Early Stage Cancer Detector: Identifying Future Lymphoma Using Epigenomics Data

Category: Life Sciences

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Objective

DNA methylation is an epigenetic process affecting gene expression which has been linked to cancer. We use this biomarker to **classify future Lymphoma,** a group of cancers beginning in white blood cells of the immune system. The Optimizing Metric for the classification model is **F1 Score**.

Data

DNA methylation

- 566 blood samples from two cohorts (m)
- 444,000 genomic probes (n)

y	sex	A_23_P100001	A_23_P100011	A_23_P100022	A_23_P100056
1	1	6.402494	5.799493	3.447526	5.439588
1	2	6.786831	3.320382	4.830281	4.955008

Immune cell fractions

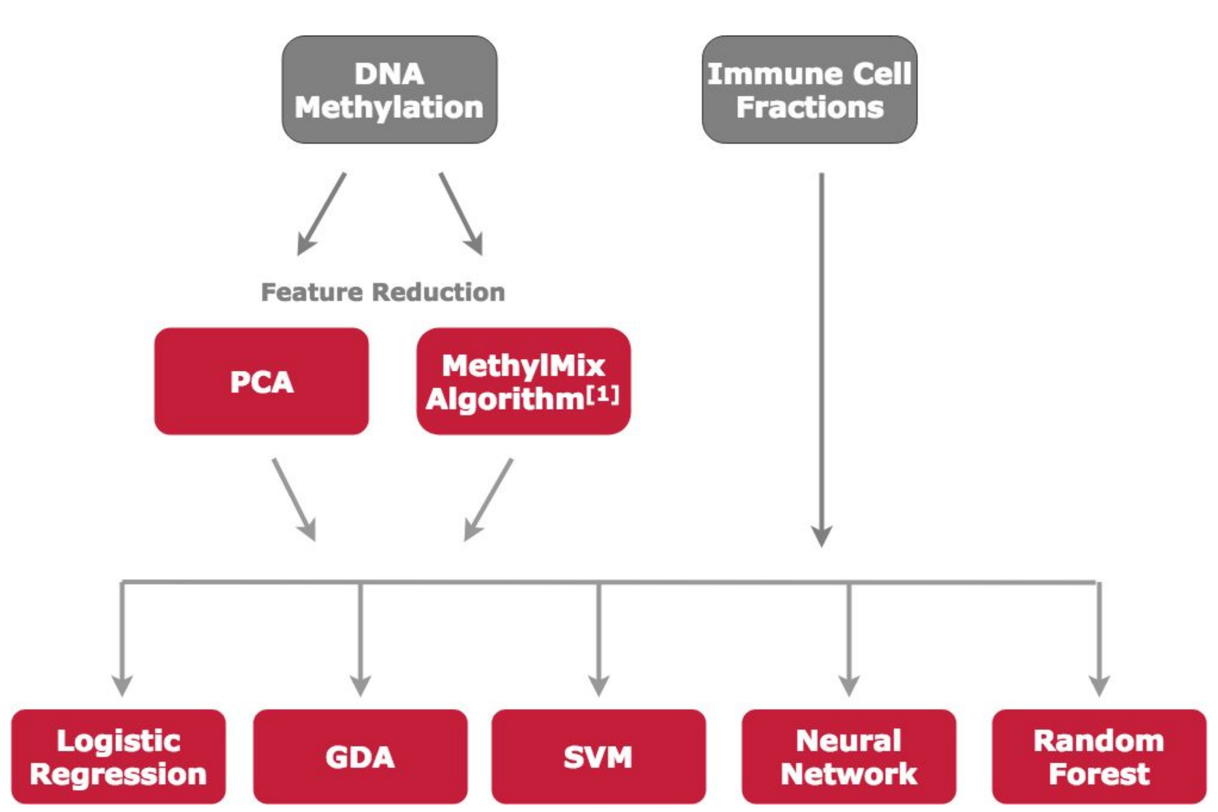
- 196 blood samples (m)
- 23 fractional components of blood (n)

Y	B.cells.naive	B.cells.memory	Plasma.cells	T.cells.CD8	T.cells.CD4.naive
0	0.0	0.030000	0.027737	0.012134	0.090172
0	0.0	0.036672	0.025804	0.001736	0.000000

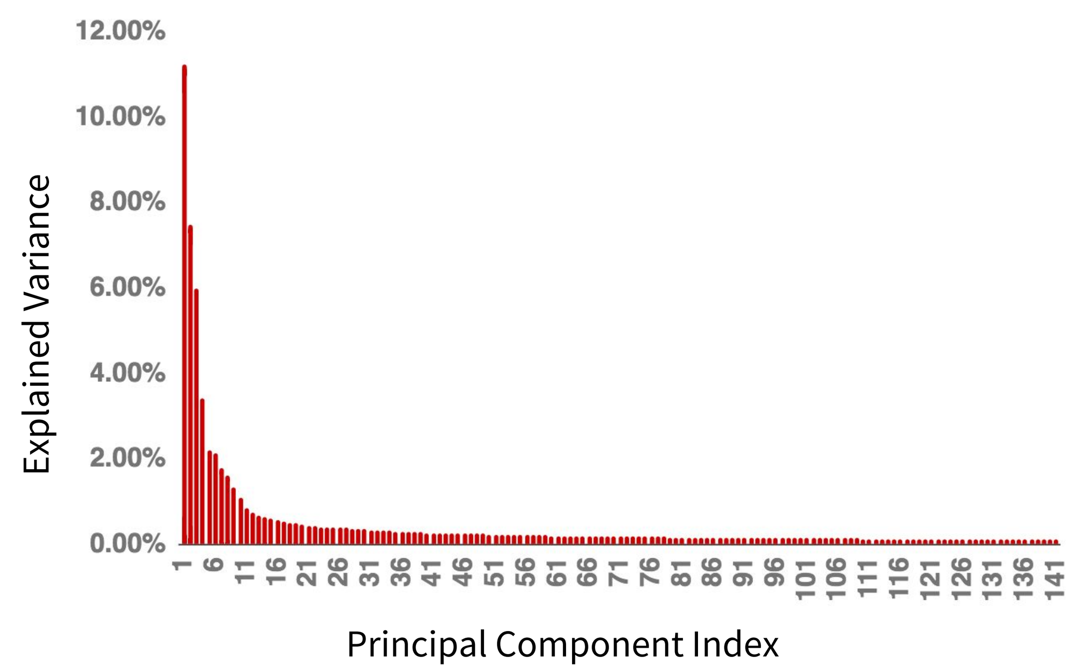
Challenges : Small data set, biological noise

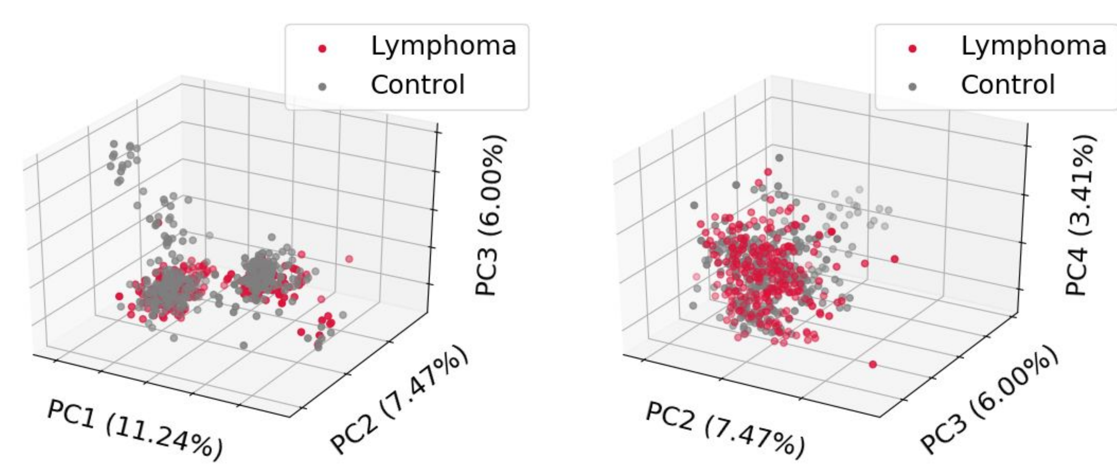
Methods

DNA methylation data is noisy with correlation across gene probes. **Feature selection** and **normalization** techniques are useful precursors to supervised learning techniques.



Feature Selection Techniques





Classification Models

Logistic Regression

$\phi(z) = log(1 + e^{(-z)})$

Techniques: L2 Regularization, Ensembling, k-Fold Cross Validation

Support Vector Machines

$\phi(z) = \max(1 - z, 0)$

Techniques: Polynomial, Gaussian RBF Kernel, Regularization

Gaussian Discriminant Analysis : MLE
Techniques : Box-Cox Transforms

$$y_i^{(\lambda)} = \begin{cases} \dfrac{y_i^\lambda - 1}{\lambda} & \text{if } \lambda \neq 0, \\ \ln y_i & \text{if } \lambda = 0, \end{cases}$$

Neural Networks

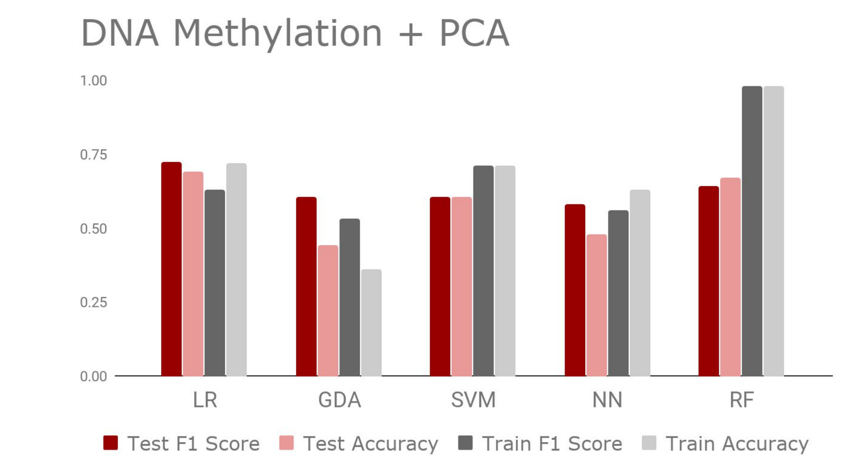
$J(y, \hat{y}) = -(Ylog(\hat{y}) + (1-y)\ log(1-\hat{y}))$

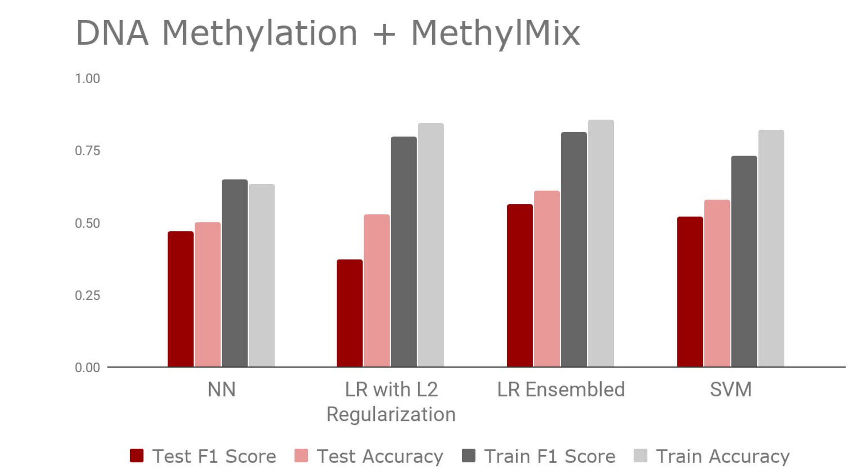
Techniques: ReLU, Sigmoid activations, L2 Regularization, Drop Out, Early Stopping, Learning Rate Decay, Adam Optimizer, Hyperparameter Tuning, Threshold Variation

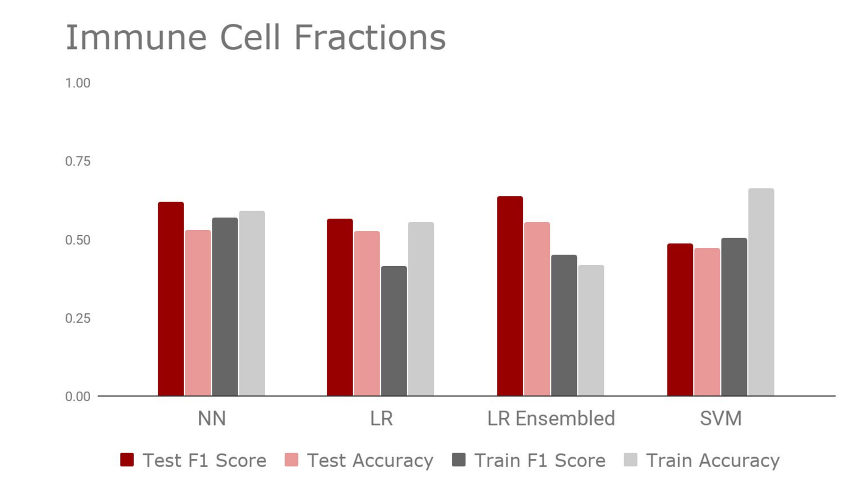
Random Forest : Gini Loss $\sum_c \hat{p}_c(1 - \hat{p}_c)$

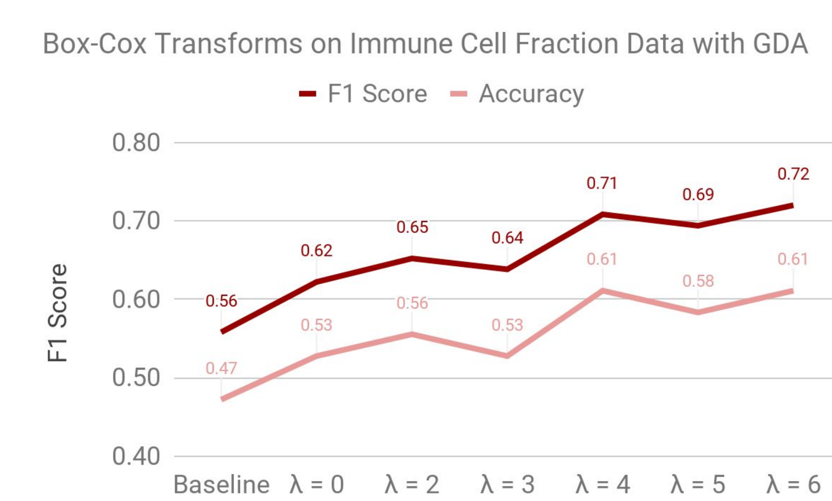
Techniques : Boosting, Hyperparameter Tuning

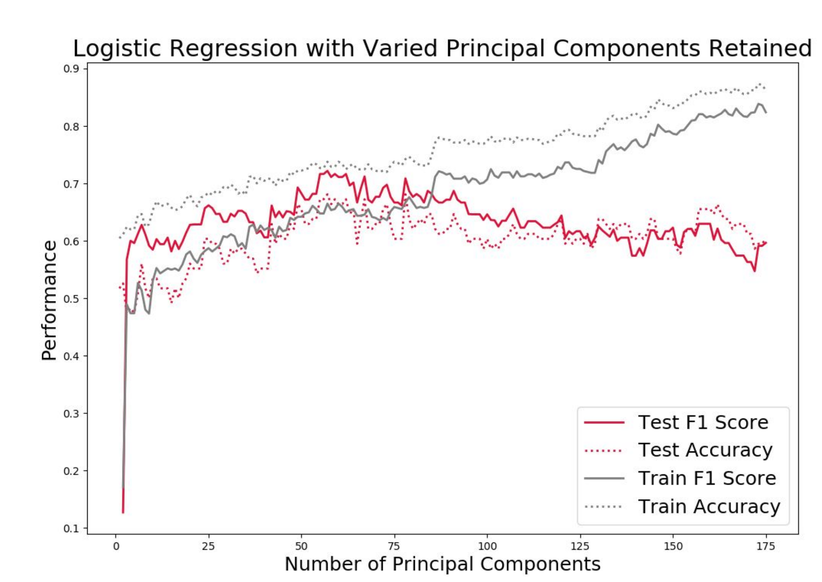
Results











Discussion

Best Lymphoma Predictor
Dataset : DNA Methylation
Features : First 59 Principal Components
Model : Logistic Regression
Test F1 Score : 72%, Test Accuracy : 69%

PCA outperforms MethylMix algorithm

The MethylMix Algorithm is used to identify disease related hyper- and hypo-methylated genes[1]. However, all models performed better on DNA Methylation + PCA dataset as compared to DNA Methylation + MethylMix dataset. PCA may be a better feature reduction technique in the context of lymphoma detection.

Immune Cells Fractions: Transform induces normality

GDA works well if the data is Gaussian. GDA's performance improved with when x was transformed using Box-Cox transforms. Normalization of the data is useful given the biological noise.

Bias Variance Trade-Offs

1. Logistic Regression: Ensembling reduced variance
2. Neural Networks, Random Forests: High Variance
3. GDA: High Bias, best model for immune cell fractions dataset (small dataset) with power transform

Future

- Model and dataset ensembling
- Pair with microRNA expression data
- Map feature importance to genes
- Softmax classification of lymphoma subtypes

References

[1] P.-L. Cedoz, M. Prunello, K. Brennan, and O. Gevaert, "MethylMix 2.0: an R package for identifying DNA methylation genes," Bioinformatics, vol. 34, no. 17, pp. 3044–3046, 2018.

Acknowledgements

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