PRESCRIBE: Predicting Single-Cell Responses with Bayesian Estimation

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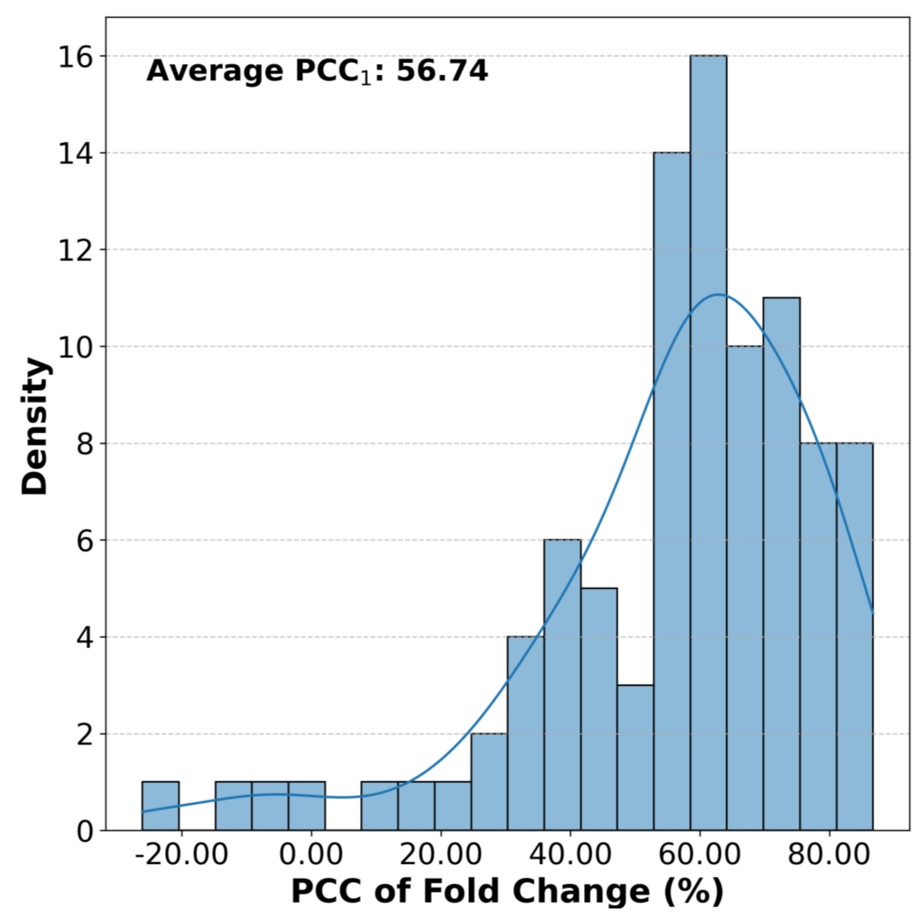
The Pitfall of Average Accuracy—— Why Prediction Confidence Matters?



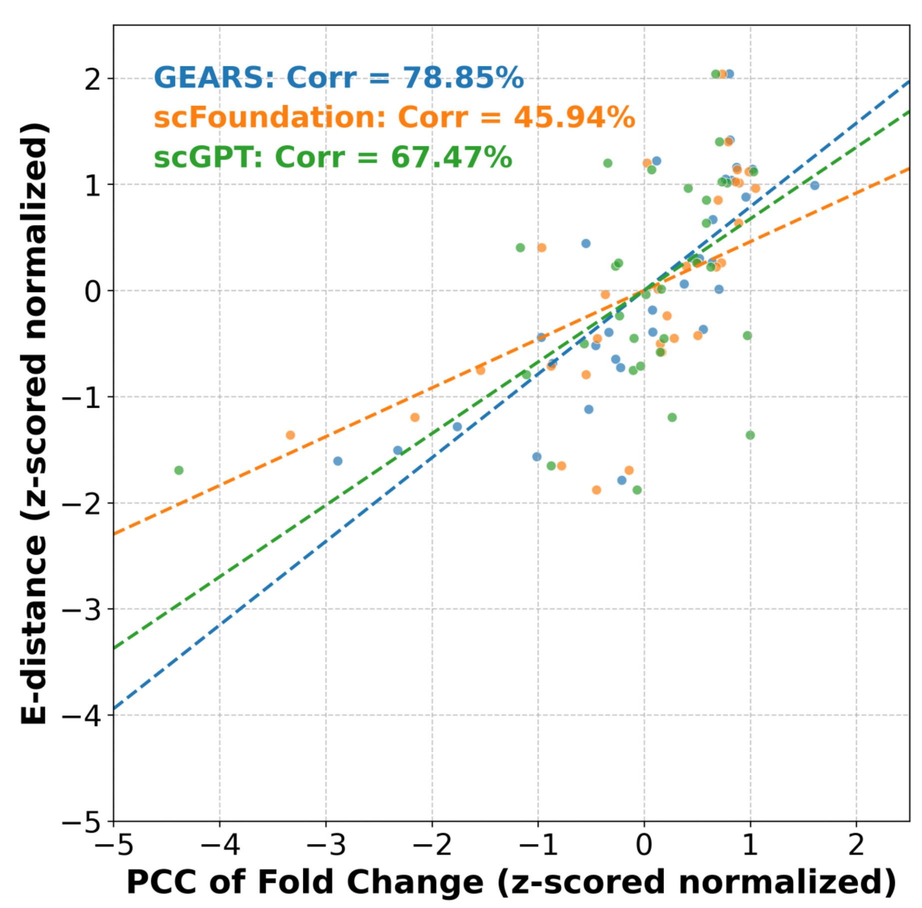
High overall predictive accuracy does not ensure individual prediction reliability.

High Average Accuracy Masks Individual Errors: Models with high overall performance can still fail dramatically on specific, individual predictions, affecting practical utility.

Existing Methods Fall Short: Current models lack robust, instance-level uncertainty scores, especially for out-of-distribution perturbations.

The Goal: A robust framework that jointly accounts for both uncertainty types to produce a holistic confidence score.

The Challenge of Uncertainty & Our Solution



E-distance exhibits a strong correlation with prediction accuracy across these models.

Deconstructing the Problem: The unreliability of predictions stems from two distinct sources of uncertainty:

(a. Aleatoric (Data) Uncertainty: The inherent randomness and variability in biological systems. The outcome of a perturbation is naturally stochastic.

(b. Epistemic (Model) Uncertainty: The model's unfamiliarity with a given input. This is especially high for perturbations unseen during training.

The Core Formula: Pseudo E-distance

$$\widetilde{E} := 2\nu^{\text{post}} - \mathbb{H}(\mathbb{P}(\boldsymbol{x_i}|\boldsymbol{\omega}))$$

- $2\nu^{\text{post}}$: **Posterior Evidence**, quantifies **Epistemic Uncertainty** (Model's confidence). High evidence indicates the prediction is well-supported by training data, while low evidence suggests an out-of-distribution input.
- $-\mathbb{H}(\mathbb{P}(\boldsymbol{x_i}|\boldsymbol{\omega}))$: **Negative Predictive Entropy** quantifies **Aleatoric Uncertainty**. Lower entropy is associated with more consistent perturbation effects, and vice versa.

More Details…

Paper

Code

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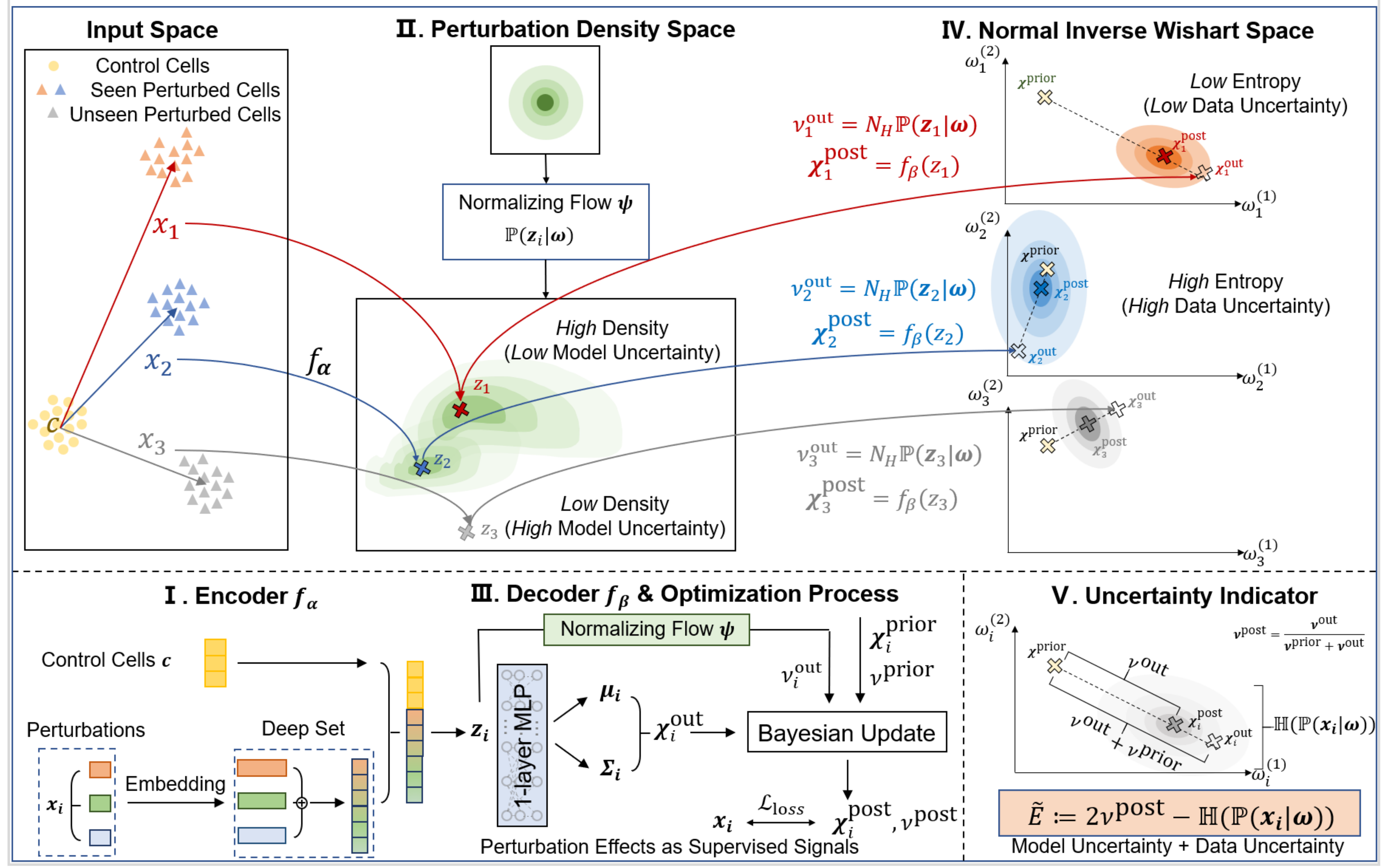
PRESCRIBE Method: Unifying Uncertainty



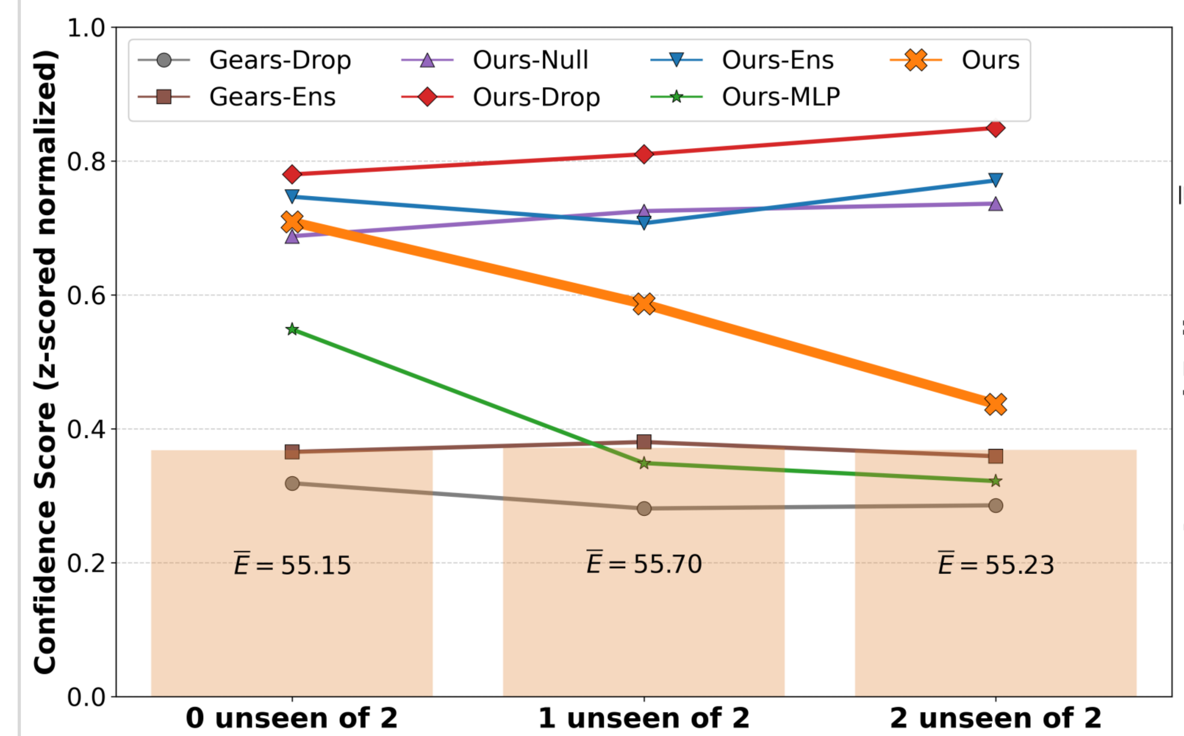
Core Workflow

- **Encoder (I)**: Generates a latent embedding z_i for each perturbation.
- **Normalizing Flow (II)** : Estimates density in the latent space to quantify epistemic uncertainty. High density implies low uncertainty.
- **Decoder (III)** : Maps the latent embedding to the parameters of the predictive distribution. To make the latent space linearly separable, a 1-layer MLP is adopted.
- **Bayesian Update (III)**: Combines the prior with the network's outputs (from the decoder and flow) to form the final posterior distribution.
- **Uncertainty Indicator (IV)**: Computes the final pseudo E-distance from the posterior distribution's parameters and the evidence output from the normalizing flow.

Algorithm 1 Training Process of PRESCRIBE

```
Input:
    Perturbation types: X;
    Condition information: c, χ^prior;
    Prior evidence: ν^prior;
    Post-perturbed transcriptomics expressions: y_i;
    E-distance of training samples: E_i;
Initialize:
    θ = {θ_α, θ_ψ, θ_β} ← initialize network parameters;
repeat
    x_i ← random mini-batch from X;
    z_i ← f_α(x_i, c); // Encoder;
    n_i ← f_φ(z_i); // Flow;
    χ_i = {χ_1, χ_2} ← f_β(z_i); // Decoder;
    // Bayesian Posterior Update;
    χ_i ← compute through Eq. 4;
    ν_i^post, ν_i ← compute through Eq. 8;
    κ_i^post ← 2 · ν_i^post;
    χ_i^post ← (ν^prior χ^prior + ν_i χ_i) / (ν_i + ν^prior);
    μ_{0x_i}^post ← χ_1^post;
    L^post ← Cholesky((χ_2^post − (χ_1^post)^2) × (ν_i^post)^2) × ν_i^post;
    ℒ ← compute through Eq. 9;
    // Update parameters according to gradients;
    θ ← θ − ∇_θ ℒ;
until deadline reached
```

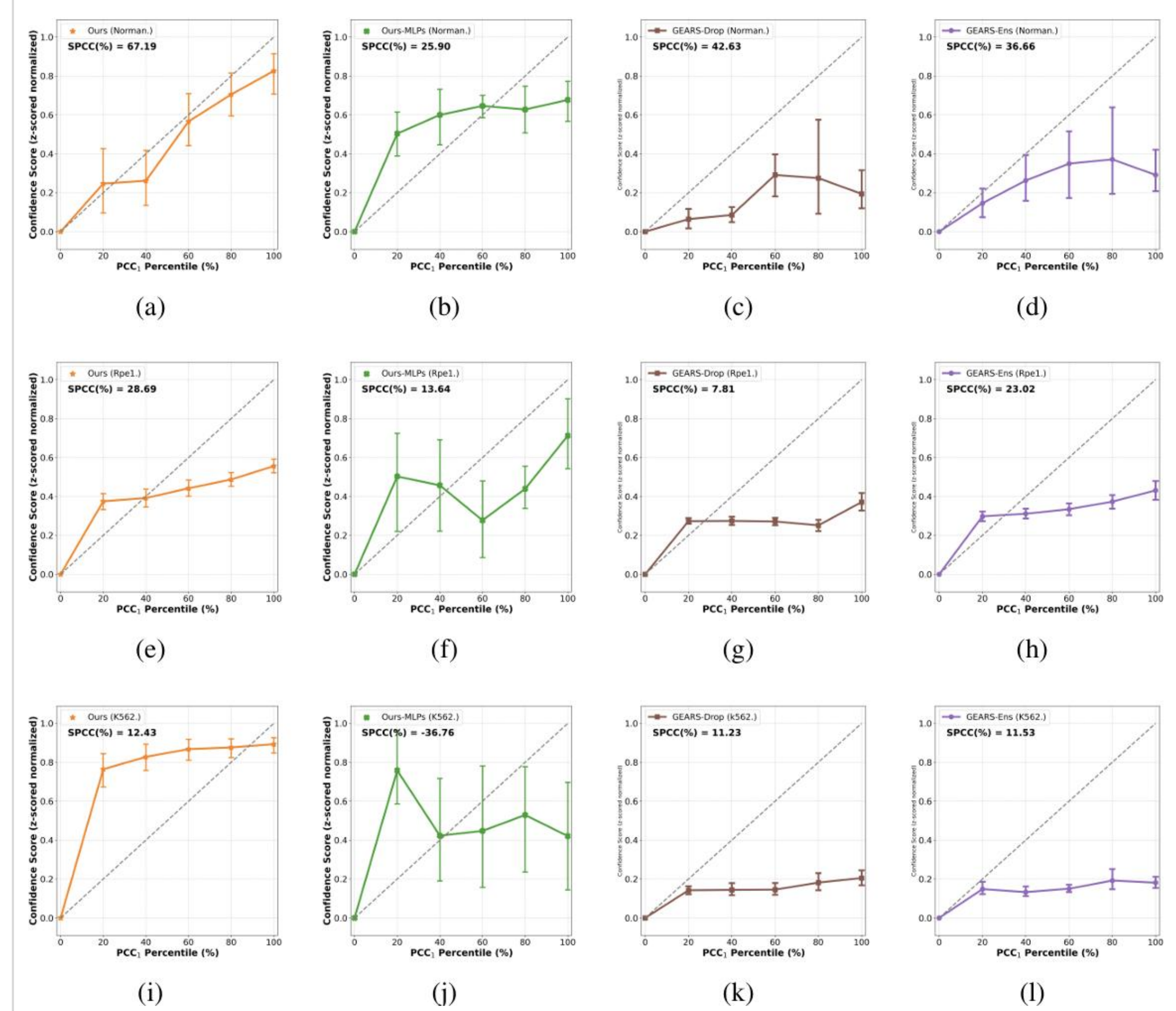
Confidence Scales with Generalization Difficulty



When predicting on more complex combinations, PRESCRIBE's confidence score drops significantly.

Baselines show a minor decrease or even an inverse trend, indicating a lack of awareness of different degrees of generalization.

Well-Calibrated Uncertainty Estimates



Uncertainty-Guided Filtering Boosts Accuracy

Models	Norman. $r_{\text{pred,truth}}\uparrow$	Norman. $r^{\text{DEG}}_{\text{pred,truth}}\uparrow$	Norman. $\text{ACC}_{\text{pred,truth}}\uparrow$	Norman. $\text{ACC}^{\text{DEG}}_{\text{pred,truth}}\uparrow$	Rep1. $r_{\text{pred,truth}}\uparrow$	Rep1. $r^{\text{DEG}}_{\text{pred,truth}}\uparrow$	Rep1. $\text{ACC}_{\text{pred,truth}}\uparrow$	Rep1. $\text{ACC}^{\text{DEG}}_{\text{pred,truth}}\uparrow$	K562. $r_{\text{pred,truth}}\uparrow$	K562. $r^{\text{DEG}}_{\text{pred,truth}}\uparrow$	K562. $\text{ACC}_{\text{pred,truth}}\uparrow$	K562. $\text{ACC}^{\text{DEG}}_{\text{pred,truth}}\uparrow$
AverageKnown	39.64	58.98	27.23	61.94	54.53	57.89	53.66	32.33	36.86	46.11	59.18	56.14
Linear	37.68	55.54	26.87	61.94	38.01	40.70	47.65	30.15	25.70	32.42	52.54	52.36
Linear-scGPT	39.20	58.66	27.23	61.94	50.09	53.95	49.69	31.31	33.86	42.97	54.79	54.37
CellOracle	9.80	12.48	19.20	16.35	39.91	7.40	37.55	23.70	4.44	5.89	41.41	41.15
samsVAE	12.48	32.05	37.42	49.63	12.59	36.45	33.04	25.08	8.51	29.03	36.44	43.55
GraphVCI	12.02	30.66	27.95	33.95	14.39	36.30	41.41	25.08	9.73	28.91	45.66	43.55
scFoundation	60.79	65.65	35.66	62.26	47.60	59.46	53.38	43.96	25.15	47.30	57.11	57.32
scGPT	61.48	65.87	61.96	74.43	50.32	65.54	61.72	67.07	32.72	43.15	57.44	57.32
GEARS	45.30	63.19	29.09	69.06	48.18	53.59	51.08	32.33	32.57	42.68	56.33	56.14
GEARS-Drop	44.96	60.38	29.92	68.28	46.49	51.05	52.25	37.08	31.26	42.88	56.34	57.67
GEARS-Drop-5%	45.05	59.61	29.72	66.83	47.01	51.27	52.25	36.79	31.66	43.54	56.28	57.44
GEARS-Drop-10%	49.72	65.23	30.57	70.18	45.34	48.68	52.09	36.93	31.94	43.65	56.48	58.22
GEARS-Ens	45.94	62.44	29.21	69.38	47.87	49.92	51.91	34.30	30.58	42.99	56.22	56.36
GEARS-Ens-5%	45.95	61.85	29.01	68.00	48.32	49.72	51.91	33.94	30.99	43.60	56.16	56.12
GEARS-Ens-10%	50.91	67.42	29.86	71.43	48.05	50.07	51.99	34.06	31.29	43.84	56.42	56.91
PRESCRIBE-Null	14.40	43.84	51.19	65.97	8.50	16.95	51.83	55.89	10.96	21.80	52.38	56.30
PRESCRIBE	58.38	64.44	63.24	74.68	59.18	65.50	67.36	79.81	36.20	44.36	60.27	69.69
PRESCRIBE-5%	61.58	66.36	64.08	75.69	60.20	66.07	67.76	79.94	38.28	46.63	60.99	71.15
PRESCRIBE-10%	64.32	68.61	64.73	75.93	60.28	66.13	67.89	80.03	38.58	47.52	61.04	71.21