Enhancing the Efficiency of the Grouping-Scoring-Modeling Framework with Statistical Pre-Scoring Component for Transcriptomic Data Analysis

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Abstract: The advent of high-throughput transcriptomic technologies has generated vast transcriptomic datasets, challenging current analytical methodologies with their sheer volume and complexity. The Grouping-Scoring-Modeling (G-S-M) approach is one of the recent approaches that treat groups of genes (or clusters of genes) by embedding prior biological knowledge with machine learning in order to detect the most significant groups for classification tasks. The G-S-M might need to treat thousand ten thousand of groups (scoring those groups) which might affect the speed and performance of the algorithm. In response, this study introduces the Pre-Scoring G-S-M model, an enhancement of the established Grouping-Scoring-Modeling (G-S-M) framework. This approach incorporates a Pre-Scoring component that leverages the Limma package for its empirical Bayes methods to optimize initial transcriptomic data evaluation through a percentage-based selection of statistically significant gene groups. Aimed at reducing computational demand and streamlining feature selection, the model also addresses data redundancy by eliminating duplicate gene-disease associations. Application to nine human gene expression datasets from the GEO database showed promising results. It demonstrated improvements in computational efficiency and analytical precision while reducing the number of features selected per dataset compared to the traditional G-S-M approach, without compromising accuracy. These initial findings highlight the Pre-Scoring G-S-M model's potential to enhance transcriptomic data analysis, indicating a promising direction for future bioinformatics research.

1 INTRODUCTION

Advancements in high-throughput technologies and cost reductions have greatly expanded transcriptomic data generation, providing valuable insights into biological systems (Wong, 2019). Instead of studying diseases through isolated "omic" lenses, researchers now employ a multi-omics approach for a comprehensive understanding of molecular mechanisms (Subramanian et al., 2020). This integrative strategy is vital for elucidating disease onset and progression (Wekesa & Kimwele, 2023). Yet, the volume and complexity of data pose analytical challenges that are increasingly addressed by machine learning and cloud computing, facilitating the discovery of new biomarkers, improved drug development, and personalized medicine (Oh et al., 2021; Camacho et al., 2018).

Machine learning models, both supervised and unsupervised, can uncover hidden patterns in large datasets, enabling accurate disease prediction, the identification of subgroups for targeted therapies, and better patient profiling (Reel et al., 2021). However, the high dimensionality of omics data necessitates rigorous feature selection techniques to avoid overfitting and data bottlenecks (Li et al., 2022; Bhadra et al., 2022; Xu & Jackson, 2019). By isolating the most relevant features, researchers can more easily interpret results, discover novel

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biomarkers, and refine disease classification (He & Yu, 2010). Approaches range from individual feature selection (IFS) to group-based feature selection (GFS), each with distinct advantages depending on computational resources and the need to capture feature interdependencies (Zheng et al., 2021; Kuzudisli et al., 2023). Strengthening these methods will be crucial for future breakthroughs in multi-omics research and personalized healthcare (Remeseiro & Bolon-Canedo, 2019; Pudjihartono et al., 2022).

To address the challenges of feature selection in omics research, new tools incorporating biological filters have been developed (Pudjihartono et al., 2022). Among these advancements, the Grouping-Scoring-Modeling (G-S-M) framework stands out for its rigorous approach to omics data analysis. The G-S-M technique is a systematic method to integrate biological data into machine learning models, enhancing the understanding of complex biological systems (Yousef et al., 2020). Utilizing databases like DisGeNET (Piñero et al., 2015) and KEGG PATHWAY (Kanehisa & Goto, 2000), G-S-M organizes omics data into biologically meaningful groups and merges this domain knowledge with statistical approaches (Yousef et al., 2024).

G-S-M has been used in many different bioinformatic tools such as PriPath (Yousef et al., 2023), CogNet (Yousef et al., 2021), maTE (Yousef et al., 2019), GediNET (Qumsiyeh et al., 2022), miRcorrNet (Yousef et al., 2021), 3Mint (Unlu Yazici et al., 2023), TextNetTopics (Yousef & Voskergian, 2022), and miRdisNET (Jabeer et al., 2023).

However, a significant challenge within the traditional G-S-M framework and its related tools is the extensive number of groups they generate, which then need to be scored using computationally intensive machine learning models. This process is both time-consuming and inefficient, as not all groups equally contribute to meaningful biological insights. To address this, our research introduces a preprocessing enhancement: the Pre-Scoring component. This new addition efficiently prioritizes biological groups based on their statistical significance before the more resource-intensive scoring phase. By initially ranking and prioritizing gene groups through statistical filtering, the Pre-scoring component facilitates quicker data processing and reduces computational demands. Early results indicate that this adaptation not only streamlines the analytical process but also enhances the precision of feature selection, representing a substantial advancement in bioinformatics.

2 METHODS

2.1 G-S-M Framework Overview

2.1.1 Grouping Component

The "G" component initiates the G-S-M process by organizing features into smaller, distinct groups based on pre-existing biological knowledge. Using a user-provided grouping file, features are categorized according to their associations with specific diseases or biological pathways, sourced from open-source databases. This step ensures the analysis is focused on biologically coherent groups, enhancing the contextual relevance and accuracy of the investigation.

2.1.2 Scoring Component

Following grouping, the "S" component evaluates the groups. Training data is split into 90% training and 10% testing set. A classifier is trained on the training set and used to predict outcomes on the testing set, generating performance metrics. This process is repeated five times, and the average metrics are used to score each group. Groups are then ranked by their scores.

2.1.3 Modeling Component

In the final phase, the Modeling component uses the top-ranked groups from the scoring phase to develop predictive models. Models begin with features from the highest-ranking group, then are incrementally enriched by adding features from the next highest-ranked groups—up to ten cumulative groups. This sequential integration highlights the incremental value each group offers. A consistent machine learning algorithm (e.g., Decision Tree, Support Vector Machine, or Random Forest) ensures reliable evaluation, while accuracy, specificity, and other metrics help identify the most effective combination of groups.

The operational workflow of the G-S-M approach relies heavily on Monte Carlo cross-validation (MCCV) for robustness and reliability. MCCV repeatedly partitions the data into training and testing sets, ensuring consistent predictive performance across different data subsets and addressing potential overfitting and biases. Undersampling is also used to manage data imbalance, ensuring fair representation of all classes in the training data. -Together, MCCV and undersampling bolster the G-S-M framework's capability to deliver dependable insights from

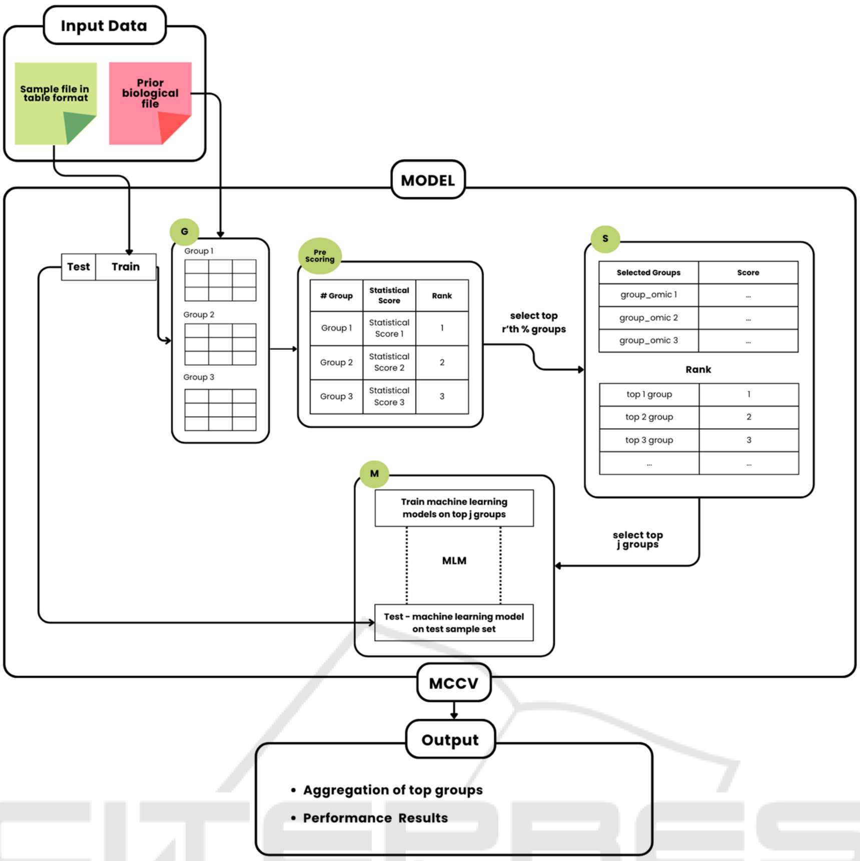


Figure 1: Displays the operation of the Pre-Scoring G-S-M Tool. The primary function of Pre-Scoring G-S-M is to combine existing biological data to categorize genes according to their association with a grouping factor, such as diseases. This information is supplied by the user.

complex biological data. Figure 1 depicts the basic flow of the Pre-Scoring G-S-M approach.

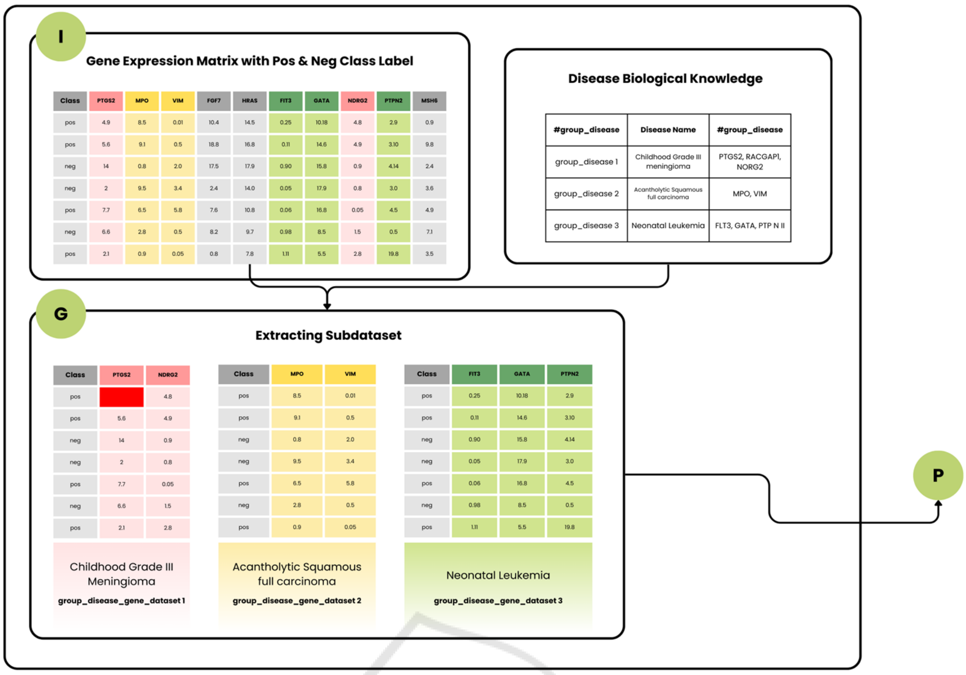
2.2 Data Collection and Preparation

While G-S-M is adaptable for various omics data, the validation used a disease-gene association database and gene expression datasets from GEO, focusing on gene-disease pairs.

Data for training and testing the machine learning model comes from DisGeNET and GEO. DisGeNET is a discovery platform with extensive gene-disease associations. It compiles data from scientific literature, public databases, and expert-curated resources, using NLP to extract relevant information. DisGeNET's v7 dataset includes 30,170 diseases and 21,666 genes, with 3,241,576 associations (Piñero et al., 2021). Filters were applied to manage data size, focusing on 'disease' entries and 'Neoplastic Process' or 'Disease' tags, resulting in 15,991 genes and 3,929 diseases with 329,936 associations. The Gene Expression Omnibus (GEO) database is an international repository for gene expression and functional genomics datasets (Clough & Barrett, 2016). Researchers submit data from experiments designed to investigate gene expression patterns (Wang et al., 2019). Nine datasets related to human gene expression for various diseases were sourced from GEO, each cataloged by disease and sample count, distinguishing between positive and negative samples.

2.3 G Component: Creating a Two-Class sub-Dataset Based on Disease Biological Knowledge

Sub-datasets specific to each group or disease are created by isolating relevant gene columns and class labels. These sub-datasets are input into the Pre-Scoring component. Figure 2 illustrates this process, showing the input panels with gene expression matrices and pre-existing biological knowledge, such as disease associations.



Gene Expression Matrix with Pos & Neg Class Label

Class	PTGS2	MPO	VIM	FGF7	HRAS	FIT3	GATA	NDRG2	PTPN2	MSH6
pos	4.9	8.5	0.01	10.4	14.5	0.25	10.18	4.8	2.9	0.9
pos	5.6	9.1	0.5	18.8	16.8	0.11	14.6	4.9	3.10	9.8
neg	14	0.8	2.0	17.5	17.9	0.90	15.8	0.9	4.14	2.4
neg	2	9.5	3.4	2.4	14.0	0.05	17.9	0.8	3.0	3.6
pos	7.7	6.5	5.8	7.6	10.8	0.06	16.8	0.05	4.5	4.9
neg	6.6	2.8	0.5	8.2	9.7	0.98	8.5	1.5	0.5	7.1
pos	2.1	0.9	0.05	0.8	7.8	1.11	5.5	2.8	19.8	3.5

Disease Biological Knowledge

#group_disease	Disease Name	#group_disease
group_disease 1	Childhood Grade III meningioma	PTGS2, RACGAP1, NORG2
group_disease 2	Acantholytic Squamous full carcinoma	MPO, VIM
group_disease 3	Neonatal Leukemia	FLT3, GATA, PTP N II

Extracting Subdataset

Class	PTGS2	NDRG2
pos	🟥	4.8
pos	5.6	4.9
neg	14	0.9
neg	2	0.8
pos	7.7	0.05
neg	6.6	1.5
pos	2.1	2.8

Childhood Grade III Meningioma
group_disease_gene_dataset 1

Class	MPO	VIM
pos	8.5	0.01
pos	9.1	0.5
neg	0.8	2.0
neg	9.5	3.4
pos	6.5	5.8
neg	2.8	0.5
pos	0.9	0.05

Acantholytic Squamous full carcinoma
group_disease_gene_dataset 2

Class	FIT3	GATA	PTPN2
pos	0.25	10.18	2.9
pos	0.11	14.6	3.10
neg	0.90	15.8	4.14
neg	0.05	17.9	3.0
pos	0.06	16.8	4.5
neg	0.98	8.5	0.5
pos	1.11	5.5	19.8

Neonatal Leukemia
group_disease_gene_dataset 3

Figure 2: Illustrates the formation of two-class sub-datasets derived from disease-group names, subsequently processed by the Pre-Scoring component for statistical scoring.

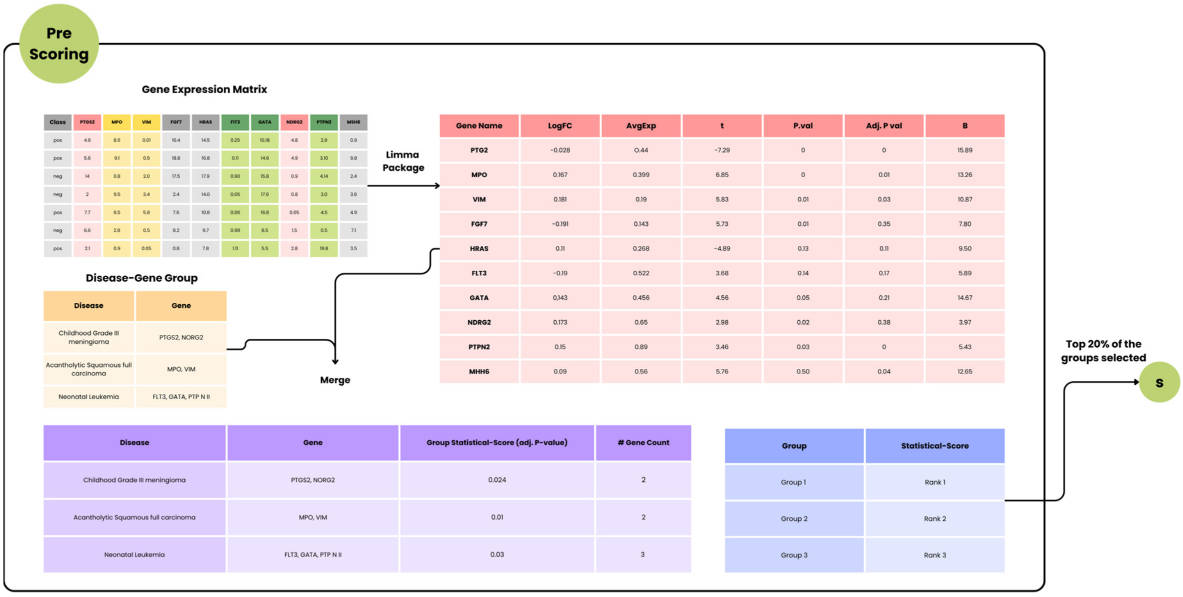
2.4 Introducing the Pre-Scoring Component with Limma Integration in the G-S-M Approach

The introduction of the Pre-Scoring component into the G-S-M approach represents a methodological enhancement in preprocessing. Central to this enhancement is the Limma package, widely recognized for its ability to analyze differential expression in gene datasets. The Limma package's strength lies in its empirical Bayes method, which effectively stabilizes the variance estimates, especially beneficial when dealing with small sample sizes often encountered in gene expression studies (Smyth, 2004). For example, one of our datasets, GDS3257, has only 107 samples, making variance stabilization particularly crucial. This stabilization allows for more reliable inferences about differential expression across a wide array of genes. Furthermore, Limma employs moderated t-statistics, leveraging information from all genes to improve variance estimates, thereby providing more stable and accurate statistical inferences (Phipson et al., 2016). The package also offers robust linear model fitting, accommodating complex experimental designs to ensure precise modeling of the relationship between gene expression and experimental conditions.

A key feature of Limma, is its adept control of the false discovery rate (FDR), crucial in studies where thousands of genes are tested simultaneously. By using the Benjamini-Hochberg adjustment method, Limma adjusts p-values to control the FDR, ensuring that the proportion of false positives among the significant results is minimized (Ritchie et al., 2015). This multiple-testing correction is essential for the validity of findings in high-dimensional data analysis. The adjusted p-value metric, which corrects for multiple testing, ensures that the likelihood of identifying genes as differentially expressed is not due to random chance alone. This statistical validation is crucial in high-dimensional data analysis, where false positives are a significant concern. By focusing on the adjusted p-values, we enhance the reliability of our differential expression analysis, providing a more robust and interpretable set of results.

The use of mean adjusted p-values in our Pre-Scoring phase, therefore, is not arbitrary but a deliberate choice to bolster the robustness of the feature selection process. By incorporating these rigorous statistical techniques, we ensure that our analysis is not only reliable but also reproducible, underscoring the methodological integrity of our approach. Within this newly established component, we implemented two key elements to enhance efficiency and specificity further.

First, the Pre-Scoring component introduces a percentage-based selection mechanism. This



Class	PTGS2	MPO	VIM	FGF7	HRAS	FIT3	GATA	NDRG2	PTPN2	MSH6
pos	4.9	8.5	0.01	10.4	14.5	0.25	10.18	4.8	2.9	0.9
pos	5.6	9.1	0.5	18.8	16.8	0.11	14.6	4.9	3.10	9.8
neg	14	0.8	2.0	17.5	17.9	0.90	15.8	0.9	4.14	2.4
neg	2	9.5	3.4	2.4	14.0	0.05	17.9	0.8	3.0	3.6
pos	7.7	6.5	5.8	7.6	10.8	0.06	16.8	0.05	4.5	4.9
neg	6.6	2.8	0.5	8.2	9.7	0.98	8.5	1.5	0.5	7.1
pos	2.1	0.9	0.05	0.8	7.8	1.11	5.5	2.8	19.8	3.5

Gene Name	LogFC	AvgExp	t	P.val	Adj. P val	B
PTG2	-0.028	0.44	-7.29	0	0	15.89
MPO	0.167	0.399	6.85	0	0.01	13.26
VIM	0.181	0.19	5.83	0.01	0.03	10.87
FGF7	-0.191	0.143	5.73	0.01	0.35	7.80
HRAS	0.11	0.268	-4.89	0.13	0.11	9.50
FLT3	-0.19	0.522	3.68	0.14	0.17	5.89
GATA	0,143	0.456	4.56	0.05	0.21	14.67
NDRG2	0.173	0.65	2.98	0.02	0.38	3.97
PTPN2	0.15	0.89	3.46	0.03	0	5.43
MHH6	0.09	0.56	5.76	0.50	0.04	12.65

Disease	Gene
Childhood Grade III meningioma	PTGS2, NORG2
Acantholytic Squamous full carcinoma	MPO, VIM
Neonatal Leukemia	FLT3, GATA, PTP N II

Disease	Gene	Group Statistical-Score (adj. P-value)	# Gene Count
Childhood Grade III meningioma	PTGS2, NORG2	0.024	2
Acantholytic Squamous full carcinoma	MPO, VIM	0.01	2
Neonatal Leukemia	FLT3, GATA, PTP N II	0.03	3

Group	Statistical-Score
Group 1	Rank 1
Group 2	Rank 2
Group 3	Rank 3

Figure 3: Illustrates the Pre-Scoring process used in the G-S-M framework for enhanced feature selection in transcriptomic data.

functionality addresses the variability in the number of groups generated by different datasets. With a fixed percentage-based system, researchers can dynamically adjust the selection to the dataset size. For instance, one dataset might produce 2,809 groups, while another yields 3,000; choosing the top 20% adapts seamlessly to each. Second, the Pre-Scoring component systematically removes duplicate gene-disease associations, preserving unique gene representations and preventing the dilution of statistical significance. After processing with Limma, average adjusted p-values are computed for each group, determining final scores. As illustrated in Figure 3, the top 20% are then selected for further analysis in our experiment.

2.5 Scoring Component of the Pre-Scoring G-S-M Framework

After selecting the top 20% of gene groups based on their statistical scores, these groups are processed in the Scoring component. In this phase, each group undergoes secondary scoring using a Random Forest classifier within a structured cross-validation framework to assess their potential for accurate disease prediction. This process involves dataset splitting, analysis through the S-Fit Test Model, and evaluation of gene groups with the Random Forest classifier. The accuracy average of the *r* splits is then calculated to determine the group score, and all group scores are compiled into a table. In the Modeling (M) component, this table is sorted in descending order, and the top-ranked j groups of diseases are chosen. Their genes are merged to form the top-ranked associated genes (as shown in Fig. 1, Modeling panel). A sub-dataset (90% training, 10% testing) is created using these top-ranked genes. An RF model is subsequently trained on this sub-dataset, and the model's performance is evaluated on the testing dataset. Performance results are documented for j = 1 to 10.

3 RESULTS

The Pre-Scoring G-S-M is evaluated using standard G-S-M practices, employing a Random Forest classifier with a 90% training and 10% testing split. To address dataset imbalance, an undersampling method is applied to achieve a 2:1 ratio of positive to negative samples during model training. Monte Carlo cross-validation (MCCV) with 10 iterations is used to average performance metrics, including accuracy, sensitivity, specificity, and area under the curve (AUC), ensuring reduced variance and reliable results.

Table 1: Presents an example of cumulative averages from a performance table for 10 MCCV, highlighting the top 10 ranked groups from the Pre-Scoring G-S-M for the GDS1962 dataset.

#Groups	#Genes	Accuracy	AUC	Precision	Specificity	F-measure	Sensitivity
1.00	4.30	0.91	0.95	0.98	0.95	0.93	0.90
2.00	10.20	0.93	0.96	0.98	0.95	0.95	0.92
3.00	17.70	0.94	0.98	0.98	0.95	0.96	0.94
4.00	20.90	0.94	0.97	0.98	0.95	0.96	0.94
5.00	23.60	0.94	0.96	0.98	0.95	0.96	0.94
6.00	27.20	0.94	0.96	0.98	0.95	0.96	0.94
7.00	30.20	0.94	0.96	0.98	0.95	0.96	0.94
8.00	34.40	0.94	0.97	0.98	0.95	0.96	0.94
9.00	37.20	0.94	0.96	0.98	0.95	0.96	0.94
10.00	41.20	0.96	0.97	1.00	1.00	0.97	0.94

3.1 Performance Evaluation of Pre-Scoring G-S-M

Table 1 presents an example of the average 10-fold MCCV performance for the top 10 groups in the GDS1962 dataset. The first row shows the performance of the top-ranked group achieving an AUC of 95% using an average of 4.30 genes. The performance metrics for the top 2 groups are also included, where genes from the first and second-highest-scoring groups are combined. This process is repeated for all top 10 groups to evaluate their collective and individual contributions to model performance.

The output of the Pre-Scoring G-S-M, similar to standard G-S-M tools, includes a ranked list of disease groups assigned p-values by the RobustRankAggreg package (Kolde et al., 2012). The framework also compiles a list of significant genes aggregated by the RobustRankAggreg tool, which can be used in facilitating functional and enrichment analyses using platforms like David, EnrichR, and GeneMANIA.

3.2 Comprehensive Evaluation Across Diverse Datasets

The Pre-Scoring G-S-M model was applied to nine diverse human gene expression datasets from the GEO database, testing the model's efficiency and precision across varying genetic expression profiles as shown in table 2. The Pre-Scoring G-S-M framework efficiently manages these complexities and preserves key biological insights, comparable to the standard G-S-M approach. Integrating the Pre-Scoring component significantly enhances both computational efficiency and analytical precision. By pre-filtering and prioritizing gene groups based on their statistical relevance, it reduces processing time and resource consumption, which is particularly advantageous in computationally constrained environments. The Limma package improves analytical precision by focusing on statistically significant groups, maintaining the quality of biological insights despite a reduced data volume. For example, on the GDS1962 dataset, the standard G-S-M achieved 0.92 accuracy with 81.1 features, whereas Pre-Scoring G-S-M attained 0.94 accuracy with only 17.7 features, illustrating the approach's efficiency and precision. Figure 4 presents performance metrics for both standard G-S-M and Pre-Scoring G-S-M across nine datasets.

Table 2: Pre-Scoring G-S-M performance results over the top-ranked groups for 9 GEO Dataset.

GEO Accession	# Genes	Accuracy	Sensitivity	Specificity	AUC
GDS1962	45.57	0.93	0.93	0.93	0.97
GDS2545	113.76	0.73	0.72	0.74	0.81
GDS2771	97.83	0.64	0.69	0.59	0.70
GDS3257	74.81	0.97	0.99	0.94	0.99
GDS3837	21.00	0.92	0.83	1.00	0.92
GDS4206	83.00	0.66	0.30	0.82	0.58
GDS4516_4718	40.72	0.99	0.99	0.99	1.00
GDS3268	115.70	0.67	0.70	0.63	0.73
GDS5499	80.23	0.90	0.96	0.77	0.95

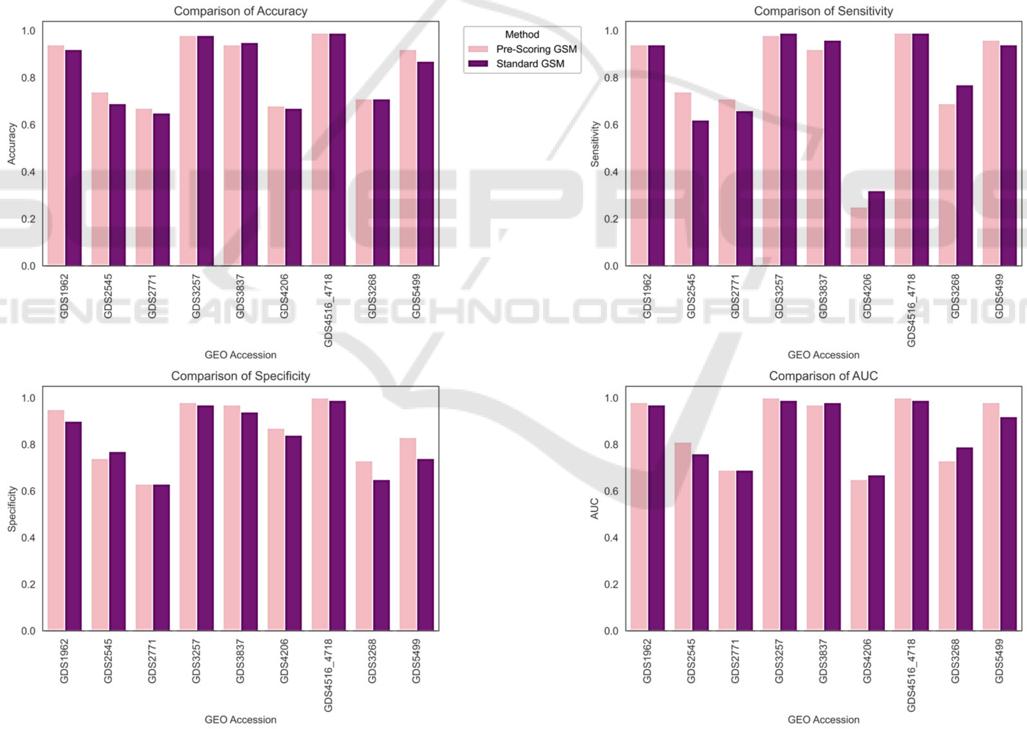

Comparison of Accuracy
Comparison of Sensitivity
Comparison of Specificity
Comparison of AUC

Figure 4: Showcases the comparison of 4 different performance metrics of Pre-Scoring G-S-M (in pink) vs Standard G-S-M (in purple) across nine GEO datasets. The first graph on the top right is accuracy comparison, the top left is sensitivity, the right bottom compares specificity and the bottom right compares AUC for both models.

The Pre-Scoring G-S-M model achieves comparable results to the standard G-S-M across all metrics but with significantly fewer features, as shown in Figure 5, highlighting the efficiency and precision of this approach in transcriptomic data analysis. Further validation will investigate the broader potential of the framework's capabilities. To reduce data redundancy, the Pre-Scoring component filters out duplicate gene-disease associations within groups, specifically targeting cases where relevant and statistically significant genes appear multiple times under different disease names. For instance, the gene ALP

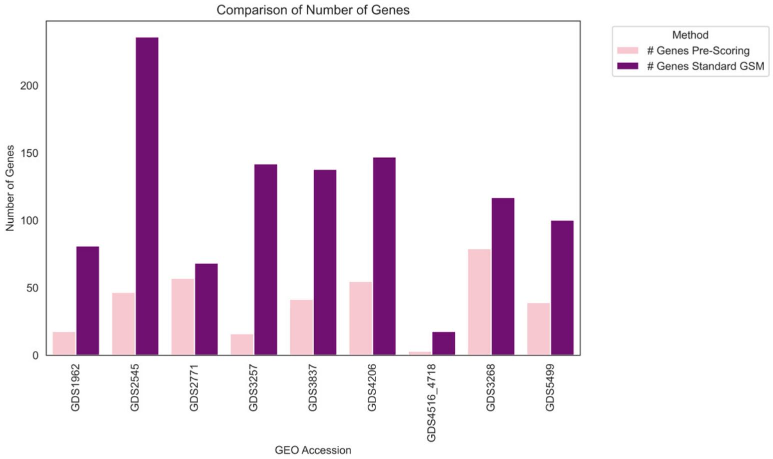


Figure 5: Depicts the number of genes (features) selected by standard G-SM in purple vs number of genes selected by Pre-Scoring G-S-M in pink.

appeared nine times, each with a different disease. Removing these duplicates retains only one instance of the gene per disease group, thereby reducing noise and complexity and enhancing the model's performance by focusing on informative biological signals.

4 DISCUSSION

4.1 Relevance of the Pre-Scoring Component in Existing G-S-M Tools

In this study, we introduce a Pre-Scoring component to address a critical bottleneck in the G-S-M framework: the computational intensity of scoring vast numbers of gene groups. For instance, in the GDS2545 dataset, which has a relatively smaller set of gene features, the standard grouping process initially generates 2809 groups. However, with the Pre-Scoring component, only 563 of these groups are selected for detailed scoring. This selective advancement is crucial because each group is still scored five times per Monte Carlo cross-validation (MCCV) iteration, cumulatively requiring substantial computational resources.

By focusing on groups with higher statistical significance, the Pre-Scoring component eliminates the need to score every group from the initial phase. This streamlines the entire scoring process, ensuring that computational efforts concentrate on the groups most likely to yield pertinent biological insights. Consequently, it enhances the efficiency of the G-S-M framework, reducing both the computational load and the time required for processing. This example underscores the value of the Pre-Scoring component in optimizing the analysis workflow.

4.2 Impact on Bioinformatics Tools

The integration of the Pre-Scoring component into tools like PriPath (Yousef et al., 2023), CogNet (Yousef et al., 2021), and GediNET (Qumsiyeh et al., 2022) could significantly improve their efficiency and effectiveness. These tools, which use similar methodologies, could benefit from the reduced computational demands and enhanced focus on statistically significant gene groups.

4.3 Potential Limitations and Future Plans

One limitation of the Pre-Scoring component is the variance in group sizes, which might bias the statistical relevance, favoring either larger or smaller groups during the scoring process. Additionally, noisy genes within a group could negatively impact the overall classification performance, a limitation that does not affect feature selection methods evaluating genes individually. Both issues can be addressed by considering a fixed number of representative genes from each group.

5 CONCLUSION

The Pre-Scoring G-S-M model's initial application showcases promising strides in enhancing computational efficiency and precision in transcriptomic analysis. By integrating this additional Pre-Scoring component alongside the standard G-S-M scoring mechanism, we introduce a dual-layered evaluation system, promising a more nuanced analysis process.

These advancements suggest a significant impact on feature selection, potentially streamlining biomarker discovery and disease classification processes. While these findings are preliminary, they underscore the potential for the Pre-Scoring G-S-M approach to facilitate more accessible and efficient transcriptomic research, even in settings with limited computational resources.

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