nature

TRANSFER LEARNING ENABLES PREDICTIONS IN NETWORK BIOLOGY

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ABOUT THE PAPER

Core Idea: Demonstrating and validating **transfer learning** to boost predictive performance

The Model: Geneformer, a neural network built to leverage vast biological data.

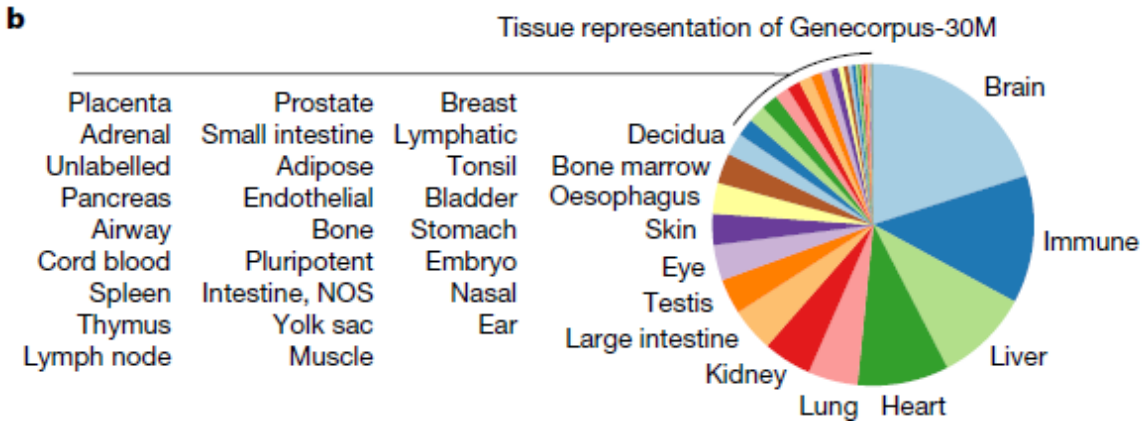
Key Advantage: Achieves **superior prediction accuracy** by fine-tuning a pre-trained model, outperforming models trained from scratch.

Leveraging Prior Knowledge: Pre-trained on a **massive corpus of 30 million single-cell transcriptomes**

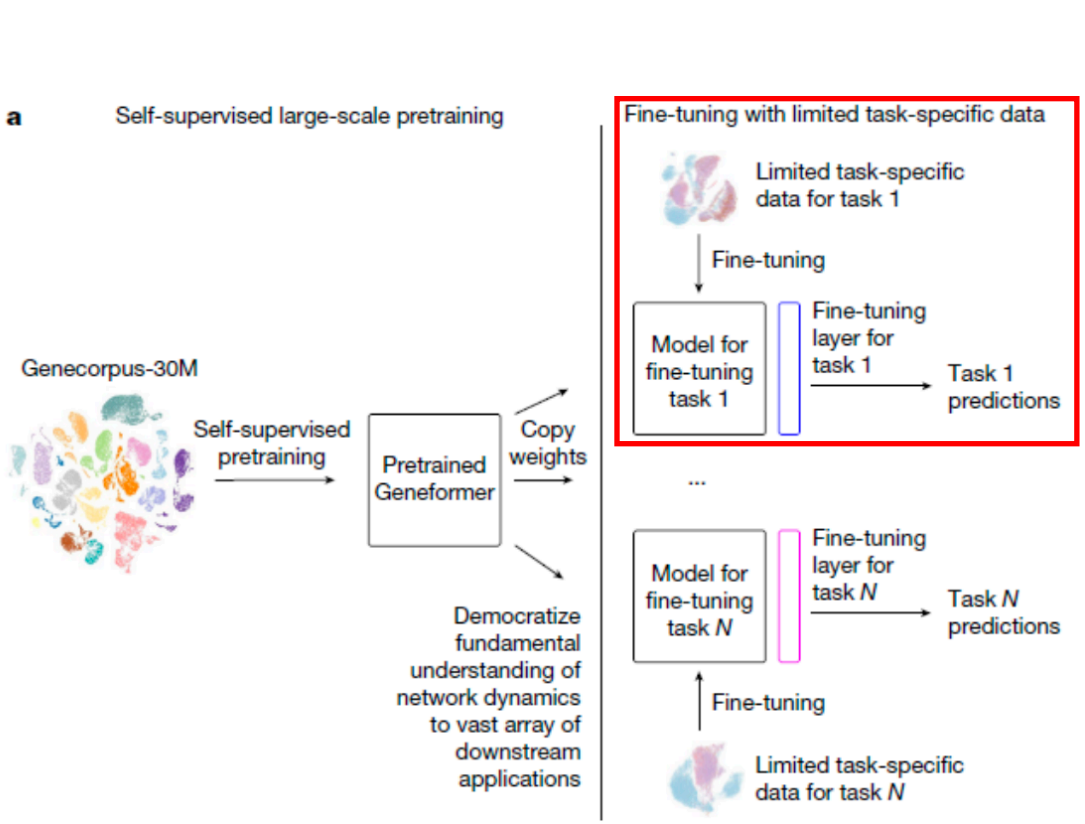
Broad Applications: Applicable across various network biology areas, including:

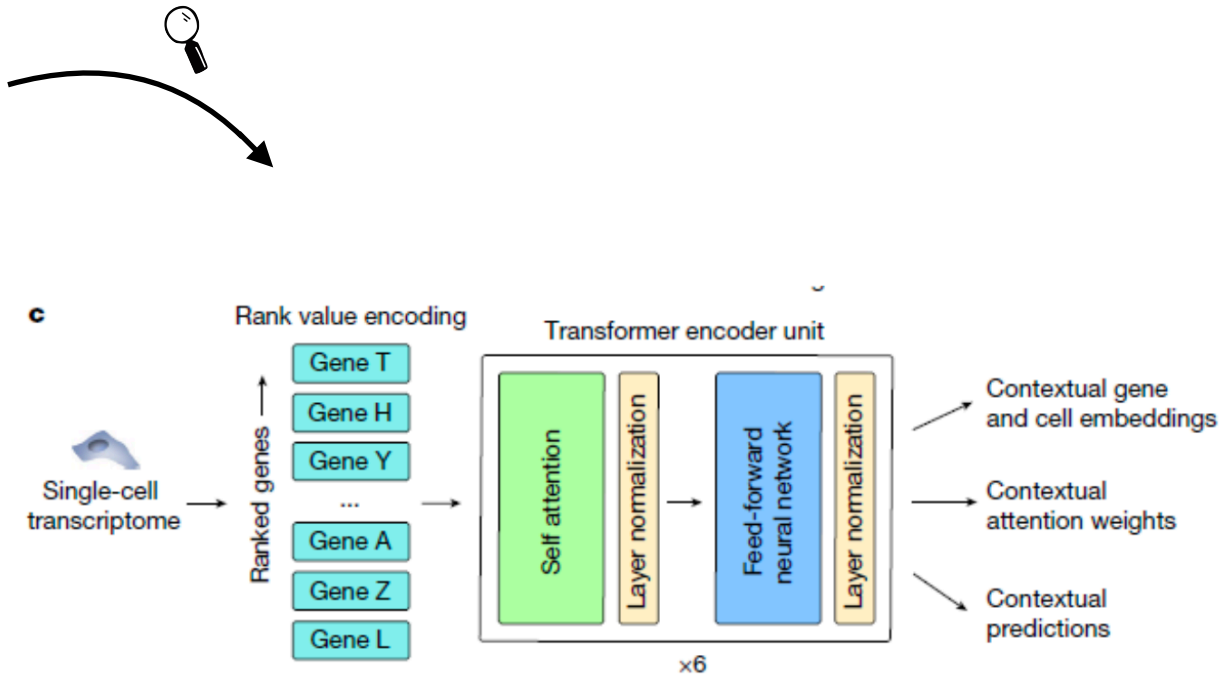
- Protein-protein interaction networks
- Gene regulatory networks
- Predicting gene function
- Identifying disease-associated genes

Biological significance: Discovery of promising therapeutic agents and targets



THE MODEL

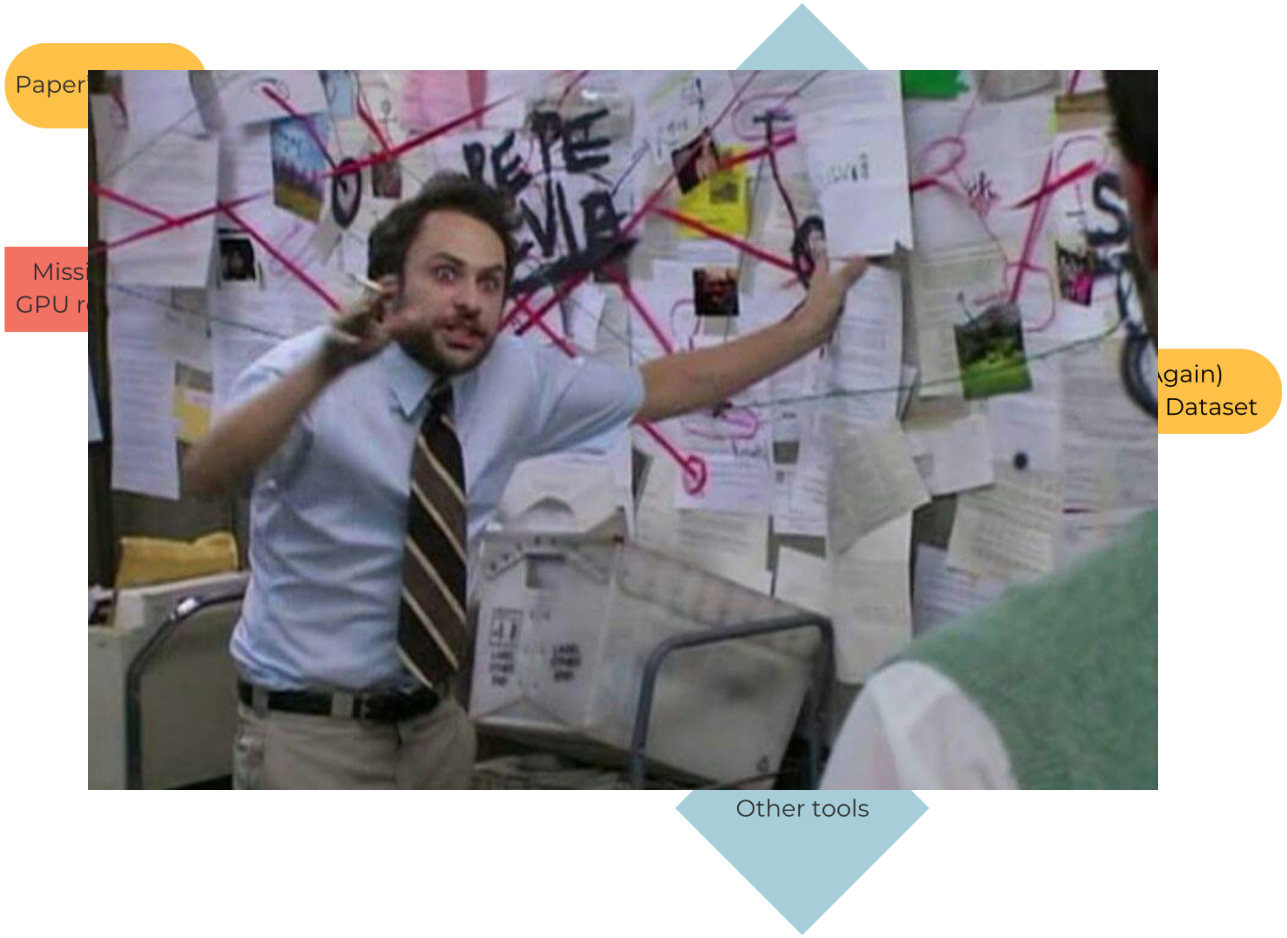

a
Self-supervised large-scale pretraining
Genecorpus-30M
Self-supervised pretraining
Pretrained Geneformer
Copy weights
Democratize fundamental understanding of network dynamics to vast array of downstream applications
Fine-tuning with limited task-specific data
Limited task-specific data for task 1
Fine-tuning
Model for fine-tuning task 1
Fine-tuning layer for task 1
Task 1 predictions
...
Model for fine-tuning task N
Fine-tuning layer for task N
Task N predictions
Fine-tuning
Limited task-specific data for task N


c
Rank value encoding
Transformer encoder unit
Single-cell transcriptome
Ranked genes
Gene T
Gene H
Gene Y
...
Gene A
Gene Z
Gene L
Self attention
Layer normalization
Feed-forward neural network
Layer normalization
×6
Contextual gene and cell embeddings
Contextual attention weights
Contextual predictions

TASK 1

CELL CLASSIFICATION

WORKFLOW



Functional Human Thymus (GSE159745)

- mTECs
- cTECs

FACS-isolation to separate the 2 distinct epithelial cell populations

Processed on the 10x Genomics Chromium Platform

Sequenced using Illumina HiSeq 4000

```
AnnData object with n_obs × n_vars = 11176 × 23937
    obs: 'sample_id', 'n_genes', 'cell_type', 'n_counts'
    var: 'gene_symbols', 'feature_types', 'n_cells', 'ensembl_id'

AnnData object prepared for Geneformer and saved to ../data/human_thymus_for_geneformer.h5ad
```

WORKFLOW (II)

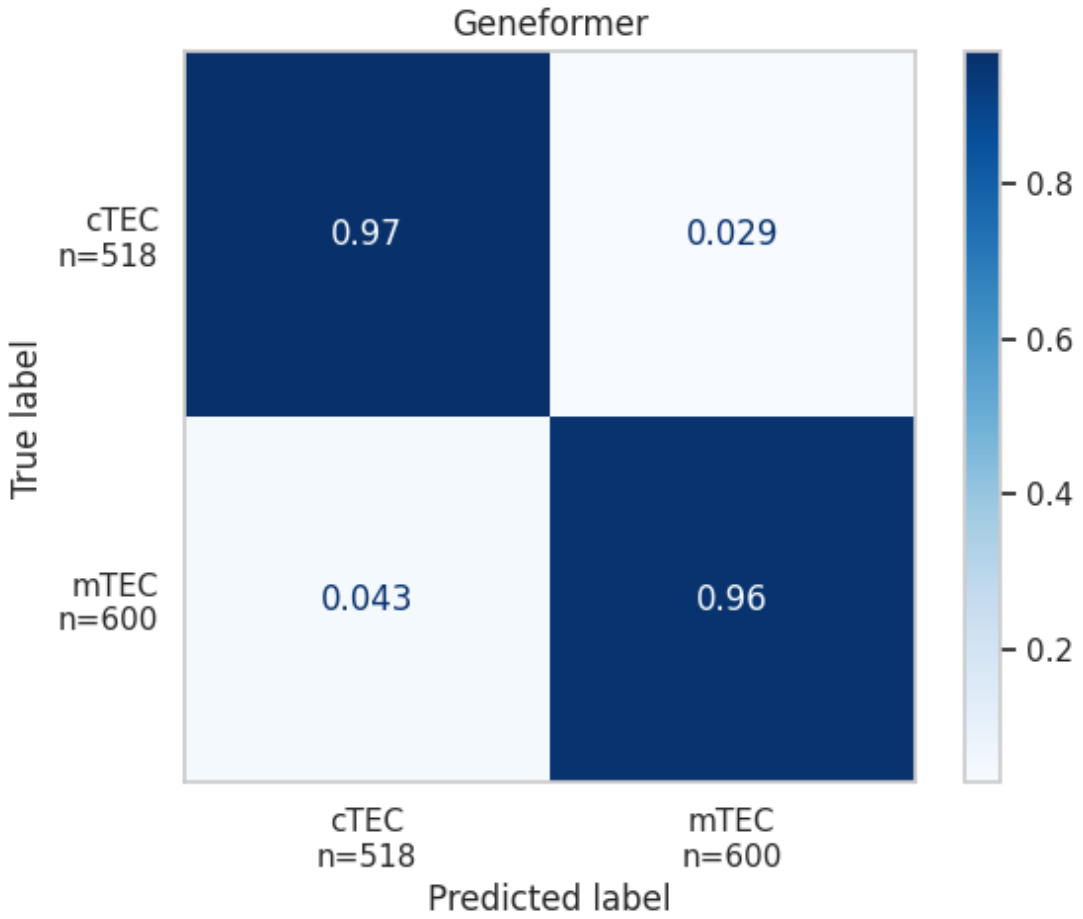
- Tokenization (tk.tokenize_data)
  - 2048 or 4096 models (depending on the model)
- classifier.prepare
  - 70% training, 15% validation, 15% testing
- classifier.validate

- classifier.evaluate_saved_model
- Plots
  - Confusion Matrix
  - Metrics
  - ROC curve
  - UMAP

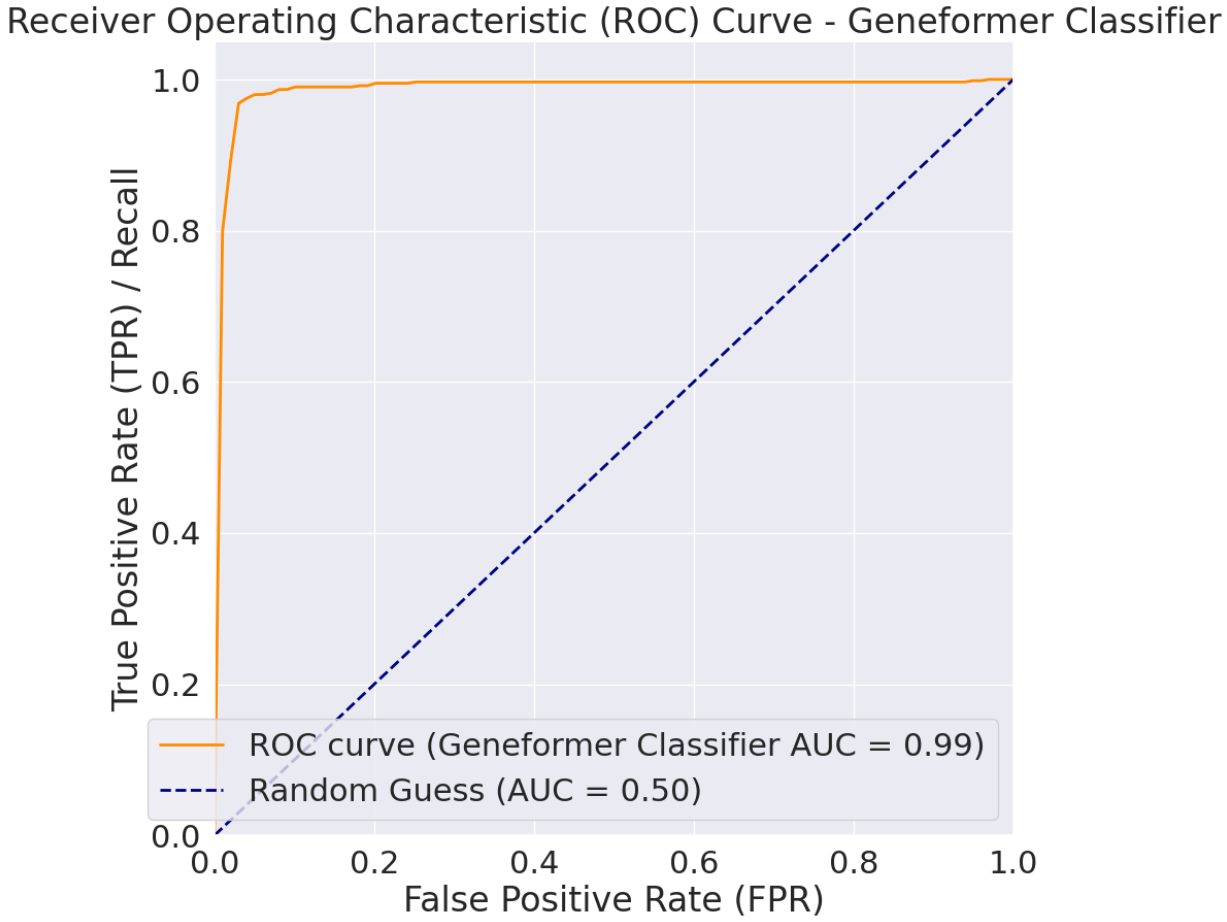
[2236/2236 03:26, Epoch 2/2]

Epoch	Training Loss	Validation Loss	Accuracy	Macro F1
1	0.310500	0.326618	0.899821	0.899551
2	0.155900	0.132791	0.957961	0.957936

RESULTS (I)

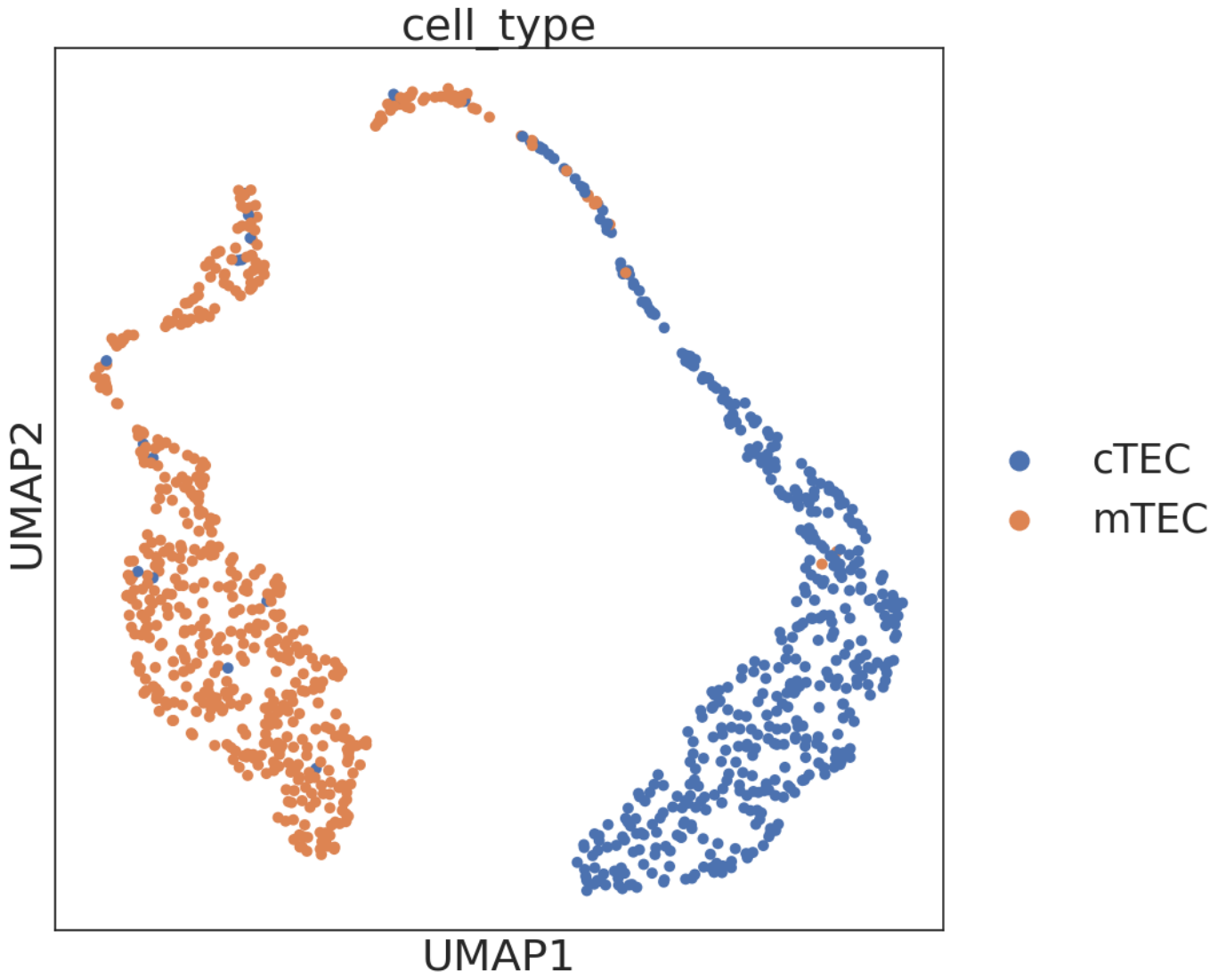



```
{'conf_matrix':       cTEC  mTEC
 cTEC   503    15
 mTEC    26   574,
 'macro_f1': np.float64(0.963178869018213),
 'acc': 0.9633273703041145,
```



RESULTS (II)

- Clear separation between populations
- The thymus has distinct cortical (cTEC-rich) and medullary (mTEC-rich) regions



RESULTS (III)

Original claim: Geneformer outperforms models trained from scratch

Explanation: Well separated clusters?

FINAL RESULTS:

Model	Accuracy
Logistic Regression (baseline)	0.969
Logistic Regression (tuned)	0.969
Random Forest (baseline)	0.976
Random Forest (tuned)	0.972
XGBoost (baseline)	0.983
XGBoost (tuned)	0.984

Conclusion: Geneformer achieved indeed high accuracy score, but maybe it is better for more complex tasks.

TASK 2

GENE CLASSIFICATION

INITIAL GOALS VS. ACHIEVED OUTCOMES

Goals:

- Examine dosage sensitivity
- Run Geneformer
- Run SVM, RF, LR
- Compare Results between Geneformer and other classifiers
- Find best performing classifier for binary classification of gene dosage sensitivity

Status:

- Classified 2033 genes in terms of dosage sensitivity
- Pretrained and finetuned SVM, RF, LR AND GNB, XGBoost
- RF and XGBoost emerged best performing classifiers for binary classification of gene dosage sensitivity

WORKFLOW (I)

Data Transformation

- Gene Expression file -> shape: (26874, 10281)
- Highly Variable Genes list -> 2033 genes
- AnnData object created and filtered down to 2033 HVG
- shape: (2033, 10281) (Genes x Cells)

Dosage Sensitivity

- Created Label Dataframe: df_labels
- Merge with AnnData object
- 0 for dosage sensitive 21
- 1 for dosage insensitive 19
- NaN for genes that had no match in the df_labels 1933

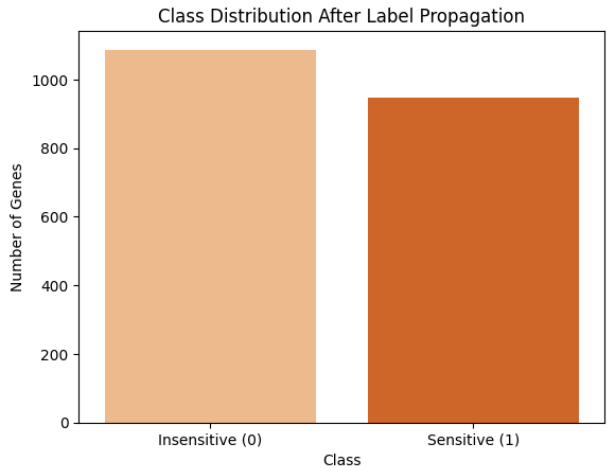
1

2

3

Pretraining & Label Propagation

- Self-Training on gene expression levels
- Train RF classifier on labeled data
- Predict labels iteratively



WORKFLOW (II)

Hyperparameter Tuning

4

- 5-fold Cross Validation
- Train tuned models

5

Model Analysis

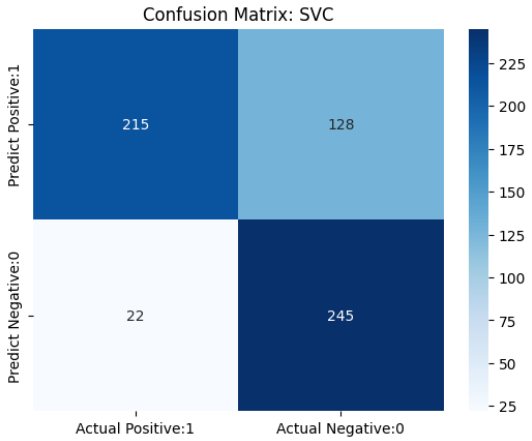
- Test Tuned Models (test set size: 30% of the original)
- Best Performing Classifier -> RandomForest
- Train tuned RandomForest classifier on whole dataset

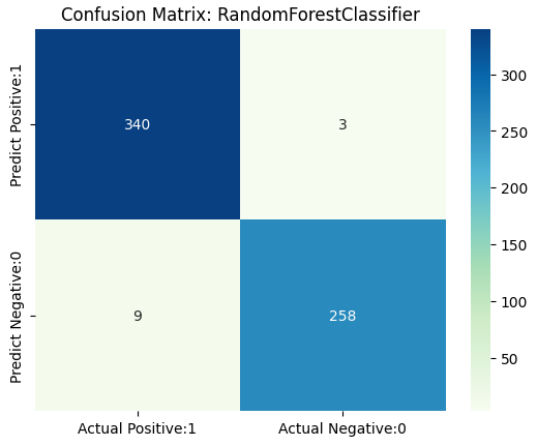
Model	Best AUC	Best Param Combo
Logistic Regression	0.7128	C=0.01, l1_ratio=0.0
Gaussian Naïve Bayes	0.6714	var_smoothing=0.01
Support Vector Machines	0.7654	kernel='rbf', C=1, gamma='scale'
Random Forests	0.9934	n_estimators=200, max_depth=20, min_samples_split=5, min_samples_leaf=1
XGBoost	0.9925	n_estimators=100, max_depth=6, learning_rate=0.1, subsample=1.0, colsample_bytree=0.8

Model	Best AUC
Logistic Regression	0.6869
Gaussian Naïve Bayes	0.6346
Support Vector Machines	0.7722
Random Forests	0.9788
XGBoost	0.9732

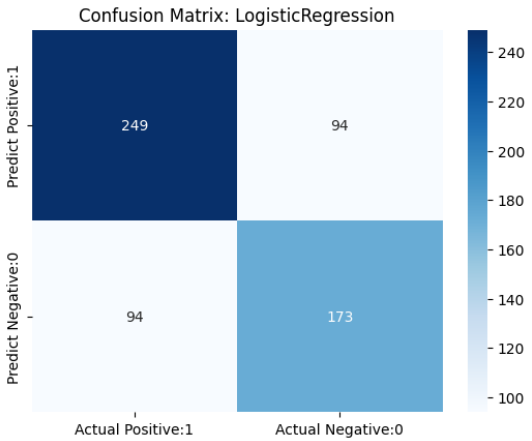
Random Forests	0.9788	(95% CI: 0.9656-0.9896)
XGBoost	0.9732	(95% CI: 0.9582-0.9852)

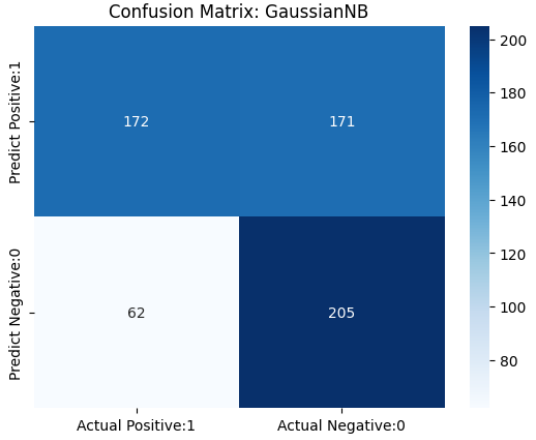
RESULTS

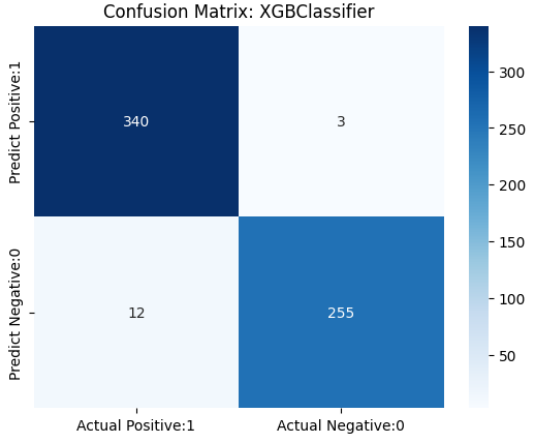


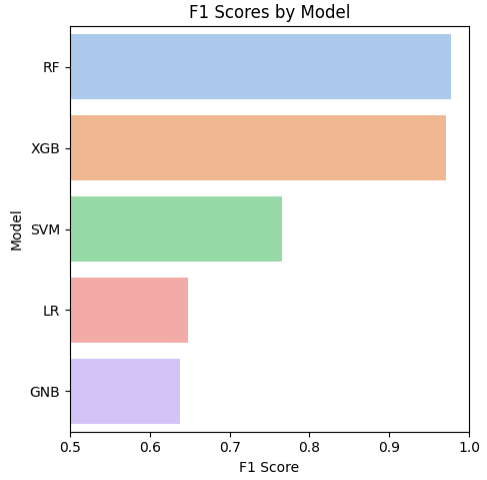


Their approach:









NEXT STEPS

- Run Geneformer with new raw data
- Compute AUC, F1 metrics and produce confusion matrix
- Compare Results between Geneformer and other classifiers

THANK YOU!