Metabolomic Analysis in Pediatric Crohn´s Disease Patients: A Machine Learning Approach

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Abstract

Inflammatory Bowel Diseases (IBD) are disorders in the intestinal tract with no permanent cure and can often lead to hospitalizations, surgeries, and life-threatening complications. Furthermore, IBD are more severe in children than in adults and carry a risk of growth failure, delayed puberty, depression, anxiety, and cancer.

Metabolomics allows to analyse the metabolic changes in the gut microbial metabolism by identifying and quantifying the compounds in biological samples. Therefore, metabolomics provide a unique opportunity to associate pediatric Crohn's disease (pCD) with an altered multivariate metabolite profile.

The objective of this work is to perform an exploratory data analysis on serum metabolomics from 56 pCD patients. Samples were collected twice: once, as a study initiation (Visit One) and second, for completion (Visit Four). Then, the collected serum underwent a liquid chromatography followed by a mass spectroscopy process to identify 131 compounds. Serum metabolites are analysed applying Unsupervised (U.ML) and Supervised (S.ML) Machine Learning algorithms. U.ML is used to reduce the dimensionality of the data and identify cluster; whereas S.ML is used to develop regression and classification algorithms to assess correlation between metabolites and disease activity.

Results show that Tryptophan is the metabolite that ranks the highest in the feature importance scoring. Histidine is another metabolite that correlates well with severity of the disease. In regression analysis, it was seen that PLS with LOL reduction setting incurred the least MSE of 0.8806. In classification process, Random Forest with LDA setting achieved the least False Negative rate of 0.53 and KNN with PCA setting yielded the highest accuracy score of 63.

In conclusion, we inferred that the above alternatives did not have any exceptional impact on our findings. The major reason for this might be the scarcity of data and imbalance or underrepresentation of some data labels.

1 Introduction

The two main subtypes of IBD are Crohn disease (CD) and ulcerative colitis (UC). In CD inflammation occurs anywhere along the gastrointestinal tract with skip lesions, while in UC inflammation is restricted to the colon in a contiguous fashion [1].

The worldwide incidence of IBD is increasing. In some Western countries, such as Canada, rates are projected to be as high as 1% of its entire population by the year 2030 [2]. Moreover, the prevalence in children has also been increasing, with up to 25% of diagnoses occurring in the pediatric population [3].

IBD in children is related with a more severe disease course that in adults [4]. Growth and development concerns are unique to pediatric IBD (pIBD). Moreover, younger age of diagnosis in pIBD is associated with more complicated disease where patients present poorer outcomes and an increased need for surgery [5]. Also, diagnosis with IBD in childhood has been associated with increased risk of cancer and mortality in adulthood [6].

The development of IBD remains poorly understood. Genetic susceptibility, diet changes, and environmental factors have been found to be associated with the disease development. Therefore, there is much work to be done in this field. Current novel procedures can be used to further study the aetiology of IBD. This includes metabolomics, metagenomics, 16s-RNA analysis of gut microbiome, and epigenetic analysis.

Metabolites are compounds necessary for or formed during metabolism and are composed of both host and microbe factors that can reflect the real-time microenvironment of the gut. Metabolomics can quantify host and microbe metabolites and help distinguish between CD, UC, and healthy controls, but there has been limited investigation into paediatric IBD metabolomics [7]. This work provides an excellent opportunity to examine metabolomic profiles and their association with disease severity among pCD patients.

2 Methodology

2.1 Data Acquisition

ImageKids is a multicentre, prospective cohort observational study that was conducted to develop magnetic resonance enterography (MRE) indices for pCD. The study was conducted over 18 months with serum and urine specimens collected as study initiation (Visit One or V1) and completion (Visit Four or V4) for 56 pCD patients.

Collected serum samples were sent to University of Alberta, and further submitted to The Metabolomics Innovation Centre (TMIC) for metabolomics analysis. Serum underwent liquid chromatography followed by mass spectroscopy and 131 compounds were identified.

Serum metabolites were analyzed applying Unsupervised (U.ML) and Supervised (S.ML) Machine Learning algorithms based on Scikit-learn library [8] in Python.

2.2 Unsupervised Learning

Unsupervised Learning techniques are used to extract useful patterns from a dataset in the absence of any label information. We apply unsupervised learning techniques like clustering on the patients dataset. Since the number of features (131) are much larger than the number of samples, we also apply well-known dimensionality reduction techniques and evaluate their performance using clustering metrics.

2.2.1 Dimensionality Reduction

Dimensionality reduction involves transformation of high-dimensional data to low-dimensional data such that some meaningful information present in the original data is retained in the low-dimensional space. We use the following dimensionality reduction techniques in this study -

- **PCA** - It is a popular approach for deriving a low-dimensional set of features from a large set of variables, by finding a sequence of linear combinations of the variables that have maximal variance and are mutually uncorrelated. It allows us to summarize a dataset with a smaller number of representative variables that collectively explain most of the variability in the original dataset.The first principal component direction of the data is the direction along which the observations vary the most. PCA is an effective technique for analysing metabolomic data [9].

- **UMAP** [10] - Uniform Manifold Approximation and Projection transforms the data by constructing a neighbourhood graph in the original data space and obtaining a similar graph in the low-dimensional space.

- **MDS** - It is a non-linear technique for embedding data in a low-dimensional space which maps points residing in a high-dimensional space to a low-dimensional space while preserving the distances between those points as much as possible. Because of this, the pairwise distances between points in the lower-dimensional space are matched closely to their actual distances.

- **PCA + UMAP** - We use PCA to obtain the first k principal components which account for the most variation in the data. Then, we use UMAP to map the data to the 2-dimensional space. Applying PCA allows us to get some computational speedup for UMAP. It also helps in reducing the noise in the data without severely distorting the distance between the data points.

- **MDS + UMAP** - We use MDS for embedding the dataset in a low-dimensional space, which preserves the distances between the points. Then, we use UMAP to map the new dataset to a two-dimensional space. Using UMAP directly can lead to error that arises from changes in the global structure of the data. Applying MDS before UMAP provides an effective way to minimize this error.

Among the above mentioned techniques, PCA and UMAP provide a way apply an inverse transformation to get high-dimensional data from low-dimensional data. Such a transformation is not possible using MDS.

2.2.2 Clustering

Clustering is an unsupervised learning technique which is used to group similar data points using a distance metric. Clustering techniques can be broadly classified into density-based clustering, centroid-based clustering and heirarchical clustering. Since density-based clustering techniques require a large amount of data, we cannot apply them to our dataset. Both heirarchical clustering and centroid-based clustering yield similar results on a small dataset. Hence, we perform our experiments using the K-Means clustering algorithm. The K-Means clustering algorithm groups data points into k clusters by assigning a cluster label to each point based on its distance from the mean of each cluster. The process is repeated until a convergence criterion is satisfied.

2.2.3 Partial Least Squares

Partial least squares-discriminant analysis (PLS-DA) has been extensively used in metabolomics[11]. PLS is a multivariate regression method where information from a data space of a larger number of variables is projected into that with a smaller number of variables[12].

In this work, the associated clusters were analyzed using PLS-DA, to identify metabolites most responsible for cluster definition. Consequently, the variables importance in projection (VIPs) corresponding to the geography of the patients are presented in Table 7777777.

PLS was also used to maximize the co-variance between the metabolites and the severity of the disease. Therefore, PLS is explained with more detail in the S.ML section.

2.3 Supervised Learning

One of the most important subcategories of Machine learning is Supervised learning which trains various algorithms to predict the outcomes or classify the data. Usually, the dataset (X, Y) comprises a set of features (X) that are associated with a target response (Y). Applying this concept to the metabolomics dataset helps in deducing a set of conclusions at scale, such as finding the metabolites that have a major impact on the severity of Crohn's disease. Figure 1 shows a fundamental set of actions for evaluating a bunch of models based on the key features extracted and training of the models.

SML was used to assess correlation between metabolites and disease activity. Therefore, PICMI index was used to label and classify patients in three different categories: remission, moderate-mild, and
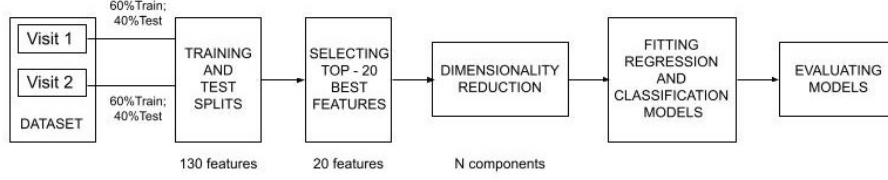
Figure 1: Set of action for evaluating models.

severe disease. PICMI is a valid, reliable, and responsive index for assessing transmural inflammation in pediatric CD[13].

2.3.1 Pre-Processing of Data

Splitting the Data

The Metabolomics dataset is composed of 56 patients' records from two different visits (Visit 1 and Visit 2) that are at an interval of 4 months. (is the dataset description written?) Due to the brevity of dataset, the "Mild+Moderate" class label is underrepresented and emanates the problem of class imbalance. To combat this issue, we extract equal proportions (60%) of every class label from both the visits for training and the remaining for testing procedures.

```
Training : class labels count for 1st visit
Counter({0: 17, 2: 12, 1: 4})
Test : class labels count for 1st visit
Counter({0: 11, 2: 9, 1: 3})

Training : class labels count for 2nd visit
Counter({0: 21, 2: 8, 1: 4})
Test : class labels count for 2nd visit
Counter({0: 15, 2: 6, 1: 2})
```

Scaling of Data

Once the unified set is obtained, the data was scaled by removing the mean and scaling to unit variance. This is known as Standard Scaling. The scaling process would avoid poor behavior of the features from the data that oftentimes occur when the data is not following a consistent distribution.

Selecting Top 20 Best Features

Originally, the dataset is constituted of 130 metabolomic features which are substantially more than the number of samples per visit. Since the sample size is typically orders of magnitude smaller than the dimensionality of the data, this results in the curse of dimensionality. Hence, generating a low-dimensional representation for valid inferences and preserving the discriminating information (for instance, does the patient suffer from Crohn's disease?) is essential. There is a need for interpretable supervised dimensionality reduction methods that scale to wide data with billions of dimensions with compelling statistical theoretical guarantees.

Initially, we apply a simple baseline approach to select the best representative features based on univariate statistical tests. This acts as a pre-processing step to fit any estimator with scaled data. The sklearn's *SelectKBest* wrapper proves useful to extract all highest scoring features in the dataset. We use the following scoring functions for our dataset:

- *fregression*: This function is utilized for a calculating cross-correlation between every sample (X) and the target response (Y) as follows:

$$crosscorrelation = \frac{(X[:,i] - mean(X[:,i])) * (Y - mean(y))}{std(X[:,i] * std(y)} \tag{1}$$

- *fclassif*: This function is utilized for calculating ANOVA value for the provided samples and target response.

4

These scores generated from the functions are converted into univariate F-scores and then to p-value statistics, thus identifying potentially predictive features for an estimator irrespective of the sign of the association of the target variable.

In addition to this, we apply a few classical statistical starter approaches to the top key features extracted ($p >> n$) along with a novel method called LOL that adapts to the complexity of the data, is robust to outliers, and is computationally efficient. The strategies pursued in our cases is as follows:

- LDA: We explored the application of linear discriminant analysis (LDA) to the Metabolomics features because this technique reduces dimensions while preserving the global structure of data. We draw our inspiration from [14],to perform scaling of every Metabolite such that the distribution of data in each class ("Remission", "Mild+Moderate", "Severe") is as close as possible to a standard normal distribution in a transformed space. Distances between the objects in this space are hence made meaningful by estimating the centroids and their distances, since the space is homogeneously deformed, and length along each dimension is expressed in multiples of intra-class variation.

- PCA: We analyzed the conventional Principal Component Analysis (PCA) to show the impact of sample reduction on the process of reducing dimensions for supervised learning [15] . We took into account the class information for calculating the class-conditional probabilities and optimizing the ratio of between-class variance to the within-class variance of the transformed data by calculating the covariance matrix. The computation of the components is based on the eigenvalue decomposition of the covariance matrix S as follows:

$$w \leftarrow eigenDecomposition(S = \sum_{i=1}^{n}(x_i - mean(X))(x_i - mean(X))^T) \quad (2)$$

- NCA: We considered the Neighbourhood Component Analysis (NCA) to carry out the supervised dimensionality reduction [16] where the Metabolites are projected onto a linear subspace consisting of the directions which minimize the NCA objective.. This distance metric learning algorithm helps us to maximize the stochastic variant of the leave-one-out k-nearest neighbors (KNN) score on the training set. Optimal linear transformation maximizes the sum over all the patient samples and records the probability of the correctly classified samples on the basis of a stochastic nearest neighbors rule:

$$P_{ij} = \frac{exp(-||Lx_i - Lx_j||^2)}{\sum_{k \neq i}^{n} exp(-||Lx_i - Lx_j||^2)}, P_{ii} = 0, \quad (3)$$

where, p_{ij} is the softmax over Euclidean distances in the learned embedded space.

- LOL: Finally, we perform the Linear Optimal Low-rank projection (LOLp) that aims to integrate the class-conditional means [17] to substantiate classification of improved representations of the Metabolites with good computational efficiency and scalability. Our inspiration to use this technique stems from its exceptional performance on genomics datasets with more than thousands of features when compared to other scalable linear linear dimensionality reduction techniques in terms of accuracy.

2.3.2 Regression Techniques

Regression analysis is a combination of statistical techniques that aims to establish relationship between independent and dependent variables along with minimizing the differences between the regression estimate or prediction and the true value. This helps us to analyze the dependence of the Metabolites on the PICMI scores and eventually on the severity of the Crohn's disease. As a reminder:

- < 40 PICMI score is considered on Remission.
- $41 - 70$ is considered Moderate.
- > 70 is considered Severe.

Our basic aim is to train our model to classify into three classes. A set of bins regarding the PICMI cut offs were introduced in the data to transform into the classes needed for the following regression techniques:

- Linear Regression: As a baseline technique, we performed simple linear regression for modelling the Metabolomics features on the Severity of the disease keeping in mind the minimization of error rates associated with the predicted and the true values.

- PLS: We incorporate Partial Least Squares (PL2S) as a technique to maximize the covariance between the Metabolites and the set of target responses (severity of the disease). This helps on emphasizing on the predictive modelling which reduces a number of factors and works well for highly collinear/noisy data which often occurs in the metabolomics experiments [18].

- Ordinal Regression: Since our dataset belongs to the field of metabolomics, usually the variables are in natural ordering format (ordinal scale) [19]. Ordinal regression acts as a fence between Regression and Classification techniques. We use it as an inclination towards regression to calculate the cumulative probabilities of the Severity scale (response variable) as a function of the Metabolites using the logistic function for constructing a Ordinal Logit model.

2.3.3 Classification Techniques

We also applied classification techniques for the analysis of our data. The current objective is to predict the outcome of the data set as a qualitative output. This is an intuitive step in our analysis, since depending on the PICMI score each patient has, it is considered at a different stage on the severity of their disease.

When talking about a classification technique, if our predictor G(x) takes values in a discrete set G, we can always divide the input space into a collection of regions labeled according to the classification. The boundaries of these regions can be rough or smooth, depending on the prediction function. There are several different ways in which linear decision boundaries can be found. In this paper we take four classification methods such as:

- Logistic Regression: Model the posterior probabilities of the K classes via linear functions in x, while ensuring that they sum to one between [0,1]. This model has the form:

$$log \frac{Pr(G = K - 1|X = x)}{Pr(G = K|X = x)} = \beta_{(K-1)0} + \beta_{K-1}^T x. \tag{4}$$

  We decided to start our classification with this method, since this is arguably the most simple algorithm to work on [20]. The results obtained from this will be only used as a control reference for the following. Moreover, logistic regression is very simple to interpret, which would be helpful for future analysis.

- Support Vector Machine: Taking things one step further, the decision of using Support Vector Machine (SVM) is a natural transition. So far we have found linear boundaries in the input feature space. However, here it is possible to to make the procedure more flexible by enlarging the feature space using polynomials and splines. Linear boundaries in the enlarged space achieve better training-class separation, and translate to nonlinear boundaries in the original space. Furthermore, the dimension of the enlarged space is allowed to get very large, and even to infinity. This is a more complex technique for classification, but at the same time it is more flexible for more entangled data. Moreover, one strong motivation to use SVM is that it has shown in previous works, that the method works well in the study of metabolomics, which greatly justifies our decision. [18]

- Random Forest Classifier: The essential idea in Random Forest is to average many noisy unbiased models, and hence reduce the variance. Trees are ideal candidates for bagging, since they can capture complex interaction structures in the data, and if grown sufficiently deep, have relatively low bias. Since trees are notoriously noisy, they benefit greatly from the averaging. When used for classification, a random forest obtains a class vote from each tree, and then classifies using majority vote. This method was also considered for a classification analysis. It would display a different behavior than of SVM, leading to a more complete inspection of our data. Furthermore, RF was also an accepted method from previous work in the study of metabolomics, the same way as SVM.[18] These are clear indicators that our methodology is coherent.

6

- K-nearest Neighbor: As for K-nearest neighbor classification, this is a simple method such as linear regression. The decision for selecting this method was made by mere curiosity of looking at the results provided by it. Since this classification is memory-based, and requires no model to be fit [20], it is not expected for it to be as precise as the previous two. Nevertheless, there is always the possibility of finding interesting patterns in other models.

3 Experiments and Results

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Table 1: Clustering results for V4 data

Dimensionality Reduction	Silhouette Coefficient	Calinski-Harabasz Index	Reconstruction Error
—	0.289	21.331	—
PCA	0.661	105.429	**0.058**
MDS	0.471	47.890	—
UMAP	0.781	454.372	45.919
PCA + UMAP	0.947	**7517.397**	183.468
MDS + UMAP	**0.948**	7512.461	—

1

3.1 K-Means, Dimensionality Reduction and PLS-DA

As indicated in previous metabolomics research [21], different scaling and transformation methods have their own advantages and disadvantages. We apply pareto scaling and log transformation to our dataset since it yields the best clusters when K-Means is performed on the raw features (metabolites). The specific parameters chosen for the different techniques are as follows (all dimensionality reduction techniques result in a 2-dimensional embedding) -

- **KMeans** - 2 clusters are specified.
- **UMAP** - The number of neighbours is chosen to be 20. The distance metric that lead to the best results (i.e. well-formed clusters) is cosine similarity.
- **PCA + UMAP** - We perform dimensionality reduction from 130 features to k features using PCA. The k was determined by performing clustering with PCA + UMAP for different values of k. Using the clustering evaluation metrics, k was chosen to be 24.
- **MDS + UMAP** - An analysis similar to **PCA + UMAP** was performed to determine the k value as 35.

3.1.1 Evaluation Methodology

We use the Silhouette Coefficient [22] [8] and the Calinski-Harabasz Index [23] to evaluate the clustering results since these metrics do not require label information for the data points. The Silhouette Coefficient measures how close each data point is to its own cluster when compared with other clusters. The coefficient's value is between -1 and 1, and a higher value indicates better clusters. The Calinski-Harabasz Index measures the ratio between within-class disperstion and between-class dispersion, where a higher value indicates well-formed clusters.

In addition to evaluation metrics for clustering, we also evaluate the dimensionality reduction techniques using the reconstruction error metric. Performing dimensionality reduction can lead to information loss and one way to quantify this loss is to determine if the original data can be reconstructed from the low-dimensional space. Hence, for PCA and UMAP, we apply their inverse transform on the low-dimensional data to obtain the reconstructed features, and then compute its MSE with the original data to obtain the reconstruction error. A lower error shows that the original metabolite information for each patient can be retrieved even from a low-dimensional space. Since MDS does not have an inverse transform, we do not report the reconstruction error for it.

7

3.1.2 Clustering results

Table 11 depicts the results for applying K-means with different dimensionality reduction techniques. Through the clustering evaluation metrics, it can be observed that K-means with MDS + UMAP and K-means with PCA + UMAP yield the best clusters. However, the reconstruction error is lower when only PCA is used. Hence, we want to highlight that both methods have their pros and cons. The formation of better clusters comes at the cost of losing some information from the original data. Figure 2 shows the cluster visualization for K-means with PCA, PCA + UMAP and MDS + UMAP. The clusters clearly separate patients from Israel and patients from other countries. Similar results were observed for other dimensionality reduction techniques as well.
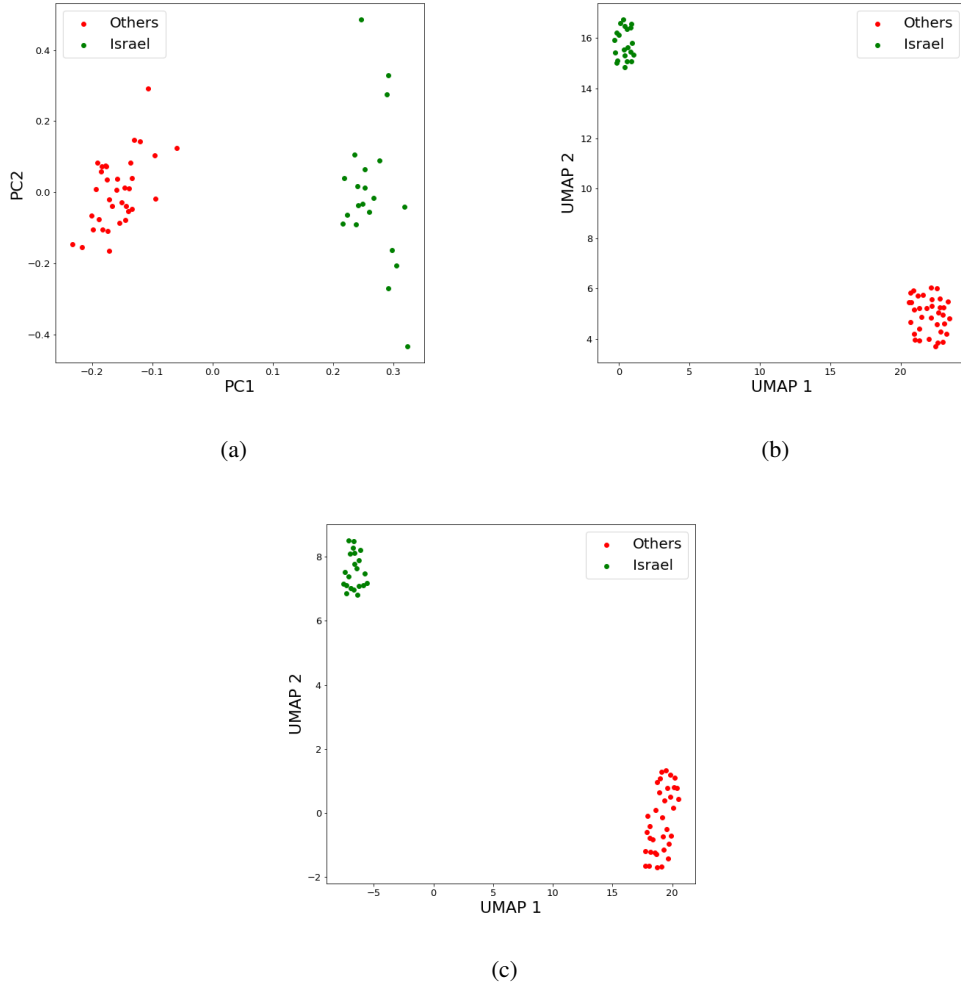

(a)

(b)

(c)

Figure 2: Clustering visualization using K-means with (a) PCA (b) PCA + UMAP (c) MDS + UMAP

3.2 Feature Selection

Models thrive under constructive criticism that gives us an opportunity to make enhancements, corrections and improvements for better performance. Hence, there are plans of actions, strategies and protocols with different metrics for analysing the behaviour of the models. It is mandatory to consider the model pipeline, constraints and environments of operation. For fair comparison of models, existing evaluation metrics are used to measure the regression and classification techniques. Our dataset consists of 130 features for analysis. Upon applying sklearn's *SelectKBest* module, we were able to extract top 20 best features along with their feature scores as follows:

```
         Feat_names    F_Scores
         Tryptophan   12.001081
        Citric acid    8.440411
              16:1SM    6.037837
                C5DC    5.986706
               C10:1    5.763595
               C5MDC    5.632694
             PC32:2AA    5.380965
            Tyrosine    5.277203
           Histidine    5.074206
Trimethylamine N-oxide   3.865438
beta-Hydroxybutyric acid  3.818782
          Methionine    3.734028
              Lysine    3.652867
              18:1SM    3.480790
            Creatine    3.335337
            LYSOC18:2    3.225121
                C7DC    3.192890
5-Hydroxyindoleacetic acid  2.669419
                C4OH    2.527650
             PC40:1AA    2.465284
```

3.3 Regression

Error estimators calculate the average squared difference between the predicted values of the target response by the regression models and the true/actual values which correspond to the expected values of the loss associated with the predicted values.

$$MSE = \frac{1}{n} \sum_{i=1}^{n} (Y_i - Y_i')^2, \tag{5}$$

where Y_i is true value and Y_i' is the predicted value of the regression model; $(Y_i - Y_i')^2$ is the square of errors upon which an average operation is performed to generate the Mean Squared Error which is sample dependent. Following is the Table 2 for MSE for different regression models.

3.4 Classification

- Confusion Matrix: An array constructed for salient mapping mechanism to perform a thorough breakdown of true and false class labels while judging a model, mainly for classification. Here, in Table 3 a confusion matrix is used to gauge our model's ability to classify the patient records to the severity scale.

- Accuracy: he most salient metric for evaluation a model's performance which calculates the percentage / proportion of the correctly classified instances by the model. Here, accuracy is computed to estimate the number of correctly classified frames and the extent of summarization of a video by our model.

$$Accuracy = \frac{(PP + NN)}{(PP + NN + PN + NP)} \tag{6}$$

  Table 4 highlights accuracy of all models.

- False Negative Rate of the "Severe" class - False Negative rates are very dangerous in medical data analysis as it has the tendency to missclassify a patient to "Remission" or "Mild+Moderate" instead of "Severe" which can lead to fatality.

4 Discussion and Conclusion

From the feature selection step, we observe that Tryptophan ranks highest in the feature importance scoring.In fact, Tryptophan has been previously identified as significantly altered in the blood of IBD patients compared to controls [24]. Histidine is another metabolite that seems to correlate well

Table 2: Regression results for data

Regression Model	Dimension Reduction Method	Mean Square Error MSE	Root Mean Squared Error RMSE
Linear Regression			
	LDA	1.1366	1.0661
	PCA	0.8811	0.9387
	NCA	1.0355	1.0176
	LOL	0.9113	0.9547
PLS			
	LDA	1.1366	1.0661
	PCA	0.8807	0.9384
	NCA	0.9855	0.9927
	LOL	0.8806	0.9384
Ordinal			
	LDA	1.5	1.2247
	PCA	1.4130	1.1887
	NCA	1.3260	1.1516
	LOL	1.5	1.2247

	PREDICTED		
		Positive	Negative
ACTUAL	Positive	True Positive (PP)	False Negative (PN)
	Negative	False Positive (NP)	True Negative (NN)

Table 3: Confusion matrix

with disease severity. As a matter of fact, histidine is known to be involved in the mediation of oxidative stress, potentially influencing intestinal inflammation[25]. Finally, lysisne and tyrosine are metabolites that have also been shown to be particularly discriminatory between IBD and control groups[26].

In the supervised learning approach, we observed that the number of metabolites was reduced from 130 to 20 best features based on the feature scores generated by sklearn's SelectKBest wrapper module. In regression analysis, it was seen that PLS with LOL reduction setting incurred the least MSE of 0.8806. In classification process, Random Forest with LDA setting achieved the least False Negative rate of 0.53 and KNN with PCA setting yielded the highest accuracy score of 63Before carrying out the experiments on the subset of features, we performed regression and classification techniques on the entire raw feature set i.e. on all the 130 features. Upon performing this experiment, we noticed that the performance metrics and error rates remained almost constant. This suggests that it is a wiser approach to reduce the large Metabolites feature set into a smaller set of essential features that would eventually ease the process of carrying out regression/classification tasks with a slightly better performance. In addition to this, we also performed L1 regularization on our dataset during the regression analysis. The reason behind the choice of L1 regularizer is size of our Metabolites feature set and applying this methodology would provide sparse solutions. With this motive, we applied the L1 penalty on our regressors but did not find any remarkable differences in our results. Considering the attempts to make our models better, we inferred that the above alternatives did not have any exceptional impact on our findings. The major reason for this might be the scarcity of data and imbalance or underrepresentation of some data labels.

Table 4: Accuracy and False Negative Rate

Classifying Model	Dimension Reduction	Accuracy	False Negative Rate
Logistic Regression			
	LDA	59%	0.6
	PCA	50%	0.73
	NCA	50%	0.73
	LOL	48%	0.73
SVM			
	LDA	50%	0.8
	PCA	41%	0.93
	NCA	39%	0.93
	LOL	37%	1
Random Forest			
	LDA	59%	0.53
	PCA	52%	0.66
	NCA	57%	0.66
	LOL	46%	0.8
K-nearest Neighbors			
	LDA	54%	0.73
	PCA	63%	0.6
	NCA	61%	0.6
	LOL	50%	0.8

In the unsupervised learning approach, we applied the K-Means clustering algorithm and observed two clusters, Israel and non- Israel. As well, we used some of the dimensionality reduction and we observed that applying MDS or PCA then UMAP is more efficient than the individual techniques. Furthermore, we evaluated the results by computing some of the evaluating measurements, the Silhouette Coefficient [22] [8], the Calinski-Harabasz Index [23], and the reconstruction error.

5 Future Work

The major thing that we would yearn for in the future is to quench our thirst of not having sufficient data. We aim to perform our experiments on a larger dataset with classes that are proportionally represented by the samples. Having more data might support our findings in a better way and deduce more relationships between the Metabolites and demographics/severity scale. A boon to us would be obtaining data from several visits to perform time-series analysis. This would provide us an insight into the specific set of Metabolites that contribute to the change in the status of the patient from more severe to less severe. This might also help us to study the trend of Crohn's disease in different geographical locations and impact of their diet on the severity of the disease. On statistics front, we would like to concentrate on the tuning of Hyperparamters for a better performance of our regression/classification models by adopting the automatic procedure of detecting the optimal hyperparameters in terms of optimization strategies such as typical brute force method like Grid search or Random search. For instance, hyperparameters for random forest could be:

- The number of trees built.
- "gini"/"entropy" measures for checking the quality of the splits and purity of the nodes.
- Control the depth of the tree and other pruning techniques

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