Preference-Based Fine-Tuning of Genomic Sequence Models for Personal Expression Prediction with Data Augmentation

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Abstract. Despite substantial progress in genomic foundation models, accurately predicting inter-individual variation in gene expression from DNA sequence alone remains a major challenge. Current sequence-based models, such as Enformer and Borzoi, trained exclusively on the reference genome, cannot capture the effects of individual-specific regulatory variants. Moreover, the acquisition of paired whole-genome and transcriptome data required for personalized modeling is hindered by privacy and data-sharing constraints. To address this limitation, we integrate genomic data synthesis with established statistical frameworks. Our approach generates thousands of virtual training samples by simulating genetic variation from the 1000 Genomes Project and assigning pseudo-expression labels using PrediXcan, a validated eQTL-based predictor. Because simulated and real expression values differ in scale and distribution, we introduce a preference-based objective that models relative rather than absolute expression patterns. Fine-tuning Enformer through alternating cycles of real-data regression and virtual-data preference optimization enables efficient learning from both real and synthesized data. Using the GEUVADIS dataset, our framework outperforms AlphaGenome, PrediXcan, and Enformer fine-tuned without synthesized data, demonstrating that simulation-based integration of population-level regulatory knowledge can effectively mitigate data scarcity and improve cross-individual generalization in sequence-based gene expression prediction.

Availability and implementation: Code and data are available at https://github.com/pacifiic/augment-finetune-genomics.

Keywords: Personalized gene expression prediction · Synthetic Data Augmentation · Preference-Based Fine-Tuning

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1 Introduction

Deep learning models such as Basenji2 [1], Enformer [2], and Borzoi [3] have progressively improved in capturing long-range cis-regulatory interactions and predicting gene expression and chromatin accessibility. However, despite these advances, their predictive power remains limited when applied to personal genomes, where naturally occurring variants modulate expression in individual-specific ways. Recent studies [4–6] have shown that such sequence-based models exhibit limited predictive power across individuals, whereas PrediXcan [7], a statistical model trained on GTEx eQTL data, achieves substantially higher accuracy in predicting personal gene-expression levels. This discrepancy arises because current deep-learning models are pre-trained exclusively on the reference genome, learning general regulatory syntax but lacking exposure to the population-level genetic diversity necessary for modeling personal transcriptomes.

Several studies have fine-tuned Enformer-based models on paired genome-transcriptome data to capture individual-specific variation, demonstrating that personal sequence diversity improves cross-individual prediction [8, 9]. Rastogi et al. [8] introduced both single-sample and pairwise regression objectives, with the latter modeling expression differences between individual pairs in an error-based contrastive manner, together with a ranking-based objective to enhance cross-individual generalization. Drusinsky et al. [9] proposed a dosage-based diploid modeling strategy that averages two one-hot encoded consensus sequences generated from unphased genotypes. To address the same challenge, Ramprasad et al. [10] proposed a convolutional model that integrates functional annotations, demonstrating the benefit of biological priors for improving generalization.

However, the limited availability of paired genome–transcriptome data remains a fundamental constraint. Publicly available datasets with both whole-genome sequencing (WGS) and RNA-seq measurements per individual are typically restricted to only a few hundred samples (e.g., GEUVADIS [11]), and even larger resources such as GTEx include fewer than one thousand individuals with matched WGS [12]. Moreover, access to many high-quality paired datasets is often restricted due to privacy and data-sharing limitations. Given these constraints, pursuing data augmentation with synthetic genome–expression pairs represents a natural and necessary direction for improving cross-individual generalization.

To address this bottleneck, we propose a scalable fine-tuning framework that integrates simulated genomic diversity with GTEx-derived pseudo-expression labels. We first generate virtual individual genomes using the `sim1000G` framework [13], which simulates realistic recombination and mutation events. Each simulated genome is annotated with pseudo-expression labels predicted by PrediXcan, a statistically validated transcriptome-imputation model trained on GTEx eQTL data. [14, 15] Because the pseudo-labeled expressions are not on the same quantitative scale as true RNA-seq expression, we adopt a Direct Preference Optimization (DPO) objective [16] that learns pairwise ranking relationships rather than absolute magnitudes. This approach enables the model to effectively leverage pseudo-labeled data while preserving the relative expression patterns

observed in real data. By combining PrediXcan-based pseudo-labeling, simulated population-scale variation, DPO-based optimization, our framework bridges statistical and deep-learning paradigms for personalized gene-expression prediction.

In our experiments, integrating both real and simulated individuals during fine-tuning yielded higher predictive accuracy than training on real data alone, highlighting the benefit of leveraging virtual genetic diversity and pseudo-labeled expressions. Moreover, whereas previous studies evaluated deep learning models on the same gene-level input–output regression task as Elastic Net [7], their reported improvements remained marginal, with increases of 0.35% (from 0.283 to 0.284) in Rastogi et al. [8] and 0.37% in Ramprasad et al. [10]. Notably, while Ramprasad et al. further incorporated functional annotation (FA) features to boost model performance, this variant was not directly compared against Elastic Net, leaving the relative improvement unclear. Under the same evaluation setting, our fine-tuned framework consistently outperformed PrediXcan, achieving an average relative improvement of 3.5% (from 0.311 to 0.322) in mean Pearson correlation across individuals and genes, showing a greater performance gain than those reported in previous studies. In summary, our study addresses two central challenges in personal transcriptome modeling:

(1) the limited availability, scale, and accessibility of matched WGS–RNA-seq data, and
(2) the leverage of statistical eQTL-based models in sequence-based deep-learning fine-tuning.

Our results show that population-level regulatory knowledge, when distilled through simulated genomes and eQTL-based pseudo labels, can consistently enhance the cross-individual generalization capacity of deep sequence models.

2 Methods

2.1 Data Preprocessing

Genotype and RNA-seq expression data for 421 phased individuals were obtained from the GEUVADIS cohort [11], with genotypes originating from the 1000 Genomes Project [17]. The dataset was randomly split into 295, 42, and 84 individuals for training, validation, and testing, respectively. From the genes analyzed in Huang et al. [4], we selected those located on chromosome 22. For each gene, a 196,608 bp sequence centered on the transcription start site (TSS; ±98,304 bp) was extracted from the hg19 reference genome. After excluding genes overlapping ambiguous N regions in hg19, 42 genes were retained for all experiments.

To increase the genetic diversity of training samples, we simulated an additional 1,000 virtual individuals using the `sim1000G` framework, which reproduces population-level recombination and linkage patterns. Predicted gene-expression levels for these simulated genomes were generated using PrediXcan's eQTL models trained on GTEx v8. The resulting pseudo-labeled (sequence, expression)

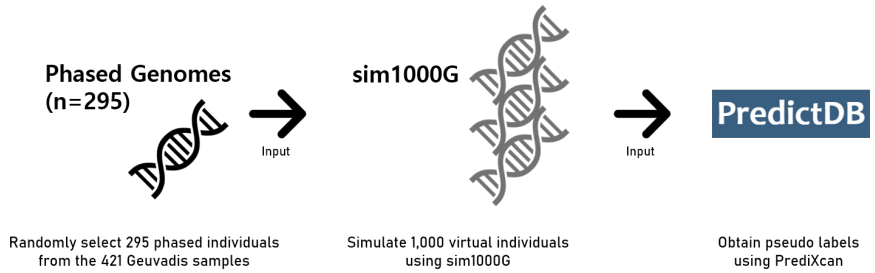

Fig. 1: Overview of the synthetic data augmentation workflow. Virtual individuals were simulated using `sim1000G`, and gene-expression pseudo-labels were predicted by PrediXcan models trained on GTEx v8 LCL data.

pairs were combined with real data for model fine-tuning. To prevent data leakage, virtual genomes were simulated using only variants present in the training-set haplotypes, ensuring that no variants exclusive to the validation or test sets were included during simulation or training.

2.2 Model Architecture and Fine-Tuning

Our model builds upon the Enformer architecture, which predicts gene expression from long genomic sequences using convolutional and transformer layers. To adapt Enformer for individual-level prediction, we froze the convolutional feature extractor and applied parameter-efficient fine-tuning to the transformer component. Each input sequence was processed once through Enformer's convolutional tower to obtain fixed-length feature vectors, which were then used as inputs during fine-tuning for computational efficiency.

This design was conceptually inspired by the parameter-efficient transfer learning framework proposed by Yuan et al. [18], which demonstrated the effectiveness of Low-Rank Adaptation (LoRA) [19] for fine-tuning large regulatory sequence models. Following this principle, we integrated LoRA modules into the self-attention mechanism of Enformer's transformer layers, enabling targeted adaptation of attention projections without updating the full model.

To capture haplotype-specific regulatory effects, we adopted a dual-Enformer ensemble configuration that models maternal and paternal haplotypes independently. Two Enformer instances, denoted as Enformer_1 and Enformer_2, were jointly trained on paired haplotype sequences. To ensure symmetry and robustness, both input orderings—$(\text{Enformer}_1, \text{Enformer}_2) = (\text{maternal}, \text{paternal})$ and vice versa—were included during training. For virtual sequences, where pseudo-expression labels were generated per haplotype rather than per individual, the same haplotype sequence was fed into both Enformer_1 and Enformer_2 to maintain architectural consistency. The outputs from the two Enformer instances

were averaged to produce the final gene-expression estimate, which was optimized against either observed values or pairwise preferences between pseudo-labeled samples. During evaluation, the final prediction was computed as the mean of the two input-order configurations.

2.3 Training Objectives

We employed two fine-tuning objectives: SMAPE loss for regression-based training, as established in prior work [8], and Direct Preference Optimization (DPO) loss for ranking-based training on mixed real and pseudo-labeled data.

SMAPE was used to directly minimize the discrepancy between predicted and observed expression values in real (WGS–RNA-seq) pairs. In contrast, DPO was designed to handle cases where target scales were not directly comparable across datasets by formulating fine-tuning as a pairwise ranking problem. Given two samples (A, B), the model was optimized to assign a higher predicted expression to the sample with the larger target value, following a Bradley–Terry formulation:

$$\mathcal{L}_{\text{DPO}} = \mathbb{E}_{(A,B)}\big[\text{BCE}(\sigma(\beta \cdot (f_A - f_B)), \mathbb{1}[y_A > y_B])\big]$$

where f_A, f_B are predicted expression values and β controls the sharpness of pairwise preference learning. To account for gene-specific expression variance, β was adaptively scaled per gene based on the empirical distribution of expression differences.

2.4 Training Configuration

Model fine-tuning was performed for 100 epochs using four NVIDIA H100 GPUs under DeepSpeed ZeRO Stage 1 optimization [20]. A per-GPU batch size of 1 and a gradient accumulation step of 4 were used, resulting in an effective global batch size of 16. All transformer layers were fine-tuned using the AdamW optimizer (learning rate 1×10^{-4}, weight decay 1×10^{-3}), with a cosine learning rate scheduler including 1,000 warm-up steps, following prior work [8]. Mixed-precision training was conducted using the `bf16` format, and gradient clipping (maximum norm = 1.0) was applied to prevent gradient explosion. During DPO training, pair sampling was controlled using an epoch- and rank-dependent seeding scheme to balance randomness and sample diversity across distributed workers. In the virtual data integration experiments, the total number of training epochs and samples per epoch were kept identical to those in the real-data experiments. This design eliminated potential confounding effects from differing training steps, ensuring that performance improvements reflected the effect of data augmentation itself.

2.5 Evaluation Metrics

Model performance was evaluated following the same protocol as prior works [4, 8]. For each gene, we computed the Pearson and Spearman correlation coefficients

between predicted and observed expression values across individuals in the same genes. Final performance metrics were obtained by averaging the correlations across all evaluated genes.

Model selection was based on validation performance: the checkpoint achieving the highest mean Pearson correlation across genes in the validation set was chosen and subsequently evaluated on the held-out test set. For the test set, both Pearson and Spearman correlations were computed in the same manner.

3 Experiments and Results

3.1 Experimental Overview

We conducted three groups of experiments to systematically evaluate the effectiveness of our proposed fine-tuning framework for personalized gene-expression prediction. First, we compared the model against three established baselines: the baseline Enformer model without fine-tuning, AlphaGenome [21], and PrediXcan. Second, we examined the predictive capacity of models trained solely on virtual data, using either a regression-based objective or Direct Preference Optimization (DPO). Finally, we investigated whether alternating real and virtual fine-tuning phases could further enhance cross-individual generalization by interleaving regression and preference-learning objectives across epochs.

3.2 Baseline Models

We first compared our fine-tuning framework with three baseline approaches for personalized gene-expression prediction: (i) the baseline Enformer model, (ii) AlphaGenome, and (iii) PrediXcan. All models were evaluated on the same set of 42 chromosome 22 genes across 84 GEUVADIS test individuals. Performance was measured using mean Pearson and Spearman correlation coefficients between predicted and observed expression levels across individuals.

As shown in Table 1, the baseline Enformer model achieved a mean Pearson correlation of 0.064 and a mean Spearman correlation of 0.047, confirming its limited generalization when applied to personal genomes. AlphaGenome, a follow-up study to Enformer that extends the input window to 1 Mb around each gene, improved performance substantially, with mean Pearson and Spearman correlations of 0.211 and 0.203 on the total RNA-seq track. Results on the polyA track were nearly identical (0.210 and 0.205).

PrediXcan, an eQTL-based statistical model trained on GTEx v8 lymphoblastoid cell line (LCL) data, achieved substantially higher performance than either deep-learning baseline (mean Pearson 0.311, Spearman 0.288). This contrast highlights the gap between sequence-based models pretrained on a single reference genome and statistical predictors explicitly leveraging population-level eQTL information.

When restricted to a 196 kb genomic window centered on the transcription start site (TSS), the performance of PrediXcan decreased to Pearson 0.299

Table 1: Baseline performance comparison on 42 chromosome 22 genes across 84 GEUVADIS test individuals. Reported values are mean Pearson and Spearman correlations between predicted and observed expression levels. AlphaGenome results are shown for both polyA and total RNA-seq tracks. Sequence length indicates the input genomic context per sample.

Model	**Sequence Length**	**Mean Pearson**	**Mean Spearman**
Enformer	196 kb	0.064	0.047
AlphaGenome (polyA)	1 Mb	0.210	0.205
AlphaGenome (total)	1 Mb	0.211	0.203
PrediXcan	196 kb	0.299	0.289
PrediXcan	full chr22	0.311	0.288

and Spearman 0.289. This reduction suggests that population-level SNP models also benefit from broader genomic context, implying the presence of regulatory eQTLs located outside Enformer's 196 kb window.

3.3 Virtual-Only Fine-Tuning

The purpose of this experiment is to evaluate the effectiveness of the augmented dataset itself. Enformer was fine-tuned solely on the pseudo-labeled synthetic data, using two independent models trained for 100 epochs each: one with the regression-based SMAPE loss and the other with the DPO (Direct Preference Optimization) objective.

As shown in Table 2, the regression-based model trained on pseudo-labeled data exhibited limited predictive capacity (mean Pearson 0.171, Spearman 0.157), likely due to scale discrepancies between PrediXcan-derived expression values and real RNA-seq measurements. In contrast, the model optimized with the DPO objective achieved substantially higher correlations (mean Pearson 0.307, Spearman 0.298), indicating that pairwise preference learning is more robust to absolute scale differences across pseudo-labeled samples. These findings suggest that although pseudo-labeled data may not reproduce absolute expression magnitudes, they still encode meaningful relative ordering information that can be effectively leveraged through ranking-based optimization.

Table 2: Validation performance of virtual-only fine-tuning experiments using pseudo-labeled data. Each model was trained for 100 epochs on 1,000 simulated individuals. Reported values are mean Pearson and Spearman correlations across 42 genes. Results shown are from runs with random seed 42.

Objective	**Mean Pearson**	**Mean Spearman**
Regression (SMAPE)	0.171	0.157
DPO (pairwise)	**0.307**	**0.298**

3.4 Evaluating the Effect of Combining Real and Augmented Data on Fine-Tuning Performance

Having confirmed the standalone utility of the augmented (virtual) dataset in the previous experiment, we next examined whether integrating real and virtual fine-tuning phases could further improve predictive performance across individuals. To isolate the contribution of data augmentation from mere scheduling effects, we compare alternating real–virtual schedules against a real-only regression baseline (100 epochs) and include an alternating schedule that uses *real* DPO instead of *virtual* DPO as a control.

In standard post-training pipelines for large language models (LLMs), supervised fine-tuning (SFT) and preference learning (e.g., DPO) are often performed sequentially, which is known to be suboptimal due to forgetting of supervised knowledge during later preference-learning stages. Recent work has addressed this by introducing joint or alternating optimization; notably, *Fernando et al.* [22] showed that alternating SFT and DPO phases mitigates forgetting relative to purely sequential post-training. Motivated by this insight, we alternate between *real* regression and *virtual* preference-based fine-tuning phases in the genomics setting.

Training schedules. We designed three training schedules under an equivalent computational budget, ensuring the same number of epochs and an equal amount of data processed per epoch: *(a)* real-only regression for 100 epochs; *(b)* alternating real regression and **virtual** DPO (30R–5V–30R–5V–30R); and *(c)* alternating real regression and **real** DPO (30R–5R–30R–5R–30R). All results below are reported as mean ± std over three fixed random seeds.

Table 3: Performance comparison with baseline models and alternating fine-tuning schedules (mean ± std over 3 seeds). Values are Pearson and Spearman correlations averaged across 42 genes and 84 individuals. Results shown are from runs with random seeds 42, 47, and 52.

Model / Training Schedule	**Mean Pearson**	**Mean Spearman**
Baselines		
AlphaGenome (1 Mb, total)	0.211	0.203
PrediXcan (196 kb)	0.299	0.289
PrediXcan (full chr22)	0.311	0.288
Fine-tuning Schedules (ours)		
Real-only (100 Reg)	0.303 ± 0.002	0.295 ± 0.003
30Reg–5D_r–30Reg–5D_r–30Reg	0.314 ± 0.000	0.306 ± 0.002
30Reg–5D_v–30Reg–5D_v–30Reg	$\mathbf{0.322 \pm 0.004}$	$\mathbf{0.312 \pm 0.005}$

Abbreviations: Reg = supervised regression on real individuals; D_r = DPO using *real* individual pairs; D_v = DPO using *virtual* pairs.
Notation: "30Reg–5D_v–..." indicates 30 epochs of Reg followed by 5 epochs of D_v.

Results and interpretation. Table 3 shows that alternating regression and DPO phases improves generalization over the real-only baseline. The real–virtual alternating schedule (30R–5V–30R–5V–30R) achieved superior performance compared to the other two fine-tuning strategies across both Pearson and Spearman correlation metrics. Because the 30R–5R schedule maintains the same alternation pattern while using only real data, the additional gains observed in 30R–5V are attributed not to scheduling but to the complementary signals from pseudo-labeled virtual data, which enhance generalization by exposing the model to a broader distribution of individual-level genotypes. Compared with AlphaGenome and PrediXcan, the proposed real–virtual alternating framework achieved higher performance under the same cross-individual evaluation setting. Specifically, it yielded mean Pearson and Spearman correlation improvements of 3.5% and 8.3%, respectively, over PrediXcan.

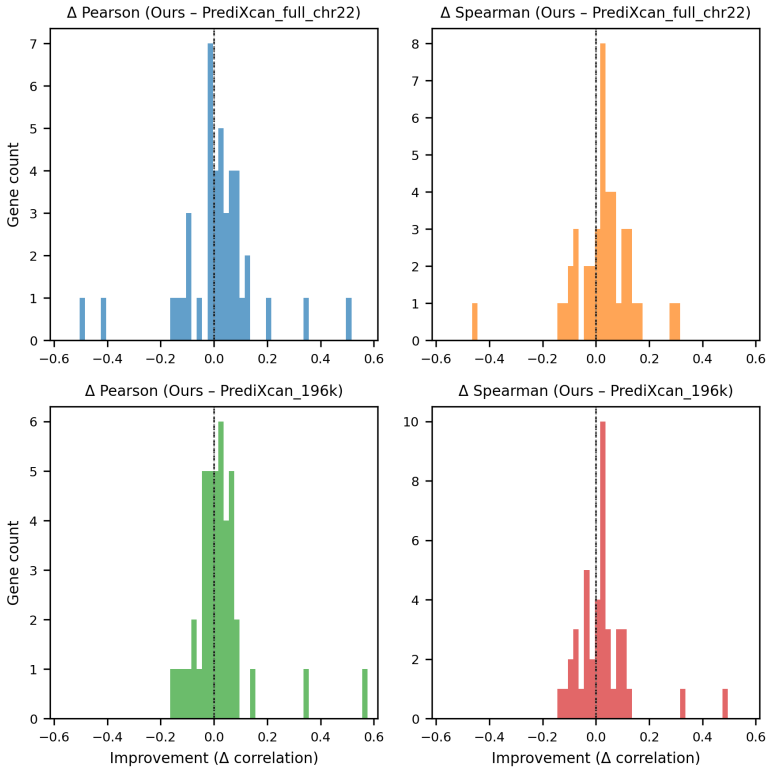

Fig. 2: Per-gene improvement analysis comparing the proposed alternating fine-tuning schedule (**Ours**: 30Reg–5D_v–30Reg–5D_v–30Reg) with two PrediXcan baselines—one using the full chromosome 22 and another with 196,608 bp windows. Each bar indicates the correlation difference for an individual gene, where positive values denote higher Pearson or Spearman correlations achieved by our model. Results are from the run with random seed 42.

While mean-based metrics summarize overall performance, they can obscure gene-specific variability. To determine whether the observed improvements were driven by a few genes or were consistent across genes, we conducted a per-gene correlation analysis (Figure 2). The per-gene distributions show that our model achieved positive Δ Pearson correlations for approximately 57% of genes in both PrediXcan baselines (full chromosome 22 and 196,608 bp window), indicating consistent improvements across the two comparisons.

Notably, two specific genes, CRYBB2 and NDUFA6, showed markedly higher Pearson correlations under the full-length PrediXcan model, as observed in Figure 2 (comparing Ours with PrediXcan_full_chr22). This likely reflects the ability of broader genomic windows to capture distal regulatory signals beyond the 196 k bp receptive field of Enformer. For these genes, the differences in Pearson correlation (Ours - PrediXcan) were -0.497 and -0.422 under the full-chromosome comparison but became +0.069 and +0.151 in the 196 k bp window setting, suggesting that meaningful regulatory variants (eQTLs) likely reside beyond Enformer's 196 k bp receptive field. PrediXcan, which leverages population-level eQTL weights without being constrained by fixed sequence windows, thus gains a clear advantage in capturing such distal regulatory effects.

4 Conclusions

We proposed a scalable fine-tuning framework that integrates simulated genomic diversity and eQTL-based pseudo-expression labels to improve personalized gene-expression prediction. By combining PrediXcan-derived pseudo labels with Direct Preference Optimization (DPO), the model effectively learns from relative expression patterns across simulated individuals. First, even when trained solely on pseudo-labeled virtual samples, the model achieved substantial predictive power, indicating that simulated genomes contain meaningful regulatory information that can be effectively exploited through ranking-based learning. Next, the real-only alternating regression–DPO schedule outperformed the real-only regression baseline, confirming the effectiveness of the alternating strategy. Finally, the fine-tuning strategy that alternates between real and virtual data consistently achieved the best performance across all settings. The model reached a mean Pearson correlation of 0.323, representing a 3.5% improvement over PrediXcan and exceeding the performance gains reported in prior deep-learning studies (0.35% in Rastogi et al. and 0.37% in Ramprasad et al.). These results indicate that pseudo-labeled virtual individuals provide stable and meaningful data augmentation that enhances model generalization. Overall, this study demonstrates that population-level statistical knowledge distilled from simulated genomes can strengthen deep sequence models, offering a practical approach to mitigating the scarcity of paired genome–transcriptome data. In future work, we plan to first enhance Enformer's efficiency through attention-optimized implementations, following recent developments such as the FlashAttention integration in Borzoi [23, 24], and subsequently extend our experiments to a broader set of genes beyond chromosome 22.

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