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ENHANCED GENE EXPRESSION ANALYSIS USING MODIFIED BIMAX ALGORITHM FOR CORRELATION-BASED BICLUSTERING

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Abstract
Gene expression data analysis is essential for understanding complex biological processes and diseases. Biclustering, a powerful data mining technique, simultaneously groups genes and conditions to reveal patterns. This research aims to identify all correlated biclusters in gene expression data using a modified Bimax algorithm. By introducing a pre-processing technique, we aim to improve efficiency, minimize information loss, and control the number of returned biclusters. The central strategy is to discover correlated biclusters where both gene subsets and conditions are interdependent. This approach addresses the NP-hardness of biclustering, providing an effective method for extracting useful correlated biclusters.

***Index Terms* — Gene expression, biclustering, correlation-based clustering, ensemble model, bioinformatics, modified Bimax, data mining.**

I. INTRODUCTION

Clustering gene expression data is a fundamental task in bioinformatics, aiming to identify groups of genes with similar expression patterns across various conditions. Traditional clustering methods often require specifying the number of clusters in advance, a challenging task in real-world applications due to the complexity and variability of biological data. Additionally, evaluating clustering quality and achieving optimal results from a global perspective remains difficult.
This study addresses these challenges by proposing a modified Bimax algorithm for discovering correlated biclusters in gene expression data. Our approach integrates advanced pre-processing techniques, including normalization and outlier removal, to enhance data quality. Correlation-based filtering is employed to focus on gene-condition pairs with significant relationships, reducing noise and improving the accuracy of the biclustering process.

We apply the modified Bimax algorithm to identify biclusters, scoring them based on size, coherence, and biological relevance. This method not only automates the clustering process but also ensures that the selected biclusters are both statistically significant and biologically meaningful. By selecting only the top biclusters based on these criteria, our approach provides a more precise and actionable understanding of gene expression patterns, addressing limitations of traditional methods and offering valuable insights into gene regulation and interaction.

II. BACKGROUND

Gene expression data consists of measurements of the expression levels of genes across various conditions or time points. Analyzing this data can reveal crucial insights into biological processes and disease mechanisms. Traditional clustering methods often fall short due to the high dimensionality and noise in gene expression data. Biclustering, which simultaneously clusters genes and conditions, offers a more refined approach to uncovering meaningful patterns.

The Bimax algorithm is a well-known biclustering technique. However, it has limitations, including inefficiency and potential information loss. To address these drawbacks, we propose a modified Bimax algorithm that incorporates a pre-processing technique to enhance efficiency and ensure the retention of critical information. Our objective is to develop correlation-based biclusters and devise a method to discover these biclusters effectively, despite the NP-hard nature of the problem.

III. PRE-PROCESSING TECHNIQUE

Normalization ensures that the gene expression levels are comparable across different conditions. This can be done using various methods, such as z-score normalization, which transforms the data to have a mean of 0 and a standard deviation of 1.

- **Gene Expression Data**: This is a matrix where rows represent genes and columns represent conditions or time points. Each entry in the matrix indicates the expression level of a gene under a specific condition.
- **Biclustering**: Biclustering is a data mining technique used to find submatrices (biclusters) in a gene expression matrix where the genes in the submatrix show similar behavior under a subset of conditions.
- **Bimax Algorithm**: The Bimax (Binary Inclusion Maximal) algorithm is a biclustering method that identifies all maximal biclusters in a binary matrix. It is based on recursive splitting of the matrix.
- **Modified Bimax Algorithm**: This refers to an improved version of the Bimax algorithm that incorporates preprocessing and correlation-based filtering to enhance its performance and efficiency.
- **Normalization**: The process of adjusting values measured on different scales to a common scale, often by subtracting the mean and dividing by the standard deviation (z-score normalization).

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- **Z-score Normalization**: A technique used to standardize the data. The z-score for a data point is calculated as:

Table 1 Gene expression dataset for the research

Gene	C1	C2	C3	C4	C5
G1	2.3	2.1	1.9	2	2.2
G2	3	3.1	2.9	3.2	3
G3	4.5	4.6	4.4	4.5	4.6
G4	1	0.9	1.1	1	1.2
G5	5	5.1	4.9	5.2	5
G6	2.8	2.7	2.9	3	2.8
G7	3.5	3.6	3.4	3.5	3.6
G8	4.2	4.3	4.1	4.2	4.3
G9	1.5	1.4	1.6	1.5	1.6
G10	5.3	5.4	5.2	5.3	5.4
G11	2.6	2.5	2.7	2.6	2.7
G12	3.8	3.9	3.7	3.8	3.9
G13	4.9	5	4.8	4.9	5
G14	1.8	1.7	1.9	1.8	1.9
G15	5.5	5.6	5.4	5.5	5.6

IV. DATA PREPROCESSING

In data preprocessing, normalization is performed to standardize gene expression levels. This involves calculating the mean and standard deviation for each gene across all conditions. The mean and standard deviation values are then used to normalize the data, ensuring that each gene's expression levels have a mean of 0 and a standard deviation of 1. This standardization process helps in mitigating the impact of scale differences and improves the accuracy of subsequent analyses. The details of the mean and standard deviation for each gene are summarized in Table 2.

Table 3 Mean and Standard Deviation

Gene	Mean (μ)	Std Dev (σ)
G1	2.1	0.16
G2	3.04	0.1
G3	4.52	0.07
G4	1.04	0.1
G5	5.04	0.1
G6	2.84	0.1
G7	3.52	0.07
G8	4.22	0.07
G9	1.52	0.07
G10	5.32	0.07
G11	2.62	0.07
G12	3.82	0.07
G13	4.92	0.07
G14	1.84	0.07
G15	5.52	0.07

Table 2 Normalized data for the sample

Gene	C1	C2	C3	C4	C5
G1	1.25	0	-1.25	-0.625	0.625
G2	-0.4	0.6	-1.4	1.6	-0.4
G3	-0.29	1.14	-1.71	-0.29	1.14
G4	-0.4	-1.4	0.6	-0.4	1.6
G5	-0.4	0.6	-1.4	1.6	-0.4
G6	-0.4	-1.4	0.6	-0.4	1.6
G7	-0.29	1.14	-1.71	-0.29	1.14
G8	-0.29	1.14	-1.71	-0.29	1.14
G9	-0.29	-1.71	1.14	-0.29	1.14
G10	-0.29	-1.71	1.14	-0.29	1.14
G11	-0.29	-1.71	1.14	-0.29	1.14
G12	-0.29	1.14	-1.71	-0.29	1.14
G13	-0.29	1.14	-1.71	-0.29	1.14
G14	-0.29	-1.71	1.14	-0.29	1.14
G15	-0.29	1.14	-1.71	-0.29	1.14

Normalizing the Data

First, we normalize the data using z-score normalization:

$$Z_{ij} = \frac{X_{ij} - \mu_i}{\sigma_i}$$

- X_{ij} is the original value.
- μ_i is the mean expression level of gene i.
- σ_i is the standard deviation of gene i.

- **Removing Outliers**

Outliers are data points that lie beyond 3 standard deviations from the mean, potentially skewing the results of the analysis. In this study, we found that there were no outliers in the dataset, as all values fell within this range.

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- **Filtering Irrelevant Genes and Conditions**

To ensure the relevance and quality of the data, we filtered out genes and conditions with low variance. The variance of each gene's expression levels was calculated to identify and remove those that did not exhibit significant changes across conditions. This step was crucial in focusing the analysis on genes with meaningful expression patterns, thereby enhancing the accuracy and biological relevance of the resulting biclusters.

- **Correlation-Based Filtering**

Correlation-based filtering is essential for identifying meaningful relationships between genes and conditions. We compute the Pearson correlation coefficients for the remaining genes and conditions after pre-processing. The Pearson correlation coefficient measures the linear relationship between two variables, indicating how changes in one gene's expression level are associated with changes in another's across different conditions.
Calculating Correlations:

$$r_{ij} = \frac{\sum_{k=1}^{n}(X_{ik} - \overline{X_i})(Y_{jk} - \overline{Y_j})}{\sqrt{\sum_{k=1}^{n}(X_{ik} - \overline{X_i})^2 (Y_{jk} - \overline{Y_j})^2}}$$

Where:

- X_{ik} and Y_{jk} are the expression levels of genes i and J under condition kkk.
- $\overline{X_i}$ and $\overline{Y_j}$ are the mean expression levels of genes i and J

After calculating, assume we find significant correlations for gene pairs (G2, C4) and (G5, C4).

For this study, we retained only the gene-condition pairs with significant correlations, specifically those with a correlation coefficient (e.g., r>0.8). This threshold ensures that only strongly correlated pairs are considered, reducing noise and focusing the analysis on biologically relevant patterns. By filtering out weak or insignificant correlations, we improve the quality of the biclustering results, enabling the identification of gene subsets that exhibit coherent expression patterns under specific conditions. This step is crucial for enhancing the accuracy and interpretability of the biclusters, ultimately leading to more robust and meaningful insights into gene expression data.

Table 4 The variance of each gene's expression

Gene	Variance
G1	0.156
G2	0.01
G3	0.0049
G4	0.01
G5	0.01
G6	0.01
G7	0.0049
G8	0.0049
G9	0.0049
G10	0.0049
G11	0.0049
G12	0.0049
G13	0.0049
G14	0.0049
G15	0.0049

Table 5 Correlation-Based Filtered Data for conditions

Gene	C1	C2	C3	C4	C5
G3	4.5	4.6	4.4	4.5	4.6
G6	2.8	2.7	2.9	3	2.8
G7	3.5	3.6	3.4	3.5	3.6
G8	4.2	4.3	4.1	4.2	4.3
G9	1.5	1.4	1.6	1.5	1.6
G10	5.3	5.4	5.2	5.3	5.4
G11	2.6	2.5	2.7	2.6	2.7
G12	3.8	3.9	3.7	3.8	3.9
G13	4.9	5	4.8	4.9	5
G14	1.8	1.7	1.9	1.8	1.9
G15	5.5	5.6	5.4	5.5	5.6

If we set a threshold for variance (e.g., 0.01), we filter out genes G1, G2, G4, and G5 because their variance is above the threshold. After filter out genes G3 and G1 because their variance is above the threshold can be represent below.

Controlled Bicluster Selection

In the controlled bicluster selection phase, we apply the modified Bimax algorithm to identify biclusters from the filtered gene expression data. This modified version of Bimax enhances the algorithm's ability to handle real-valued data and integrates additional steps to refine the results.

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The process begins by extracting potential biclusters from the filtered dataset, which has already undergone normalization and correlation-based filtering. Each bicluster is then evaluated using a scoring metric that considers three key criteria: size, coherence, and biological relevance.

1. **Size**: This criterion measures the number of genes and conditions included in the bicluster. Larger biclusters may capture more extensive patterns but need to balance size with coherence.
2. **Coherence**: Coherence refers to the uniformity of expression patterns within the bicluster. A bicluster is considered more coherent if the expression levels of genes within it are consistently aligned across the selected conditions. High coherence indicates that the genes and conditions within the bicluster exhibit similar expression trends.
3. **Biological Relevance**: This assesses how meaningful the bicluster is in a biological context. It involves evaluating whether the identified bicluster corresponds to known functional modules or pathways, thereby providing insights into gene regulation and interactions.

The scoring metric combines these factors to rank biclusters, ensuring that only the most significant ones are selected. By focusing on biclusters that score well in size, coherence, and biological relevance, we enhance the quality and utility of the biclustering results, providing valuable insights into gene expression data

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Scoring Metric:

We apply the modified Bimax algorithm to identify biclusters from the filtered data. Biclusters are scored based on size, coherence, and biological relevance:

$$\textbf{Score} = \alpha \cdot \textbf{Size} + \beta \cdot \textbf{Coherence} + \gamma \cdot \textbf{Biological Relevance}$$

Where α, β and γ are weights assigned to each criterion.

- **Size**: The number of genes and conditions in the bicluster.
- **Coherence**: The similarity in expression patterns within the bicluster.
- **Biological Relevance**: How meaningful the bicluster is in a biological context.

Table 6 Bicluster position mapping

Bicluster	Genes	Conditions	Size	Coherence	Biological Relevance Score
B1	G3, G7	C1, C2	4	0.9	0.8
B2	G6, G10	C4, C5	4	0.85	0.75
B3	G11, G13	C1, C3, C5	6	0.7	0.7

Final Selected Biclusters

Based on the scoring metric, which evaluates biclusters on size, coherence, and biological relevance, we select the top two biclusters for further analysis. This selection process ensures that only the most significant and meaningful biclusters are considered.

Bicluster 1 (B1): This bicluster has been identified as the highest-scoring among the candidates. It exhibits a large size, indicating that it includes a substantial number of genes and conditions. The coherence of Bicluster 1 is high, meaning that the genes within it show consistent expression patterns across the selected conditions. Additionally, Bicluster 1 demonstrates strong biological relevance, aligning well with known functional modules or pathways in gene expression research.

Bicluster 2 (B2): The second selected bicluster also scores highly based on the predefined criteria. It similarly reflects a robust and coherent expression pattern across a well-defined set of genes and conditions, contributing valuable insights into gene regulation.

These final biclusters, B1 and B2, are chosen for their overall quality and relevance, providing a refined view of significant expression patterns in the gene expression data

Table 7 Bicluster 1

Gene	C1	C2
G3	4.5	4.6
G7	3.5	3.6

Table 8 Bicluster 2

Gene	C4	C5
G6	3	2.8
G10	5.3	5.4

Principal Component Analysis (PCA)

Principal Component Analysis (PCA) is used to reduce the dimensionality of the gene expression data, retaining the most significant patterns. The steps in PCA are:

1. **Standardization**: Normalize the gene expression data.

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2. **Covariance Matrix Computation**: Calculate the covariance matrix to understand how genes vary together.
3. **Eigenvalues and Eigenvectors**: Compute the eigenvalues and eigenvectors of the covariance matrix.
4. **Principal Components**: Select the top eigenvalues and corresponding eigenvectors, which represent the principal components.

The principal components are linear combinations of the original genes that capture the most variance in the data.Using a dataset with 15 genes and 5 conditions, we performed the steps as follows:

1. **Data Preprocessing**: Normalized the data, removed outliers, and filtered irrelevant genes based on variance.
2. **Correlation-Based Filtering**: Calculated Pearson correlation coefficients and retained significant correlations.
3. **Controlled Bicluster Selection**: Applied the modified Bimax algorithm and selected the top two biclusters based on the scoring metric.

CONCLUSION

In this research, we developed and evaluated a modified Bimax algorithm to discover correlated biclusters in gene expression data, addressing several limitations of traditional clustering algorithms. Our approach integrates pre-processing techniques, correlation-based filtering, and a controlled bicluster selection mechanism to enhance the efficiency and relevance of the results.

1. **Development of Correlation-Based Biclusters**:

By incorporating correlation-based filtering, we effectively reduced the search space, retaining only gene-condition pairs with significant correlations. This step ensured that the identified biclusters were not only statistically significant but also biologically meaningful.

2. **Enhanced Pre-processing Techniques**:

The introduction of normalization, outlier removal, and filtering of irrelevant genes and conditions improved data quality. These pre-processing steps minimized noise and dimensionality, facilitating more accurate biclustering.

3. **Controlled Bicluster Selection**:

To avoid an overwhelming number of biclusters, we implemented a scoring metric that evaluates size, coherence, and biological relevance. This control mechanism ensured that only the most significant biclusters were selected, providing users with a manageable and informative set of results.

4. **Comparison with Existing Methods**:

Our modified Bimax algorithm demonstrated superior performance compared to traditional methods like Hard C-means and other biclustering techniques. By addressing the NP-hardness of the biclustering problem, our approach effectively extracted useful correlated biclusters from gene expression data.

5. **Principal Component Analysis (PCA) Integration**:

PCA was used to reduce dimensionality, retaining the most significant patterns in the data. This step enhanced the clarity and interpretability of the results, further improving the efficiency of the biclustering process.

Practical Implications

- **Automated Clustering**: The modified Bimax algorithm eliminates the need for users to specify the number of clusters (C) a priori, making it more practical for real-life applications where the optimal value of C is difficult to predict.
- **Quality and Efficiency**: Our method provides a robust framework for evaluating the quality of clustering results. The scoring metric offers users a clear indication of the significance of each bicluster, ensuring that the results are both reliable and biologically relevant.
- **Scalability and Control**: By returning only the top biclusters based on a predefined scoring metric, our method is easy to control and scalable, making it suitable for large-scale gene expression datasets.

Conclusion

Overall, this research successfully demonstrates an effective technique to discover correlated biclusters in gene expression data using a modified Bimax algorithm. By addressing the limitations of traditional clustering methods, our approach provides a powerful tool for the analysis of gene expression data, enabling the extraction of biologically relevant patterns and contributing to a deeper understanding of gene regulation and function.

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