

Supplemental Methods Results Generation

1 Geneformer

Geneformer was implemented using the original repository[1] as a BERT-based transformer (BertForMaskedLM). Training was performed using the HuggingFace Trainer API with length-grouped batching to improve efficiency by grouping cells with similar numbers of expressed genes. To ensure consistent training across diverse dataset sizes, epochs scale dynamically as $\max(1, \lfloor 10 \times (10,000,000/\text{dataset_size}) \rfloor)$, ensuring smaller datasets receive proportionally more training while larger datasets train for fewer epochs, thus maintaining a constant effective training budget. Early stopping prevents overfitting by monitoring validation loss, and the model uses masked language modeling with 15% token masking.

Parameter count scales linearly with vocabulary size (number of genes) due to the embedding layer and language model head. Measured parameter counts across datasets range from 1.9M to 13.5M depending on the number of genes in each dataset (Table 4). Complete hyperparameters are provided in Table 1.

We use a reduced-parameter Geneformer architecture compared to many single-cell transformer models (Table 2) to support training thousands of models across different dataset sizes, qualities, and random seeds—conditions where computational cost and overfitting are serious concerns. Larger models such as Geneformer-V1[1] (6 layers, 2048 tokens, pretrained on \sim 30M cells), Geneformer-V2-104M[2] (12–18 layers, 4096 tokens, pretrained on \sim 95M cells), Tahoe-X1[3] (12 layers, 1024 tokens, \sim 70M parameters, pretrained on \sim 271M cells), and scGPT[4] (12 layers, 5000 tokens, \sim 100M parameters, pretrained on \sim 33M cells) were all trained with massive compute budgets and far more pretraining data than is available for most biological problems. Even larger models in this space, such as TranscriptFormer[5] (12 layers, 2047 tokens, 368–542M parameters depending on variant, pretrained on 57–112M cells across multiple species) or STATE[8] (8 layers, 512 tokens, \sim 600M parameters for the embedding model, pretrained on large-scale perturbation datasets), were trained on even more extensive datasets spanning multiple species and hundreds of millions of cells, making such large-scale pretraining infeasible for systematic benchmarking. For our scaling law study, where model throughput matters and parameter counts must fit diverse data size regimes, using a reduced model is critical to feasibility.

Figure 1 shows the training and validation loss curves for the Geneformer model trained on the developmental task using the full dataset of 10 million cells at full quality level. The model demonstrates stable convergence with both the training and validation losses decreasing monotonically, and the validation loss closely tracks the training loss, indicating good generalization without overfitting. Early stopping was triggered based on validation loss monitoring, preventing overfitting while allowing sufficient training.

2 SCVI

SCVI[6] was implemented using `scvi.model.SCVI` with a shallow architecture to balance expressiveness and computational efficiency. The model uses gene-specific dispersion and zero-inflated negative binomial (ZINB) likelihood to capture the over-dispersed and sparse nature of single-cell count data. Parameter count scales with input genes due to gene-specific parameters in the decoder. Measured parameter counts across datasets range from 1.3M to 116.8M depending on the number of genes in each dataset (Table 4). Complete hyperparameters are provided in Table 3.

Training employs a conservative learning rate schedule with minimal weight decay to allow stable optimization of the generative model. Similar to Geneformer, epochs scale dynamically to maintain consistent training across dataset sizes, though with a lower scaling factor reflecting the faster convergence of variational

Table 1: Hyperparameters and Implementation Details for Geneformer

Parameter	Value
<i>Model Architecture</i>	
Number of layers	3
Hidden dimension	256
Attention heads	4
Intermediate size	512
Max sequence length	512 tokens
Activation function	ReLU
Attention dropout	0.02
Hidden dropout	0.02
Initializer range	0.02
Layer norm epsilon	1×10^{-12}
<i>Training Hyperparameters</i>	
Learning rate	1×10^{-3}
Optimizer	AdamW
Weight decay	0.001
Train batch size (per device)	64
Eval batch size (per device)	100
<i>Learning Rate Schedule</i>	
LR scheduler type	Linear
Warmup steps	5,000
<i>Training Configuration</i>	
Evaluation strategy	Steps
Evaluation steps	1,000
Max epochs	Dynamic (depends on dataset size)
<i>Early Stopping</i>	
Early stopping	Based on validation loss
Patience	5 steps

Table 2: Architectural comparison of our Geneformer implementation with published single-cell transformer models.

Model	Layers	Hidden Dim.	Heads	Intermed. Size	Max Seq. Length
Our Geneformer	3	256	4	512	512
Geneformer-V1[1]	6	256	4	512	2048
Geneformer-V2-104M[2]	12	768	12	3072	4096
Tahoe-X1 (70M)[3]	12	512	8	2048	1024
scGPT[4]	12	512	8	512	5000
TranscriptFormer[5]	12	2048	16	2048	2047
STATE (SE-600M)[8]	8	768	12	3072	512

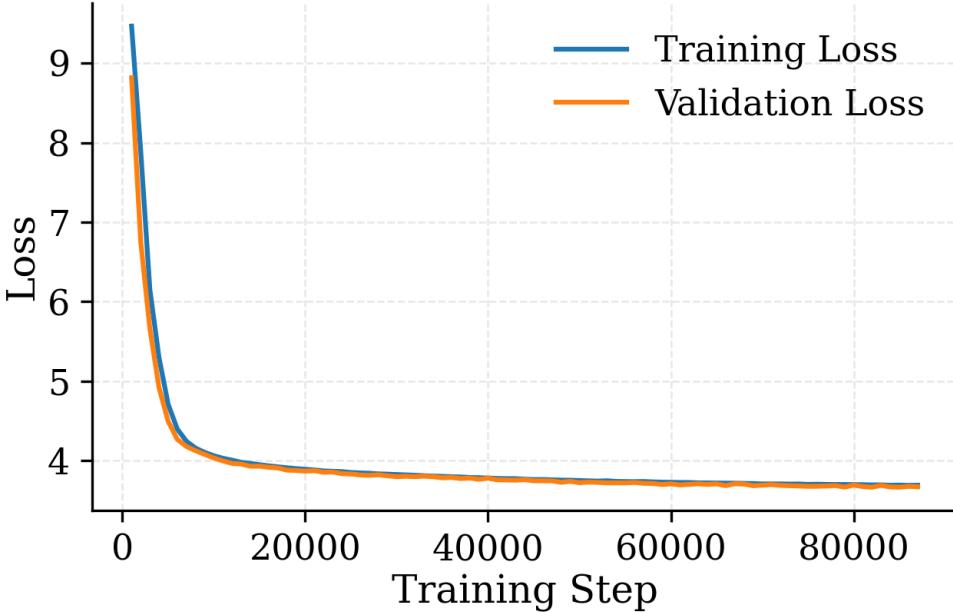


Figure 1: Training and validation loss curves for Geneformer trained on the developmental task with 10 million cells at quality level 1. The model shows stable convergence with both losses decreasing consistently throughout training.

autoencoders. KL divergence warmup is applied to gradually introduce the regularization term, preventing the model from collapsing to the prior early in training. SCVI operates on raw count data without preprocessing. The encoder outputs both mean and variance parameters of the approximate posterior distribution over latent variables, but embeddings are extracted as the posterior mean to provide deterministic 16-dimensional representations, following standard practice in the field.

3 PCA

PCA was implemented using `sklearn.decomposition.TruncatedSVD`[7] with 16 components. Preprocessing includes total count normalization to 10,000 counts per cell, $\log(x + 1)$ transformation, and selection of the top 750 highly variable genes. The method computes a linear transformation matrix of size 750×16 .

4 Random Projection

Random Projection was implemented using `sklearn.random_projection.GaussianRandomProjection`[7] with 16 components and random state 42. The method operates on raw counts without normalization and provides 16-dimensional embeddings.

5 Computational Scale

This study required the execution of approximately 4,000 training runs across tasks, dataset sizes, data qualities, algorithms, and different random seeds. Most models required GPU access for training, embedding extraction, or computation of mutual information. To manage this scale, we developed a custom scheduling system that dynamically allocates GPUs based on real-time memory availability, maintains hundreds of concurrent worker processes, and executes each training run as an isolated subprocess. The system monitors GPU memory usage and assigns jobs. All models and embeddings were saved for reproducibility. To enable

Table 3: Hyperparameters and Implementation Details for SCVI

Parameter	Value
<i>Model Architecture</i>	
Hidden size	512
Latent dimension	16
Number of hidden layers	1
Dropout rate	0.1
Dispersion	Gene-specific
Gene likelihood	Zero-inflated negative binomial (ZINB)
Latent distribution	Normal
<i>Training Hyperparameters</i>	
Learning rate	1×10^{-3}
Optimizer	Adam
Weight decay	1×10^{-6}
Adam epsilon	0.01
Batch size	512
<i>Learning Rate Schedule</i>	
LR scheduler	Reduce on plateau
LR scheduler metric	Validation ELBO
Minimum LR	1×10^{-6}
<i>KL Annealing</i>	
KL warmup epochs	1
Max KL weight	1.0
Min KL weight	0.0
<i>Training Configuration</i>	
Train/Val split	80% / 20%
Shuffle split	True
Max epochs	Dynamic (depends on dataset size)
<i>Early Stopping</i>	
Early stopping	Based on validation ELBO
Patience	5 epochs
Min delta	0.01

Table 4: Parameter counts for SCVI and Geneformer models across different datasets

Dataset	SCVI (M)	Geneformer (M)
Larry	64.9	8.3
MERFISH	1.3	1.9
PBMC	53.2	7.1
Shendure	116.8	13.5

processing of datasets containing up to 10 million cells, we developed a custom H5AD reader that handles sparse CSR matrices by directly accessing HDF5 `indptr`, `indices`, and `data` arrays, reconstructing sparse matrices only for requested row ranges. This enables efficient chunked reading with a low memory footprint.

References

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