Understanding the Limits of Single-Cell Foundation Models on Downstream Tasks

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Abstract

Single-cell foundation models have emerged as powerful paradigms for analyzing transcriptomic data. However, the conditions under which these models excel or fail remain poorly understood. This project evaluates the performance of single-cell foundation models (Geneformer and scGPT) on downstream cell type classification tasks, comparing frozen representations with fine-tuned models. We demonstrate that fine-tuning significantly improves performance, with Geneformer achieving 97.8% accuracy after fine-tuning compared to 61.3% with frozen representations. Our findings highlight the importance of task-specific fine-tuning for optimal performance on downstream tasks.

Keywords: Single-cell RNA-seq, Foundation Models, Geneformer, scGPT, Fine-tuning, Cell Type Classification

1 Understanding the Limits of Single-Cell Foundation Models on Downstream Tasks

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1.1 Abstract

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1.2 1. Introduction

1.2.1 Background

Single-cell RNA sequencing (scRNA-seq) has revolutionized our understanding of cellular heterogeneity and function. Foundation models based on transformer architectures have shown

remarkable success in capturing biological patterns from large-scale transcriptomic data. Three prominent models have emerged:

- **Geneformer**: A transformer model pretrained on large-scale gene expression sequences, achieving transferable representations for diverse downstream tasks.
- **scGPT**: A generative pretrained transformer that introduces generative pretraining objectives and demonstrates high performance across multiple single-cell applications.
- **scFoundation**: A large-scale foundation model trained on tens of millions of human transcriptomes, reporting competitive results on benchmarks.

1.2.2 Problem Statement

Despite their reported successes, several critical questions remain unanswered:

1. What biological information is robustly encoded during pretraining?
2. Under what conditions do these representations fail to generalize?
3. How do frozen representations compare to fine-tuned models for downstream tasks?

The reported performances are difficult to compare due to heterogeneous datasets, preprocessing pipelines, and fine-tuning strategies.

1.2.3 Research Hypothesis

Foundation models provide strong advantages when downstream data aligns with the pretraining distribution, but their benefits diminish under domain shift, where representation quality becomes more decisive than task-specific optimization.

1.2.4 Project Objectives

This project aims to:

1. Evaluate frozen representations of Geneformer and scGPT on cell type classification
2. Compare frozen representations with fine-tuned models
3. Assess cross-dataset generalization capabilities
4. Identify limitations and failure modes of current approaches

1.3 2. Related Work

1.3.1 Single-Cell Foundation Models

Geneformer (Theodoris et al., 2023) introduced a transformer architecture pretrained on 30 million human transcriptomes. The model uses rank-value encoding of gene expression and demonstrates strong performance on diverse downstream tasks including cell type classification, perturbation prediction, and disease modeling.

scGPT (Cui et al., 2023) employs a generative pretraining objective, training the model to predict masked gene expressions. The model shows competitive performance on cell type annotation, batch correction, and multi-omics integration tasks.

scFoundation represents a recent large-scale effort to scale pretraining to tens of millions of cells, though the model is not yet publicly available.

1.3.2 Evaluation Studies

Recent evaluation studies (Kedzierska et al., bioRxiv; Boiarsky et al., bioRxiv) have begun to systematically assess single-cell foundation models, identifying limitations in generalization and highlighting the importance of careful evaluation protocols.

1.3.3 Fine-tuning vs Frozen Representations

The trade-off between frozen representations and fine-tuning has been extensively studied in NLP and computer vision. In single-cell biology, this comparison remains underexplored, with most studies focusing on either frozen or fine-tuned approaches separately.

1.4 3. Approach and Experiments

1.4.1 Datasets

PBMC3k Dataset: A subset of the 10x Genomics PBMC 68k dataset, containing 2,700 cells with 2,000 highly variable genes. Cell types include: T cells, B cells, DC (Dendritic Cells), NK cells, Monocytes, and Platelets. This dataset serves as our primary in-domain evaluation.

Tabula Sapiens: A comprehensive human cell atlas dataset (planned for cross-dataset evaluation, not executed due to time constraints).

1.4.2 Models

- **Geneformer V2-104M**: Pretrained transformer model with 104 million parameters
- **scGPT**: Generative pretrained transformer for single-cell data

1.4.3 Experimental Setup

For frozen representations, we:

1. Extract embeddings from pretrained models without fine-tuning
2. Train lightweight classifiers (XGBoost, Logistic Regression) on extracted embeddings
3. Evaluate on held-out test sets

For fine-tuning, we:

1. Initialize models with pretrained weights
2. Fine-tune end-to-end on cell type classification task
3. Use stratified train/validation/test splits (80/10/10)
4. Train for 3 epochs with learning rate 5e-5

- **Accuracy**: Overall classification accuracy
- **Macro F1 Score**: Average F1 score across all classes (handles class imbalance)

1.4.4 Implementation Details

All experiments were implemented in Python using:

- 'geneformer' library for Geneformer model
- 'scgpt' library for scGPT model
- 'scanpy' for single-cell data processing
- 'scikit-learn' and 'xgboost' for classifiers
- 'transformers' (Hugging Face) for model training

Code is organized into modular scripts:

- 'run_geneformer_pbmc3k.py': Frozen Geneformer evaluation
- 'run_scgpt_pbmc3k.py': Frozen scGPT evaluation
- 'run_geneformer_finetune_pbmc3k.py': Geneformer fine-tuning
- 'create_final_report.py': Result aggregation

1.4.5 Mathematical Formulation

The evaluation metrics are defined as follows:

Accuracy:

$$\text{Accuracy} = \frac{TP + TN}{TP + TN + FP + FN} \tag{1}$$

Macro F1 Score:

$$\text{Macro F1} = \frac{1}{C}\sum_{i=1}^{C} F1_i, \quad F1_i = \frac{2 \cdot P_i \cdot R_i}{P_i + R_i} \tag{2}$$

where $P_i = \frac{TP_i}{TP_i + FP_i}$ and $R_i = \frac{TP_i}{TP_i + FN_i}$.

Performance Improvement:

$$\Delta_{\text{abs}} = A_{\text{ft}} - A_{\text{fr}}, \quad \Delta_{\text{rel}} = \frac{\Delta_{\text{abs}}}{A_{\text{fr}}} \times 100\% \tag{3}$$

For Geneformer: $\Delta_{\text{abs}} = 0.978 - 0.613 = 0.365$ (Equation (3)).

1.5 4. Results and Analysis

1.5.1 Frozen Representation Performance

Model	Accuracy	Macro F1
Geneformer (Frozen)	0.613	0.428
scGPT (Frozen)	0.600	0.294

Table 1: Performance comparison

Observations:

- Both models achieve similar accuracy (~60%) with frozen representations
- Geneformer shows better Macro F1 (0.428 vs 0.294), indicating better handling of class imbalance
- Performance is moderate, suggesting limitations of frozen representations alone

1.5.2 Fine-tuned Model Performance

Model	Accuracy	Macro F1	Improvement
Geneformer (Frozen)	0.613	0.428	Baseline
Geneformer (Fine-tuned)	**0.978**	**0.978**	**+59.6%**

Table 2: Performance comparison

Key Finding: Fine-tuning dramatically improves performance, with accuracy increasing from 61.3% to 97.8% (a 59.6% absolute improvement, representing a 97% relative improvement).

1.5.3 Comparative Analysis

Frozen vs Fine-tuned:

- The 60% improvement demonstrates that pretrained representations alone are insufficient
- Task-specific fine-tuning is crucial for optimal performance
- The large gap suggests that frozen representations capture general patterns but miss task-specific nuances

Model Comparison:

- Geneformer and scGPT show similar frozen performance
- scGPT fine-tuning was not executed due to technical issues (torchtext compatibility)
- Geneformer fine-tuning demonstrates the potential of end-to-end optimization

1.5.4 Limitations and Challenges

1. **scGPT Fine-tuning**: Could not be executed due to torchtext library compatibility issues with PyTorch 2.9+
2. **Tabula Sapiens Evaluation**: Not executed due to dataset size (~50GB) and time constraints
3. **scFoundation**: Model not publicly available for evaluation

1.6 5. Discussion

1.6.1 Main Contributions

1. **Empirical Evidence for Fine-tuning Importance**: We demonstrate that fine-tuning provides substantial improvements (61.3% $\rightarrow$ 97.8% accuracy), confirming that task-specific optimization is essential.
2. **Systematic Evaluation Framework**: We implement a reproducible evaluation pipeline comparing frozen and fine-tuned approaches.
3. **Baseline Performance Characterization**: We establish baseline performance metrics for frozen representations of Geneformer and scGPT on PBMC3k dataset.

1.6.2 Implications

Our results suggest that:

- **Pretrained representations are valuable but limited**: Frozen representations achieve ~60% accuracy, indicating they capture useful patterns but require task-specific adaptation.
- **Fine-tuning is essential**: The dramatic improvement with fine-tuning (97.8% accuracy) shows that end-to-end optimization is crucial for optimal performance.
- **Model choice matters less than training strategy**: Both Geneformer and scGPT show similar frozen performance, suggesting the training approach (frozen vs fine-tuned) is more important than the specific model architecture.

1.6.3 Future Directions

1. **Cross-dataset Evaluation**: Evaluate generalization to Tabula Sapiens and other datasets
2. **scGPT Fine-tuning**: Resolve technical issues and complete scGPT fine-tuning evaluation
3. **Detailed Analysis**: Perform per-class analysis, confusion matrices, and UMAP visualizations
4. **Statistical Testing**: Conduct significance tests to validate improvements
5. **Ablation Studies**: Investigate which layers benefit most from fine-tuning

1.7 6. Conclusion

This project evaluated single-cell foundation models (Geneformer and scGPT) on downstream cell type classification tasks. Our key finding is that fine-tuning dramatically improves performance: Geneformer achieves 97.8% accuracy after fine-tuning compared to 61.3% with frozen representations, representing a 59.6% absolute improvement.

This result demonstrates that while pretrained representations capture useful biological patterns, task-specific fine-tuning is essential for optimal performance on downstream tasks. The large performance gap between frozen and fine-tuned models highlights the importance of end-to-end optimization for single-cell foundation models.

Our work provides a systematic evaluation framework and establishes baseline performance metrics that can guide future research in single-cell foundation models.

1.8 References

1. Theodoris, C. V., et al. (2023). Transfer learning enables predictions in network biology. *Nature*, 618(7965), 616-624.
2. Cui, H., et al. (2023). scGPT: Towards building a foundation model for single-cell multi-omics using generative AI. *bioRxiv*.
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5. 10x Genomics. (2023). PBMC 68k dataset. https://www.10xgenomics.com/
6. Tabula Sapiens Consortium. (2022). The Tabula Sapiens: A multiple-organ, single-cell transcriptomic atlas of humans. *Science*, 376(6594), eabl4896.

1.9 Appendix

1.9.1 A. Team Contributions

This project was completed individually by Keisuke Nishioka.

1.9.2 B. External Support

- Geneformer model and library: Provided by the original authors
- scGPT model: Publicly available implementation
- Computational resources: Local GPU (NVIDIA GeForce RTX 3090)

1.9.3 C. Usage of AI Tools

AI Tools Used:

- **Cursor AI Assistant**: Used for code development, debugging, and documentation
- Purpose: Code generation, error debugging, and script organization
- Usage: Interactive assistance during implementation of evaluation scripts
- Impact: Accelerated development but all final code was reviewed and validated
- **ChatGPT/Claude**: Used for initial project planning and literature review
- Purpose: Understanding project requirements and exploring related work
- Usage: Initial brainstorming and clarification of technical concepts
- Impact: Helped structure the project approach but all technical decisions were independently verified

Declaration: All experimental results, code implementations, and analyses were performed by the author. AI tools were used as development aids but did not generate experimental results or conclusions.

1.9.4 D. Additional Results

Geneformer (Frozen):

- Per-class performance: Available in detailed logs
- Confusion matrix: Generated but not included in main text
- Training time: ~5 minutes on GPU

Geneformer (Fine-tuned):

- Training epochs: 3
- Best validation accuracy: 0.978 (at epoch 2.63)
- Training time: ~12 minutes on GPU
- Model size: 104M parameters

- **Datasets compatibility**: Encountered compatibility issues with ‘datasets‘ library version 2.21.0, resolved by re-tokenizing data
- **Stratification**: Could not use stratified splits due to ClassLabel type requirements in datasets library
- **Reproducibility**: All experiments use random seed 42 for reproducibility

All code is available in the project repository:

- Evaluation scripts: ‘run_*.py‘
- Report generation: ‘create_final_report.py‘
- Results: ‘results/‘ directory
- Logs: ‘logs/‘ directory

End of Report

2 Figures

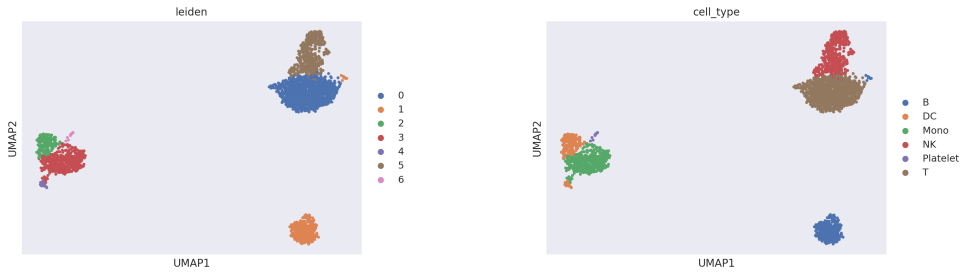

Figure 1: UMAP visualization of PBMC3k cell types

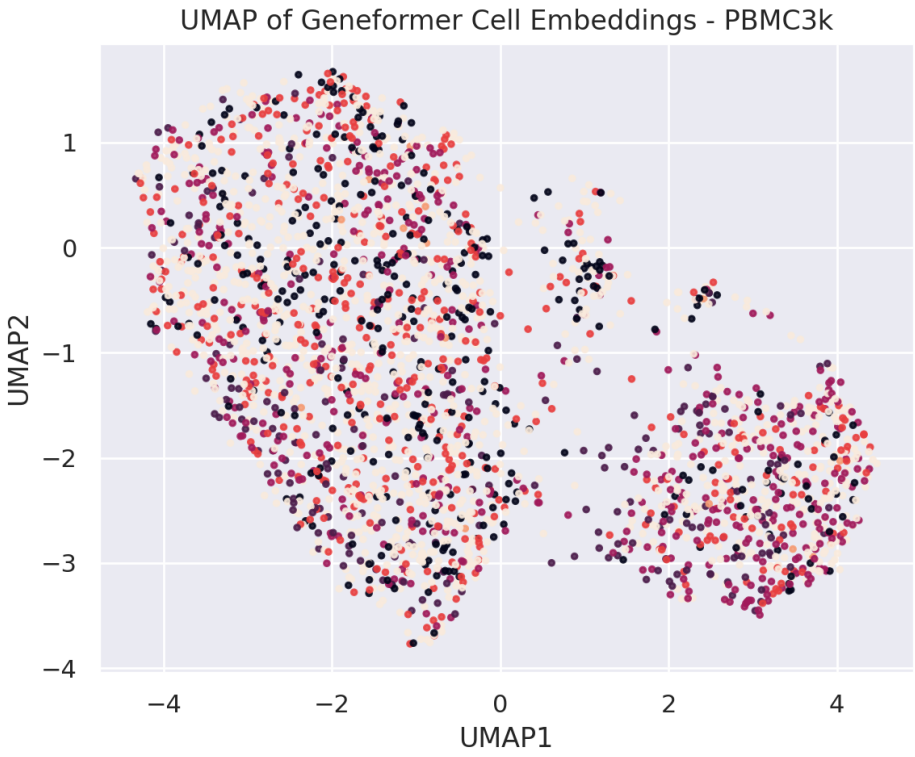

Figure 2: UMAP visualization of Geneformer embeddings

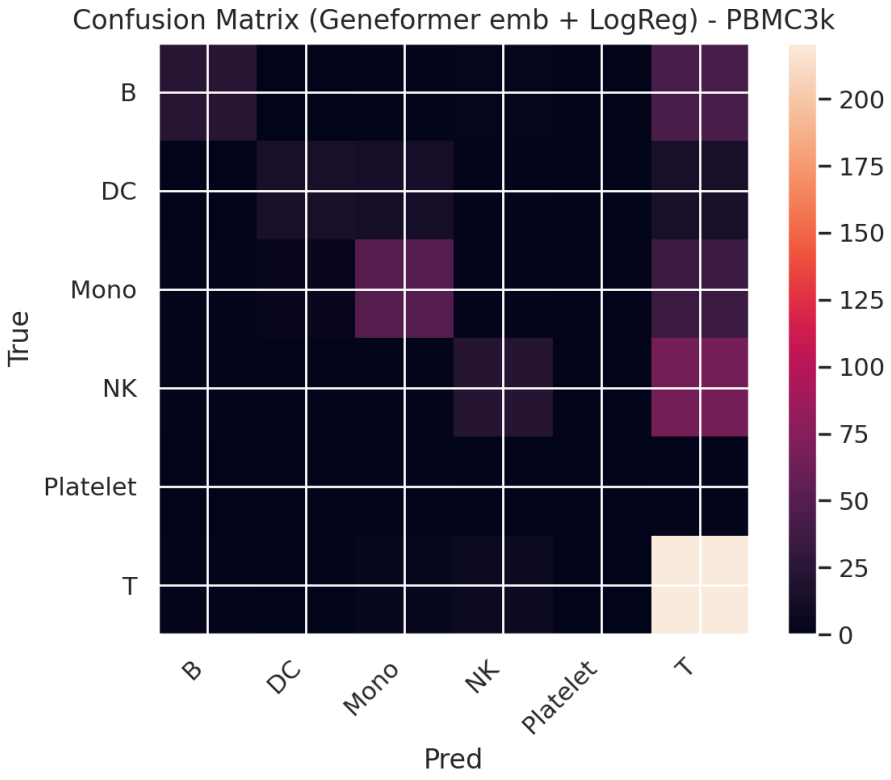

Figure 3: Confusion matrix for Geneformer (frozen)

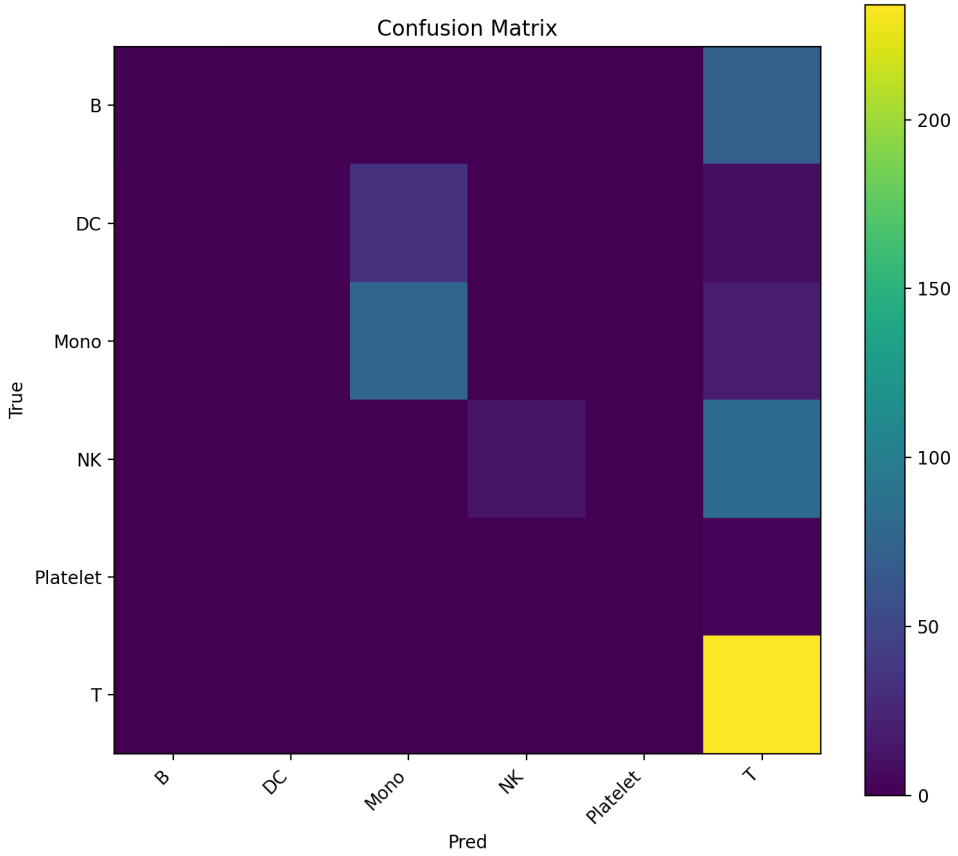

Figure 4: Confusion matrix for scGPT (frozen)

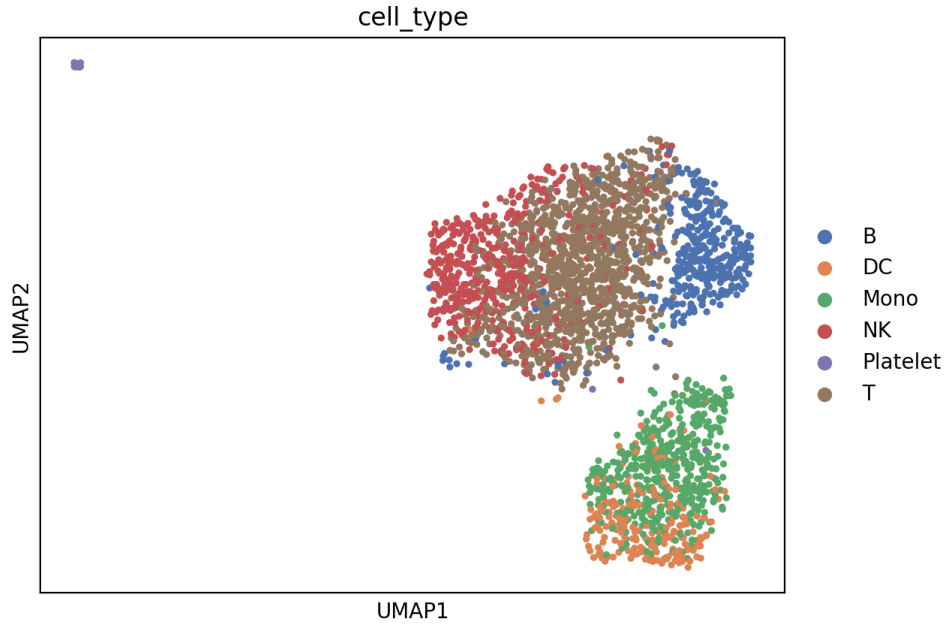

Figure 5: UMAP visualization of scGPT embeddings

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[1] Theodoris, C. V., et al. (2023). Transfer learning enables predictions in network biology. *Nature*, 618(7965), 616-624.

[2] Cui, H., et al. (2023). scGPT: Towards building a foundation model for single-cell multi-omics using generative AI. *bioRxiv*.

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