TCR Dist

TCRDist was used to calculate the distance metric between alpha and beta chains and alpha+Beta chain combined.

In this methodology, T-cell receptor (TCR) repertoire analysis conducted using TCRdist, a computational tool designed to quantify the similarity between TCR sequences. This analysis is focused on the alpha and beta chains of TCRs from mouse and human samples, which are part of the immune system's mechanism for recognizing and responding to pathogens.

In the context of immunology, TCRs are highly variable receptors that enable T cells to recognize a vast array of antigens presented by the major histocompatibility complex (MHC) on the surface of other cells. The unique variability in the TCR regions, especially the Complementarity Determining Regions (CDRs), is crucial for the immune system's ability to respond to diverse pathogens.  
  
Regarding the images which represent the results from the UMAP dimensionality reduction applied to the TCRdist matrices:

The mouse data shows clusters of TCR sequences with similar characteristics, which likely correspond to TCRs that recognize similar antigens. The clustering pattern is relatively spread out, indicating diversity in the TCR repertoire.

The human data also shows clustering, which indicates that certain TCR sequences are more similar to each other than others, likely due to common antigen recognition.

Weights (weights\_a and weights\_b) are assigned to different regions, such as the CDR3, to emphasize their importance in antigen recognition. In the provided code, the cdr3 regions are given a weight of 3, reflecting their critical role in specificity, as the CDR3 region is the most variable and directly interacts with the peptide presented by MHC molecules. The weights of the hypterparameter was chosen after tedious process of predictions from the KNN algorithm.

Hamming distance is used for its simplicity and effectiveness in capturing sequence similarity.

Other distance metrics were tried out like the default and Euclidean distance , hamming distance had given the better accuracy of them all.

The ability to discern subtle differences between TCR sequences is critical because small changes can significantly alter antigen specificity. UMAP's preservation of both local and global structures helps in identifying clusters that might represent TCRs targeting the same antigen or similar antigens. This is crucial in understanding the immune response, which is often the goal of such analyses. This clearly shown in the clusters formed and shown in the UMAP dimension reduction algorithm.

The choice between UMAP and other dimensionality reduction methods should be based on the specific requirements of the data and the goals of the analysis. For the visualization of complex immunological datasets where both local similarity (fine-grained clustering of very similar TCRs) and broader trends (such as the overall diversity of the TCR repertoire) are important, UMAP is often the preferred choice.

1. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9719034/

2. https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2021.640725/full

3. https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2020.01803/full

4.https://www.annualreviews.org/content/journals/10.1146/annurev-immunol-082119-124838

5.https://elifesciences.org/reviewed-preprints/88837v1#abstract

6. Vujovic M, Degn KF, Marin FI, Schaap-Johansen AL, Chain B, Andresen TL, Kaplinsky J, Marcatili P. T cell receptor sequence clustering and antigen specificity. Comput Struct Biotechnol J (2020) 18:2166–2173. doi:10.1016/j.csbj.2020.06.041

A map of different colored dots

Description automatically generated

A diagram of a number of dots

Description automatically generated with medium confidence

Modeling for TCRDist

After calculating the similarity distance with TCRDist, this metric will be utilized for prediction purposes. Given that the extracted data already constitutes a similarity matrix, it will be concatenated with our primary dataset, excluding the CDR3 region, which is already depicted as a matrix within the dataset. To establish a foundational understanding of feature significance and to obtain preliminary predictive outcomes, a baseline model is constructed using a random forest algorithm. This methodology will be applied specifically to human data concerning the Alpha and Beta chains.

the considerable imbalance present in the dataset was addressed by designating epitopes as the target variable. Categorical variables within the dataset were transformed using one-hot encoding before being input into a random forest model. This preprocessing approach was also employed to establish a baseline model for GIANA. Furthermore, the Grid Search CV method was utilized to determine the optimal number of estimators. Both TCRDist and GIANA demonstrated promising outcomes; however, GIANA slightly outperformed TCRDist in the baseline model comparison.

The top 50 features of importance were derived from the random forest algorithm. As illustrated in the accompanying graph, it is evident that all the features represented originate from the matrix itself. Notably, none of the variables from the original dataset, such as j\_a\_gene, v\_b\_gene, and v\_a\_gene, contribute significantly to the results.

A graph of a number

Description automatically generated with medium confidence

As we can see from the above graph, the distance matrix forms an important part of the prediction. So now, we filter the data into having epitopes and distance matrix only to be pushed into an algorithm.

Consequently, the data is refined to include only epitopes and the distance matrix, which are then input into a predictive algorithm. Among the myriad supervised learning algorithms suitable for leveraging distance matrices, the k-nearest neighbors (KNN) algorithm stands out. Renowned for its nonparametric approach, KNN contrasts sharply with parametric models, which require adherence to a preset distribution. The KNN algorithm is particularly efficacious in cases where the data forms complex clusters or groups. It operates by computing distances from a query instance directly to training instances, thus allowing for an adaptive evaluation of interrelationships within the dataset. This process is elaborated upon in the study available at this (<https://link.springer.com/content/pdf/10.1007/s10472-023-09882-x.pdf>). In this context, sequence similarity typically encoded as vectors within a multidimensional space plays a pivotal role. The KNN algorithm effectively utilizes these distance calculations to predict attributes or classify data points, providing a sophisticated method in biological data analysis.

we employ the GIANA and TCRDist similarity distance matrices as inputs to the K-Nearest Neighbors (KNN) model. Due to the data imbalance, epitopes represented fewer than five times in the datasets were excluded. This approach ensures the robustness of the KNN model, which utilizes these matrices as precomputed distance metrics. Typically, KNN algorithms utilize Euclidean, Manhattan, or cosine similarity measures. In our methodology, we integrated the precomputed distances from GIANA and TCRDist into the KNN framework. After extensive testing on both mouse and human data concerning the Alpha+Beta chains, we observed superior performance from the GIANA model compared to the TCRDist model. This phase of the study also included hyperparameter tuning to ascertain the optimal k value for the model.

Results

Random forest Baseline model utilizing TCRDist data, exhibits high accuracy, suggesting overall correct predictions. Nevertheless, the significant disparity between accuracy and other performance. The model demonstrates low precision and recall, indicating a tendency to misclassify instances and overlook numerous positive cases. Consequently, the F1 score is also low, reflecting suboptimal performance. Whereas, baseline model based on GIANA, shows lower accuracy than TCRDist model but better performance across other metrics, suggesting a more balanced approach to class prediction. It achieves higher precision, indicating more reliable positive predictions, and superior recall, which suggests it is more effective at identifying positive instances. The higher F1 score further confirms that GIANA model maintains a better balance between precision and recall. Comparing both models, between precision and recall, GIANA is evidently the superior model. It not only provides more reliable predictions but also captures a broader spectrum of positive instances. All this analysis was done using the Alpha+Beta chain of humans and mouse.

After establishing a reference point(baseline model) for evaluating the performance of our next model KNN. As we have already reduced the data with epitopes less then 5 representation.

KNN algorithm using TCRDist demonstrates a viable method for predicting T-cell receptor (TCR) epitope specificity, with distinct performances observed between human and mouse models. The model achieves an accuracy of 68.53% in humans and 82.84% in mice, indicating better performance with mouse TCR data. This discrepancy may be attributed to differences in immune system complexity, data quality, or TCR repertoires between species. While the results are promising, especially for mice, there is potential for further improvement in the algorithm's precision and accuracy, particularly for human data.

the GIANA framework to predict epitope specificity demonstrate significantly better performance in mice than in humans. For mice, the precision, recall, F1 score, and accuracy are notably high (0.82, 0.83, 0.82, and 0.83, respectively), indicating a robust ability of the model to accurately predict and correctly identify true positives. In contrast, the results for humans show lower values across these metrics (0.52, 0.62, 0.55, and 0.62, respectively), suggesting challenges in the model's efficacy likely due to the complex nature of the human immune system.

TCRDist using KNN- Humans

Results for K=5:

Accuracy: 0.6853

Precision: 0.6290

Recall: 0.6853

F1 Score: 0.6488

A graph of a line

Description automatically generated with medium confidence

TCRDist using KNN- Mouse

Results for K=5:

Accuracy: 0.8284

Precision: 0.8441

Recall: 0.8284

F1 Score: 0.8303

A graph of a graph

Description automatically generated with medium confidence

GIANA using KNN- humans

Precision: 0.52

Recall: 0.62

F1 Score: 0.55

Accuracy: 0.62

GIANA using KNN- mice

Precision: 0.82

Recall: 0.83

F1 Score: 0.82

Accuracy: 0.83

The assertion that TCRDist is more suited for human TCR data analysis due to its higher precision, recall, F1, and accuracy scores. Meanwhile, both GIANA and TCRDist deliver comparably high performance for mouse data, which supports the use of either algorithm when working with mice in predicting TCR epitope specificity using KNN. This balance highlights the need to select an algorithm based on specific performance strengths relevant to the species and data characteristics.