-scale biclusters.

Both VE and VE^T required standardized biclusters. A bicluster is standardized by subtracting the row mean from each element of the bicluster and dividing by the row standard deviation, i.e.

$$\hat{\mathcal{B}} = \frac{\mathcal{B}_{ij} - \mu_{iJ}}{\sigma_{iJ}}, \quad i = 1,2,...,|I|, \quad j = 1,2,...,|J| \quad (6)$$

where μ_{iJ} is the mean of row i in $\mathcal{B}$ and σ_{iJ} is the standard deviation of row i in $\mathcal{B}$.

VE computes a virtual gene ρ, which is a vector imitating a gene whose entries are column means across all genes in the bicluster. Explicitly, the standardized virtual gene is calculated for a standardized bicluster $\hat{\mathcal{B}}$ as

$$\hat{\rho_j} = \frac{1}{|I|}\sum_{i=1}^{|I|}\hat{\mathcal{B}}_{ij}, \quad j = 1,2,...,|J| \quad (7)$$

Finally, VE is defined as

$$VE(\mathcal{B}) = \frac{1}{|I|\cdot|J|}\sum_{i=1}^{|I|}\sum_{j=1}^{|J|}|\hat{\mathcal{B}}_{ij} - \hat{\rho_j}| \quad (8)$$

To compute VE^T, transpose the bicluster prior to calculating VE. VE^T computes a virtual condition ρ and measures the deviation of conditions in the bicluster from ρ. The virtual condition ρ is calculated as

$$\hat{\rho_i} = \frac{1}{|J|}\sum_{j=1}^{|J|}\hat{\mathcal{B}}_{ij}, \quad j = 1,2,...,|J| \quad (9)$$

and VE^T is calculated as

$$VE^{\text{T}}(\mathcal{B}) = \frac{1}{|I|\cdot|J|}\sum_{i=1}^{|I|}\sum_{j=1}^{|J|}|\hat{\mathcal{B}}_{ij} - \hat{\rho_i}| \quad (10)$$

VE^T is equal to zero for perfect shifting or scaling or shift-scale patterns.

Special Cases for VE^T. Constant rows in expression data pose an issue when computing VE^T. When one or more rows are constant, the standard deviation of at least one row is zero, and thus the result of equation (3.2) is undefined.A constant row is highly unlikely in real data applications, so a standard deviation of zero should be a non-issue. For the context of this work with synthetic data, VE^T is set to one if any zero-division errors occurred. This does produce false negatives in the case that a constant row is part of a constant bicluster.

Mean Squared Residue. The mean squared residue score (MSR) describes how well a bicluster follows a shifting pattern (Cheng and Church, 2000). MSR is defined as

$$MSR(\mathcal{B}) = \frac{1}{|I|\cdot|J|}\sum_{i=1}^{|I|}\sum_{j=1}^{|J|}(b_{ij} - b_{iJ} - b_{Ij} + b_{IJ})^2 \quad (11)$$

where the bicluster $\mathcal{B}$ consists of rows I and columns J. Values b_{iJ} and b_{Ij} denote the mean of the i^{th} row and j^{th} column, respectively, and b_{IJ} denotes the mean of all entries of the bicluster.

By design, biclusters that follow a perfect shifting pattern have an MSR score of zero. Larger MSR scores represent more deviation from a perfect shifting pattern.

Scaling Mean Squared Residue. The Scaling Mean Squared Residue (SMSR) is an evaluation measure for biclusters that detects scaling patterns in biclusters (Mukhopadhyay et al., 2009). SMSR is very similar to MSR except that it is suited for biclusters with scaling patterns while MSR is suited for shifting patterns. SMSR is defined as

$$SMSR(\mathcal{B}) = \frac{1}{|I|\cdot|J|}\sum_{i=1}^{|I|}\sum_{j=1}^{|J|}\frac{(b_{iJ}\cdot b_{Ij} - b_{ij}\cdot b_{IJ})^2}{b_{iJ}^2\cdot b_{Ij}^2} \quad (12)$$

The SMSR score of a bicluster with a perfect scaling pattern is zero. Neither MSR nor SMSR perform well on shift-scale biclusters.

3.3 Enhancement Framework

Gene expression data matrices are usually very large. It is not uncommon for these matrices to have tens of thousands of rows (genes) and hundreds of columns (samples). It is generally unknown how many biclusters will be returned by a biclustering algorithm on a given dataset. Some biclustering algorithms usually output a very large set of biclusters (based on algorithm specific stop criterion) while some include a user specified parameter to define the number of biclusters to generate. A large portion of recent biclustering algorithms use stochastic approaches, and hence are not deterministic. This means that multiple repetitions of the same experiment with such algorithms do not necessarily yield identical results. Properties of algorithms analyzed in this paper, such as determinism vs. non-determinism, are described in Table 1. It is desirable for the discovered set of biclusters to be a manageable number of highly relevant since the discovered biclusters require significant human effort for further evaluation to determine biological significance.

In this section, we present a method of improving the relevance score of any set of biclusters by using either of these two internal validation measures: Average Spearman's Rho and Transposed Virtual Error. This can be applied to both types of algorithms i.e. the ones that have a defined stop criterion as well as the ones that require a user-specified parameter of number of biclusters to generate. The strength of the proposed framework is that it serves a "filter" to help detect highly relevant bicluster among a large set

of output biclusters. The framework can be applied using any desired internal validation metric, though from the results obtained, we recommend using the best performing ones (VE^T and ASR). The next step is to determine an ensemble method for leveraging the usefulness of both metrics.

The method of improving the relevance of a set of biclusters $\mathcal{S}$ is described as follows:

1. Choose an internal validation measure M and a number of desired biclusters n, where $n < |S|$.
2. Compute $M(\mathcal{B})$ for each bicluster $\mathcal{B} \in \mathcal{S}$.
3. Order each bicluster in $\mathcal{B} \in \mathcal{S}$ from best to worst according to $M(\mathcal{B})$.
4. Retain the best n biclusters according to M.

It is important to note that while relevance scores are improved with our method, recovery scores are negatively impacted. By reducing the number $|S|$, the initial size of the output biclusters, the recovery score will be less than or equal to that of the initial list. Thus, our goal is to maximize the increase in relevance scores while minimizing the decrease in recovery scores. Ideally, we desire to filter out biclusters with redundant or insignificant information.

4 EXPERIMENTAL RESULTS AND ANALYSIS

4.1 Experimental Setup

The eight biclustering algorithms analyzed in this work were set to their default parameters and conducted using existing implementations (Table 1). To ensure that the experiments presented in this work are replicable, the source code is publicly available via GitHub[1] along with detailed instructions on the specifications of implementations. For algorithms (CC, FLOC, and PPM)that required user-specified parameter k on the number of biclusters to generate, we set $k = 20$. In addition, CC was set to return biclusters with a maximum MSR score of 0.1. For OPSM, the number of passed models between iterations used was 10. PPM was implemented using the recommended parameters of the GPE method (Chekouo and Murua, 2015).

In the computation of ASR, we have to compute Spearman's Rho according to equation (2). This requires us calculate the rank of each element in both vectors x and y. When there are ties in the elements of x or y, ranking becomes problematic and subsequently results in Spearman's Rho not being defined. There are different tie correction methods available to alleviate this problem (Zar, 1998). The method of tie correction implemented in this work was to assign all tied values to the minimum rank.

The experimental results presented are two-fold. In section 4.2, we present the results of the comparative analysis of the eight algorithms using relevance and recovery scores on the 119 benchmark datasets while section 4.3 focuses on empirical evaluation of the proposed enhancement framework. For the performance enhancement evaluation, the desired number of biclusters n is set to $3g$, where g is the actual number of biclusters present in the dataset (based on the ground truth information). Thus, the evaluation results presented demonstrate the impact on both relevance and recovery scores with a very minimal number of clusters selected - $3g$. In actual practice, n can be set to the number that the user is comfortable using for further biological evaluation.

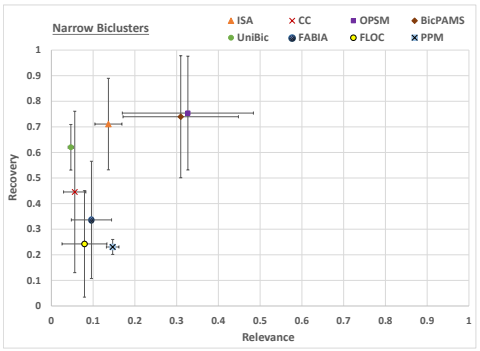
4.2 Performance Evaluation Results

Figure 1 illustrates the results of the performance of the eight algorithms in terms of relevancy and recovery scores for eight types of biclusters datasets: 6 types of square biclusters (trend-preserving, column-constant, row-constant, shift-scale (combined), shift, scale) with each type having 15 associated datasets, as well as a set of 20 overlapping datasets and a set of 9 narrow datasets.

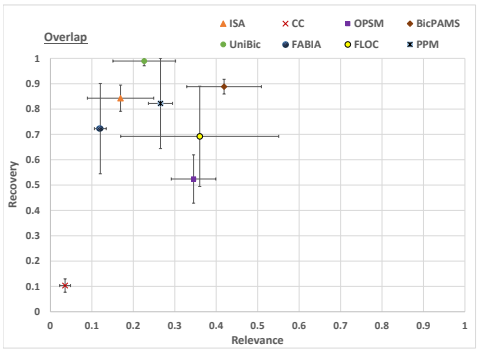
As can be observed from Figure 1a, OPSM is the best performing algorithm on narrow biclusters in terms of both relevance and recovery scores. This is useful for practical gene expression datasets where the number of conditions is much less than the number of genes. For the datasets with overlapping biclusters (Figure 1b), BicPAMS performed the best in terms of relevance, and UniBic performed best in terms of recovery. For all the datasets, except for narrow, UniBic had very high recovery scores.

Table 2 illustrates the average rank of each algorithm across all 119 synthetic datasets. The ranking results for the performance evaluation results is contained in the first 4 columns after the algorithm name column (i.e. before enhancement). The average rank is calculated by ranking each algorithm's performance on each dataset, with 1 being the best performer and 8 (in this case) being the worst. We rank the performance using relevance and recovery scores, ASR, and VE^T. The average rank of an algorithm is simply the sum of its ranks for each dataset divided by the number of datasets. The statistical sig-

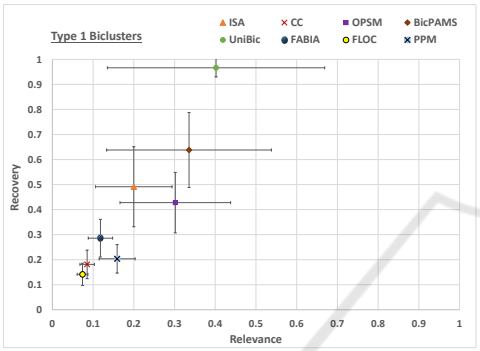
[1] github.com/clslabMSU/Biclustering-Algorithm-Comparison



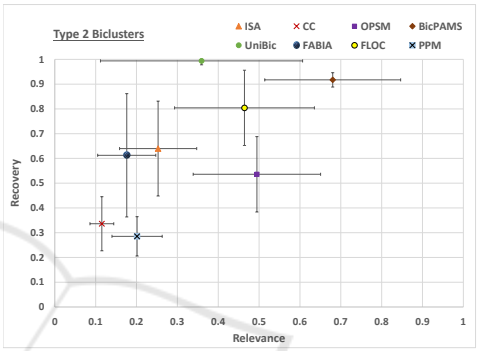
(a) Narrow Biclusters



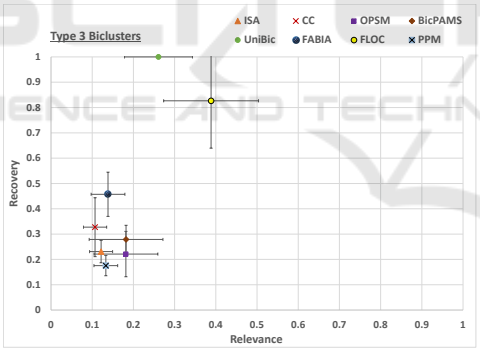
(b) Overlapping Biclusters



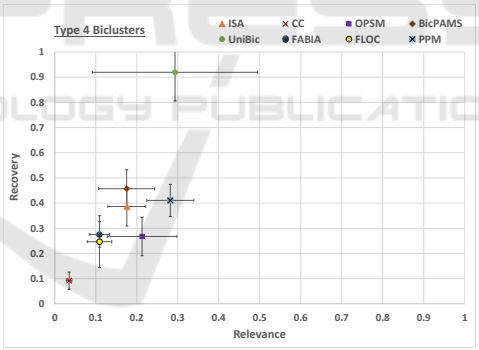
(c) Square Type 1 (trend-preserving) Biclusters



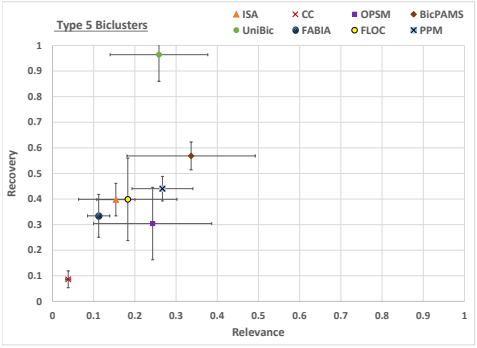
(d) Square Type 2 (column-constant) Biclusters



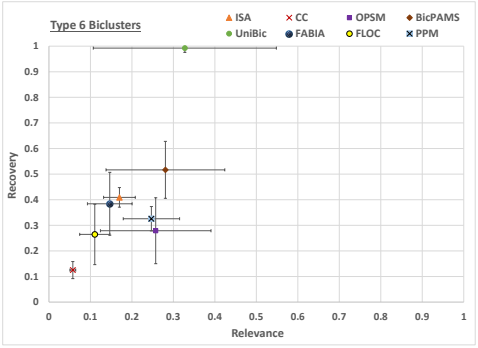
(e) Square Type 3 (row-constant) Biclusters



(f) Square Type 4 (shift-scale) Biclusters



(g) Square Type 5 (shift) Biclusters



(h) Square Type 6 (scale) Biclusters

Figure 1: Comparisons of recovery and relevance scores across biclustering algorithms on different types of bicluster datasets.

nificance of these ranks is measured using Friedman test statistic. The critical value of a chi-square distribution with 7 degrees of freedom is 14.067, so Friedman statistics higher than 14.067 are considered statistically significant. The p-values associated with the Friedman statistics were all significant: < 0.001.

From Table 2, one can observe that BicPAMS had the best average rank in terms of relevance score before performance enhancement, and UniBic had the best average rank in recovery score by a very large margin. Similarly, OPSM had the best average rank according to the ASR value (internal validation measure) in every dataset, hence an average rank of 1.0. OPSM also had the best average rank according to VE^T, closely followed by FLOC.

4.3 Performance Enhancement Results

UniBic and BicPAMS both tended to have high recovery scores but low relevance scores according to the experimental results in section 4.2. They also returned a very large number of clusters as indicated in Table 3 which probably helped their recovery scores but degraded the performance in terms of relevance. Figure 2 demonstrates the effect of the performance enhancement (PE) framework on the performance of the algorithms in terms of relevancy and recovery scores. For each algorithm, the top n biclusters selected is set to three times the actual number of ground truth present in the dataset. The algorithms that benefit the most from the PE method are those that return a very large number of biclusters, such as BicPAMS and UniBic. When these algorithms are applied to real gene expression datasets, the number of returned biclusters is usually too large to manually examine. By applying the PE method, results of these algorithms are much more manageable, and each bicluster examined is more likely to contain biologically significant information. According to Table 3, PPM algorithm is the only algorithm that actually returns less than this parameter initially i.e. before enhancement. Given that the returned number of biclusters is less, some loss in recovery is inevitable however, it is interesting to observe the effect on the relevance of the results.

Table 3 also demonstrates that, overall, applying the PE framework using the ASR or VE_T measure yields a more significant positive impact on the relevance scores compared to MSR or SMSR measures. We can observe from Figure 2 that relevance scores were improved for six of the eight tested algorithms, with the most dramatic improvement being on the UniBic algorithm and the ASR quality measure. In this case, the relevance of the UniBic biclusters were increased by well over 50%. Naturally, removing biclusters from a set will have a negative impact on the recovery score of that set. The ASR validation measure showed the largest increase in relevance scores among every algorithm except OPSM and FABIA, thus indicating most superior performance compared to VE^T, SMSR and MSR. Table 4 summarizes the effect of the enhancement framework, based only on the ASR measure according to the eight different types of dataset tested.

The last two sets of four columns of Table 2 present the average ranking results of each algorithm after applying the PE framework using the ASR and VE^T validation measures, respectively across all datasets. For both evaluation measures, we observe that the best performing algorithms are largely the same as before we performed our enhancement. However, the average ranks have shifted slightly. Filtering on the ASR measure has further set BicPAMS apart from the competition in terms of relevance, lowering its rank from 2.18 before enhancement to 1.62 after ASR filtering. UniBic still performs best in terms of recovery, but by a smaller margin. Filtering by VE^T has produced less compelling results. The average ranks for recovery are much closer together than the ranks before enhancement and the ranks using ASR filtering, which implies that the ranks of each algorithm across all datasets were inconsistent. This is reflected in the lower Friedman statistics of VE^T filtering compared to the Friedman statistics before enhancement and with ASR filtering.

For the evaluation (metric)-based methods, CC and FLOC, which are based on MSR, applying ASR to select the top n biclusters still improves the relevance scores, even though the original mean number of clusters returned by these algorithm is 20 which is close to the mean top n that we select $[12, 20]$. According to Table 3, though recovery scores were hurt, the algorithm with the highest recovery score was unchanged after our enhancement, implying that the percentage loss was almost uniform across best performing algorithms. The PE framework results demonstrate that the ASR quality measure tended to lead to a larger increase in relevance scores, while maintaining a relatively low loss in recovery scores. At this point, it becomes a trade-off between obtaining a manageable number of biclusters and losing accuracy. On larger datasets for real data applications, it quickly becomes difficult to inspect the biological significance of a large number of biclusters. Thus, the proposed PE framework would be useful for gene expression data analysis, in determining significance and relevance of the results.

Table 2: Statistical comparison of average ranking of algorithm performance using Friedman test before and after enhancement method.

Algorithm	Before Enhancement				Filtering on ASR				Filtering on VE^T			
	Rel.	**Rec.**	**ASR**	**VE^T**	**Rel.**	**Rec.**	**ASR**	**VE^T**	**Rel.**	**Rec.**	**ASR**	**VE^T**
BicPAMS	**2.18**	2.75	3.39	3.75	**1.62**	3.62	1.92	2.12	**1.67**	3.91	2.14	**1.62**
CC	7.67	7.06	4.43	3.25	7.47	6.86	5.46	3.88	7.55	7.03	5.38	5.25
FABIA	6.10	4.87	7.42	8.00	6.60	5.84	7.48	7.12	6.56	5.69	7.50	8.00
FLOC	4.66	5.12	3.47	1.62	4.28	4.58	4.37	**1.25**	4.60	4.58	4.09	2.88
ISA	5.04	4.07	6.35	6.62	4.42	3.99	5.26	4.75	4.22	3.39	5.61	5.62
OPSM	2.77	5.42	**1.00**	**1.38**	3.73	4.55	**1.22**	3.50	3.46	4.16	**1.03**	3.88
PPM	4.09	5.39	5.52	6.00	4.86	4.49	6.46	6.12	4.49	4.22	6.40	7.00
UniBic	3.49	**1.32**	4.41	5.38	3.03	**2.07**	3.83	7.25	3.45	**3.02**	3.85	1.75
Friedman[1]	276	290	265	335	289	260	313	390	192	163 *	280	425

Rec.: Recovery Score; Rel.: Relevance Score; [1] P-values for all Friedman tests < 0.001 with the exception of: * P-value = 0.004.

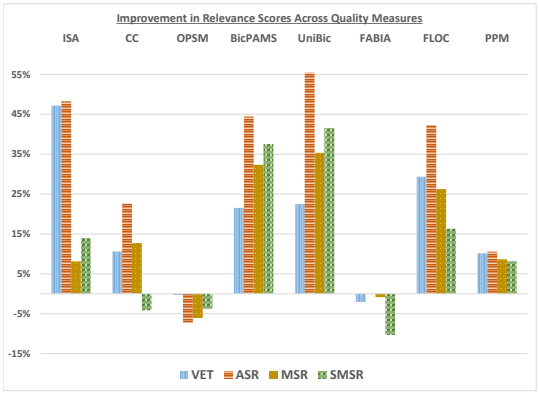
Table 3: Mean number of biclusters returned by algorithm.

Biclusters	Range of g[1]	PE Exp.[2] $n = 3g$	Mean No. of biclusters returned by each algorithm. BicPAMS	FABIA	ISA	OPSM	PPM	UniBic	CC	FLOC
Narrow	3	9	320	12	65	11	10	92	20	20
overlap	3	9	557	20	26	14	10	53	20	20
Type 1	[3 5]	12	243	20	48	10	10	42	20	20
Type 2	[3 5]	12	746	20	37	10	10	47	20	20
Type 3	[3 5]	12	712	19	46	9	10	61	20	20
Type 4	[3 5]	12	768	19	53	9	10	40	20	20
Type 5	[3 5]	12	353	20	35	10	10	56	20	20
Type 6	[3 5]	12	374	19	53	10	10	43	20	20

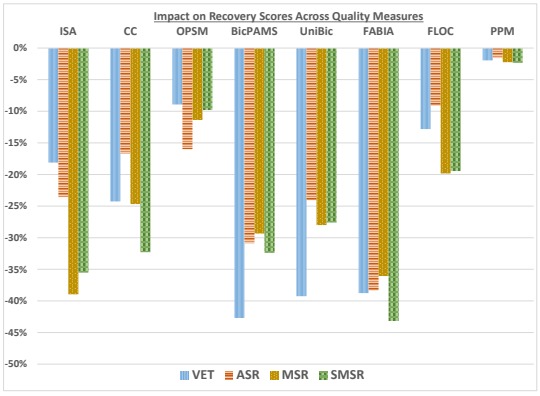
[1] g: Mean number of biclusters in ground truth data; [2] PE Exp: Performance Enhancement Experiment.

Table 4: Best performing algorithm before and after enhancement (by ASR).

Type of dataset	Best relevance before	Best recovery before	Best relevance after	Best recovery after
Narrow Bicluster	OPSM	OPSM	BicPAMS	OPSM
Overlap Bicluster	BicPAMS	UniBic	FLOC	UniBic
Type 1 Biclusters	UniBic	UniBic	BicPAMS	UniBic
Type 2 Biclusters	BicPAMS	UniBic	FLOC	UniBic
Type 3 Biclusters	FLOC	UniBic	FLOC	UniBic
Type 4 Biclusters	UniBic	UniBic	BicPAMS	UniBic
Type 5 Biclusters	BicPAMS	UniBic	BicPAMS	UniBic
Type 6 Biclusters	UniBic	UniBic	BicPAMS	UniBic



(a) Improvement in Relevance Scores.



(b) Improvement in Recovery Scores.

Figure 2: Effect of applying evaluation measures to enhance performance of the biclustering algorithms.

5 CONCLUSION

In this paper, we presented a systematic comparison of eight popular biclustering algorithms, and objectively evaluated their performance using Recovery and Relevance scores on 119 synthetic datasets. We also ranked these eight algorithms using the average rank across each dataset, and verified the statistical significance of these ranks using the Friedman statistic. Across the synthetic datasets used in our experiment, we determined that UniBic was the best performing algorithm in terms of recovery score and BicPAMS was the best in terms of relevance, both before and after the enhancement framework. The datasets were highly skewed towards square biclusters. It should be noted that for the narrow datasets, which constituted a small fraction, OPSM had the best relevance and recovery scores prior to the PE framework. After the PE method, BicPAMS had the best relevance performance. Thus, applying the PE framework enabled BicPAMS to obtain a better performance. It should also be noted that the biclusters hidden in these synthetic datasets are all sequential, that is, all genes and conditions in each bicluster appear consecutively. Future analysis would include performance evaluation on non-sequential biclusters. We evaluated the performance of our proposed enhancement framework of improving relevance scores (and significance of) biclustering results using internal validation measures. This new method of improvement offers an option to improve the relevance of biclustering results at the cost of recovery, a choice that we believe will be valuable in the analysis of biological significance of biclusters found in real gene expression datasets.

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