

1. Introduction

Depression, a leading cause of disability [1], lacks objective diagnostic tools [2]. Metabolomics, which analyzes small molecules, holds promise for improving diagnosis and understanding [2]. Despite the complexity of metabolomics data, deep learning methods have not been extensively explored due to issues with interpretability [3].

2. Research Questions

Q1: How well can biologically interpretable deep learning model, MetaboNet, trained on metabolomics predict depression?
Q2: Can MetaboNet identify biologically relevant metabolites and pathways associated with depression?

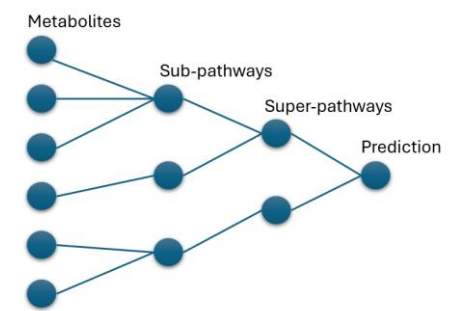
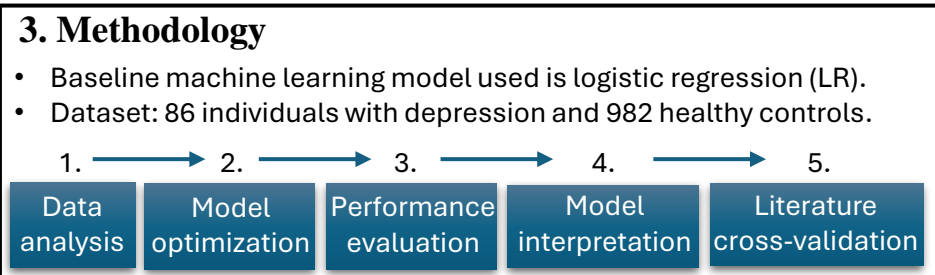


Figure 1: MetaboNet constructed using prior biological knowledge about biochemical sub-pathways and super-pathways. This architecture makes the network inherently interpretable and lightweight.

4. Results Q1

Metric	MetaboNet	LR	p-value
MCC	0.171 ± 0.066	0.148 ± 0.078	0.023
F1 score	0.236 ± 0.043	0.225 ± 0.068	0.173
PR-AUC	0.189 ± 0.060	0.160 ± 0.044	2 · 10 ⁻⁴
ROC-AUC	0.702 ± 0.054	0.650 ± 0.060	5 · 10 ⁻⁹

Table 1: Classification performance metrics with paired t-test p-values. Random baselines are: 0 for MCC, 0.08 for F1 score and PR-AUC, and 0.5 for ROC-AUC.

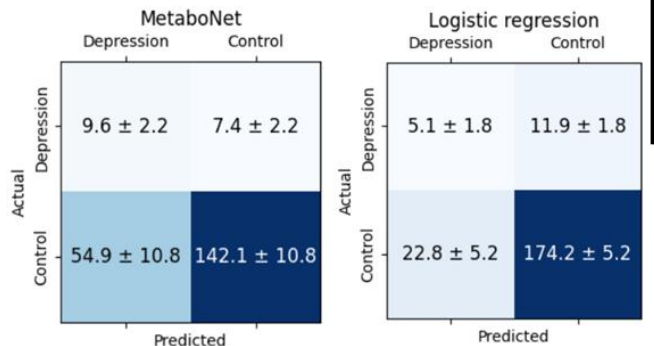


Figure 2: Averaged confusion matrix. MetaboNet shows better identification of depressed individuals.

5. Results Q2

- Metabolite level not validated
- Top sub-pathways validated by literature:
 - Food component/plant [4]
 - Leucine, isoleucine and valine [5]
 - Benzoate metabolism [6]
 - Fatty acid dicarboxylate [7]
- Top super-pathway, lipids, also validated by literature [8]
- Limited research in metabolomics and depression to validate our findings.

- MetaboNet statistically significantly outperforms LR in key metrics.
- Classification results revealed sex-related differences, with better performance observed in females.

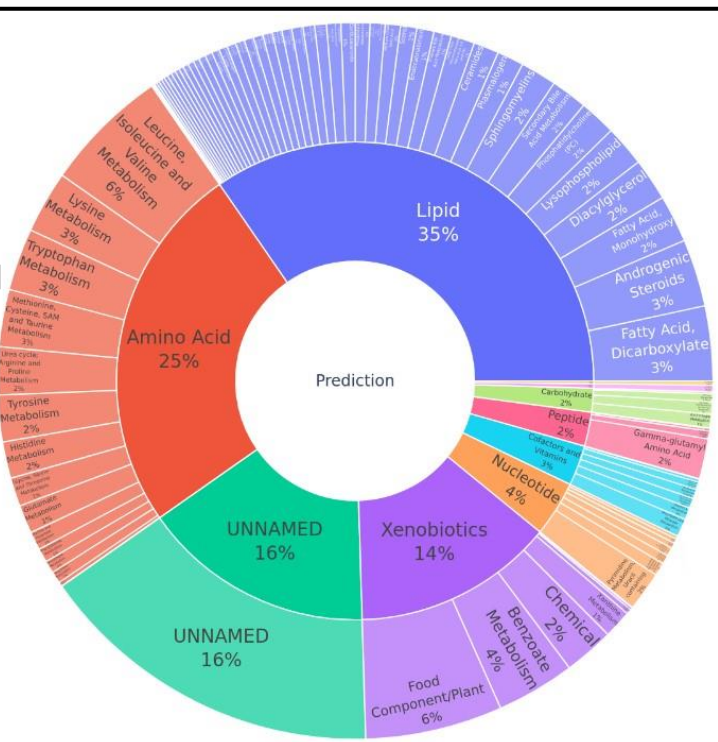


Figure 3: MetaboNet biochemical pathways relative importance sunburst. The outer ring is sub-pathways and the inner ring is super-pathways.

6. Future research

Need for unbiased, diverse, and large datasets for studying depression. MetaboNet can suggest important factors, but experimental validation is necessary to confirm.

7. Conclusions

Q1: MetaboNet outperforms LR, though the overall classification performance remains modest.
Q2: Findings do not support the capability of MetaboNet to identify biologically relevant individual metabolites. However, MetaboNet shows promise in identifying relevant biochemical sub-pathways and super-pathways.

