



# scDFM

## Distributional Flow Matching for robust Single-Cell Perturbation Prediction

**Chenglei Yu<sup>1, 2\*</sup>, Chuanrui Wang<sup>2\*</sup>, Bangyan Liao<sup>1, 2</sup>, Tailin Wu<sup>2†</sup>**

[1] Zhejiang University, [2] School of Engineering, Westlake, \* Equal Contribution, † Corresponding Author

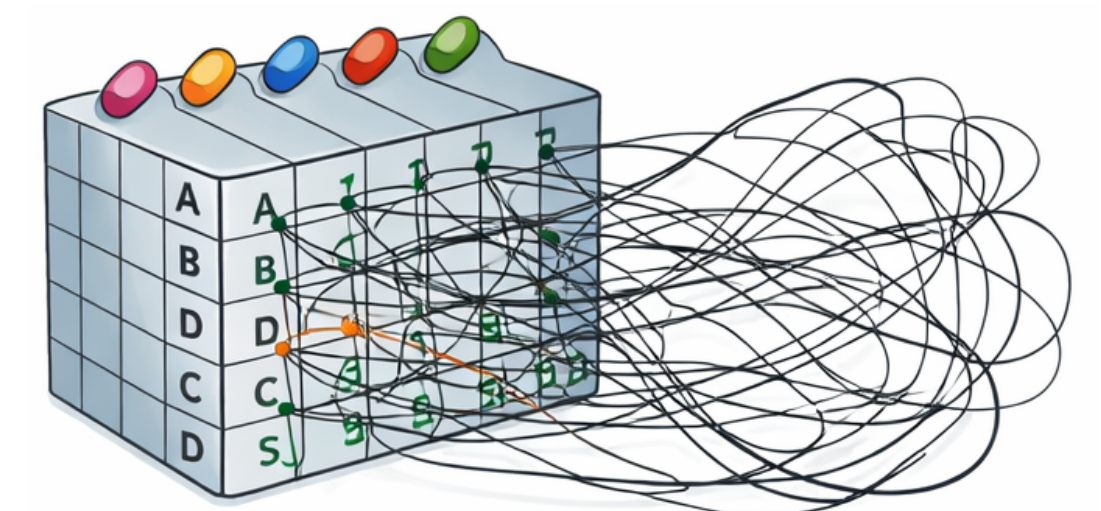
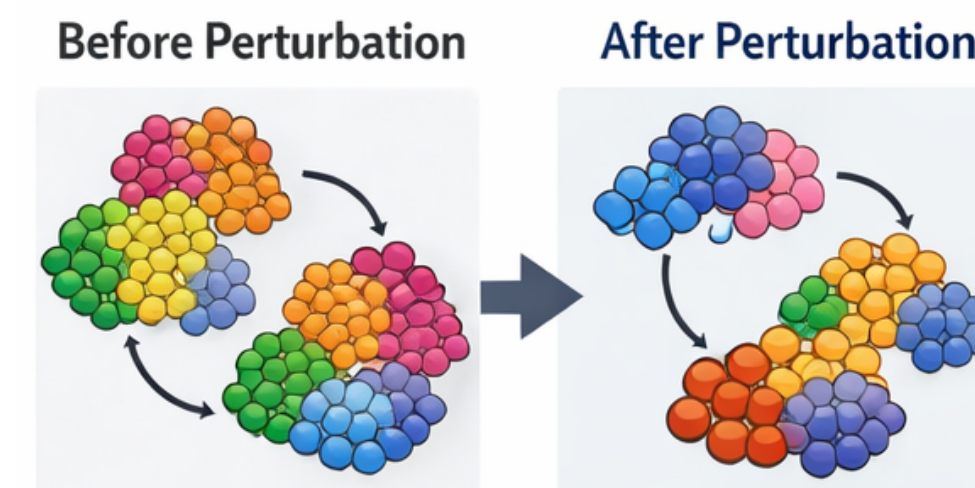
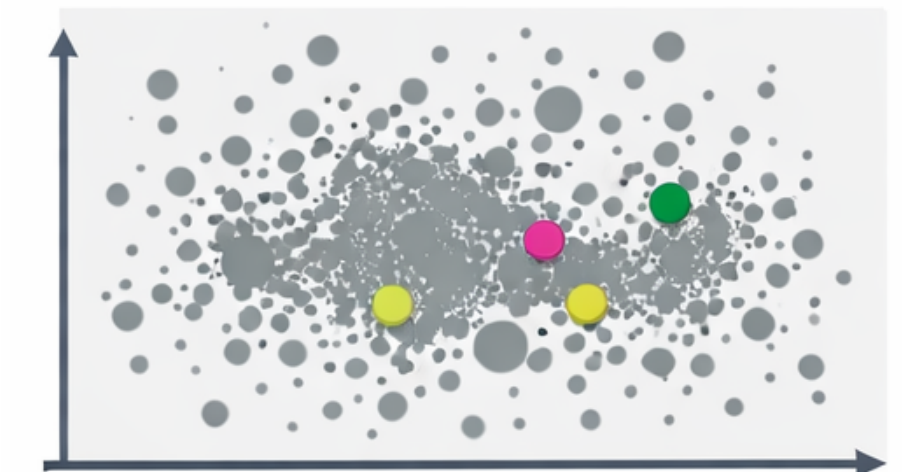
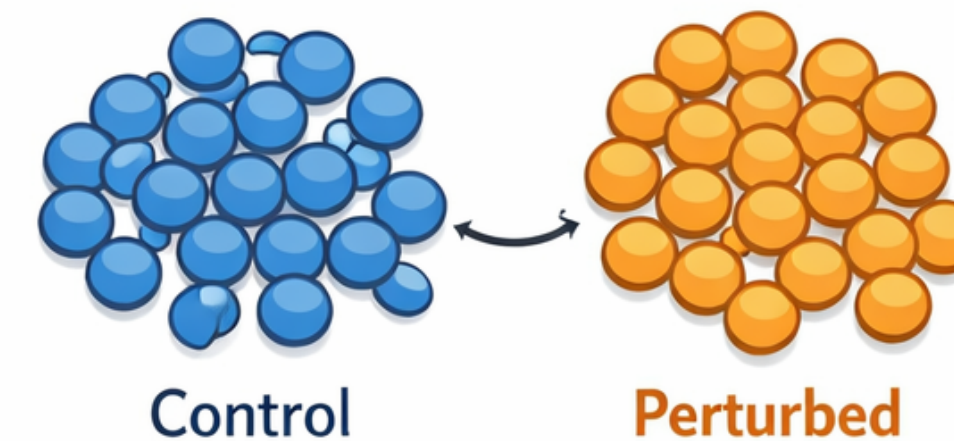
# Motivation

Single-cell perturbation prediction is a distribution shift problem



Why is this hard?

- Unpaired data
- High noise & Sparsity
- Perturbations induce population-level shifts
- Combinatorial space explodes for multi-gene/Multi-drug perturbation



# Motivation



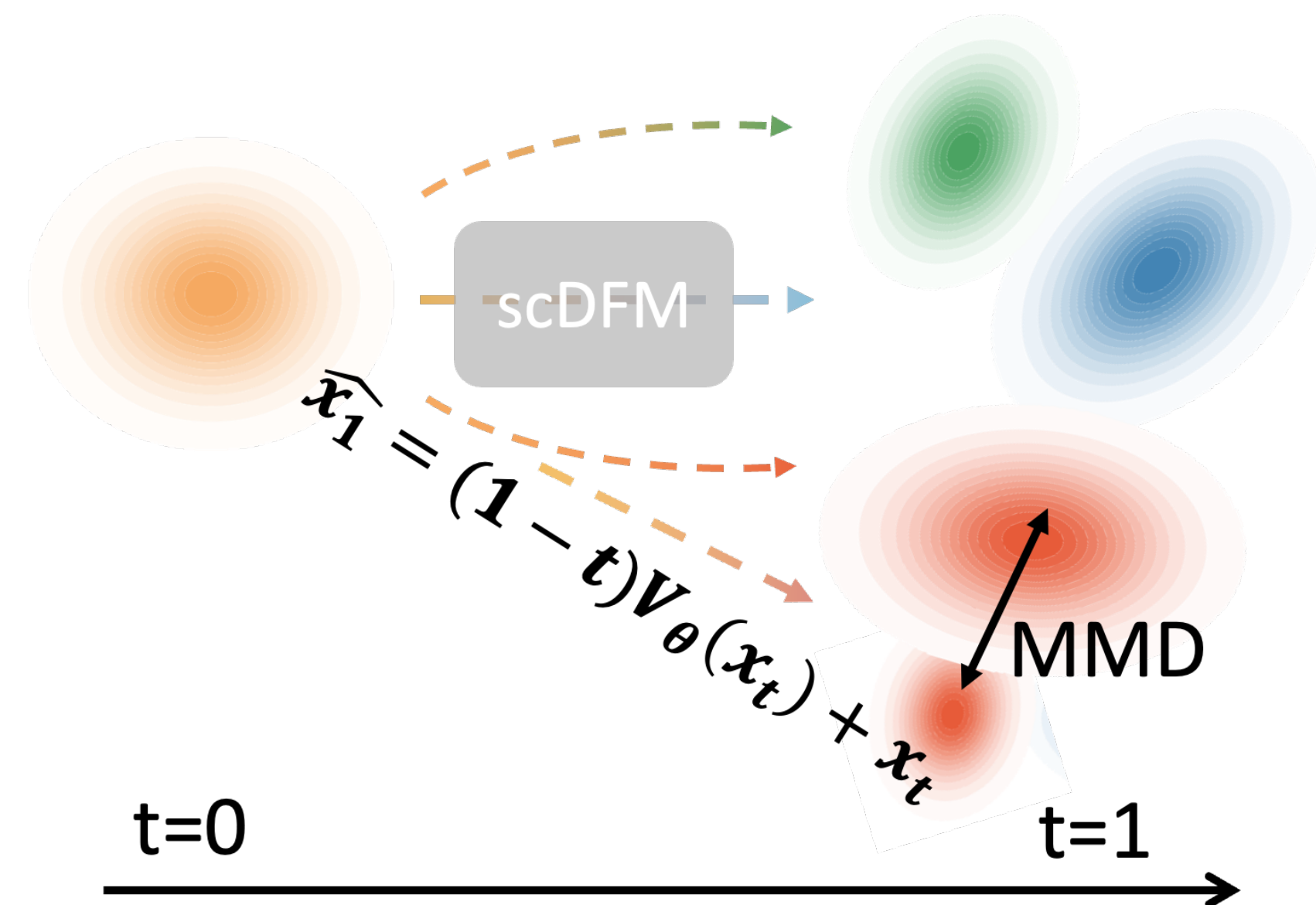
Single-cell perturbation prediction is a distribution shift problem

## Common pitfall

Assuming cell-level correspondence  
(Control Cell  $\leftrightarrow$  Perturbed Cell)

## What we want instead

Model the whole  
perturbed population



# Key Idea

## From “cell matching” to conditional distribution generation



Reformulate perturbation prediction as :

**Learn  $p_{\theta}(x | c_x, c_p)$  that generates the entire perturbed population**

$c_x$  = control state,  $c_p$  = perturbation condition

### Flow Matching

Learn a continuous velocity field to transform samples from source  $\rightarrow$  target distributions.

### MMD Alignment

Regularize endpoint to match the true perturbed population (multi-kernel MMD).

### PAD-Transformer

Noise-robust backbone using gene-graph masks + differential attention.

# Method

## Conditional Flow Matching + distribution-level regularization

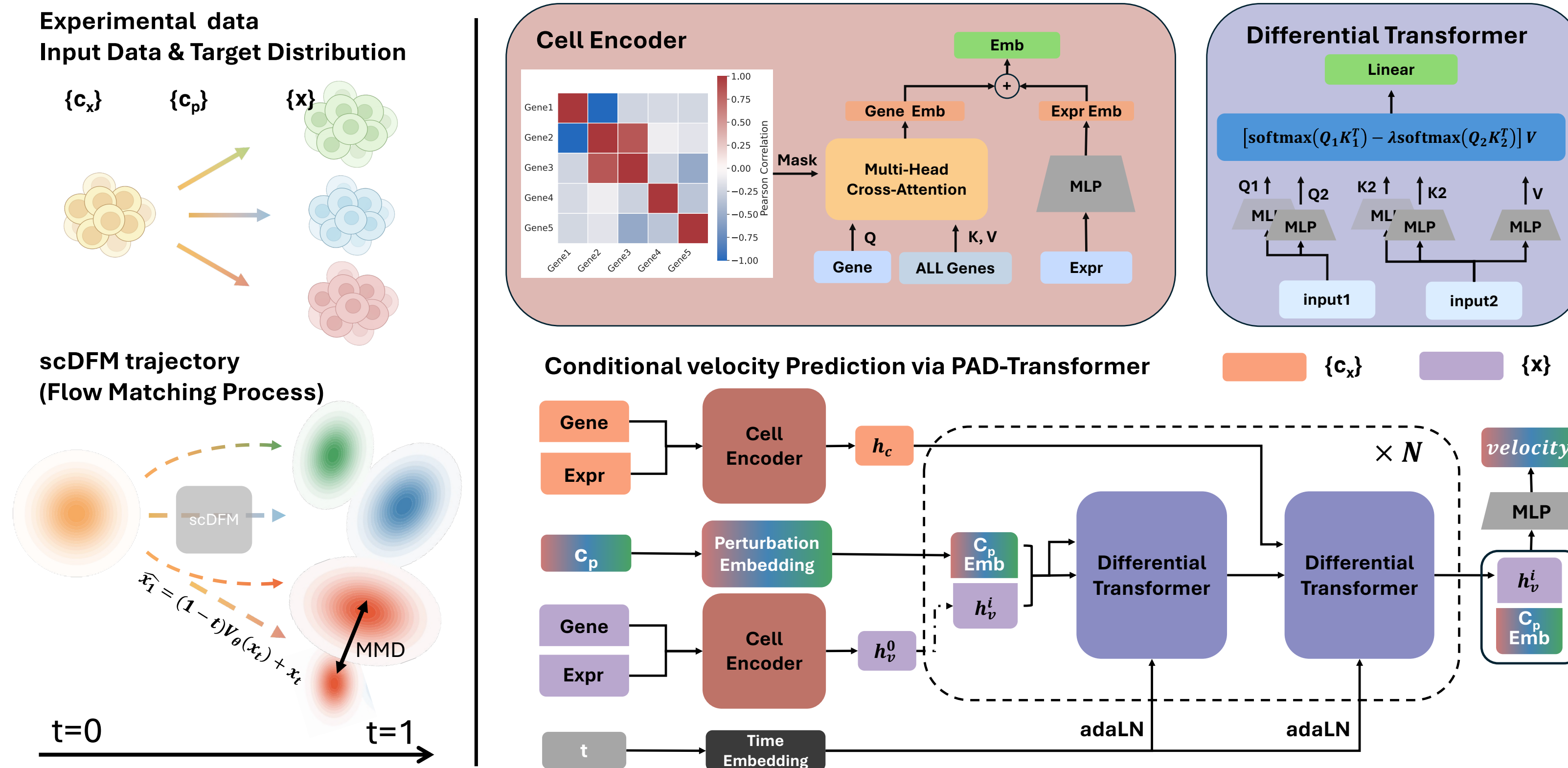


Figure: scDFM overview (flow matching trajectory + PAD-Transformer velocity predictor + MMD)

Training objective:  $L = L_{CFM} + \lambda L_{MMD}$



# Method

## Conditional Flow Matching + distribution-level regularization

1. Learns a time-dependent velocity field that continuously transforms control cells into perturbed cells.

$$L_{CFM}(\theta) = \mathbb{E}_{c_x, c_p} \mathbb{E}_{x_0 \sim q_0, x_1 \sim q_1(\cdot | c_x, c_p)} \mathbb{E}_{t \sim \mathcal{U}(0,1)} \left[ \left\| v_{\theta}(x_t | t, c_x, c_p) - v(x_t | x_0, x_1, t, c_x, c_p) \right\|_2^2 \right].$$

2. Multi-kernel Gaussian RBF loss enforces distributional fidelity between predicted and real cell populations.

$$L_{MMD}(\theta) = \mathbb{E}_{c_x, c_p} \mathbb{E}_{x_0 \sim q_0, x_1 \sim q_1(\cdot | c_x, c_p)} \mathbb{E}_{t \sim \mathcal{U}(0,1)} k_{\text{mix}} \left( x_1, \hat{x}_1(x_t, t, c_x, c_p) \right)$$

3. Uses perturbation-aware differential attention and gene-graph context to predict biologically meaningful velocity fields.

$$L = L_{CFM} + \lambda L_{MMD}$$

# Experimental setup

## Datasets, splits, and metrics



### Benchmarks

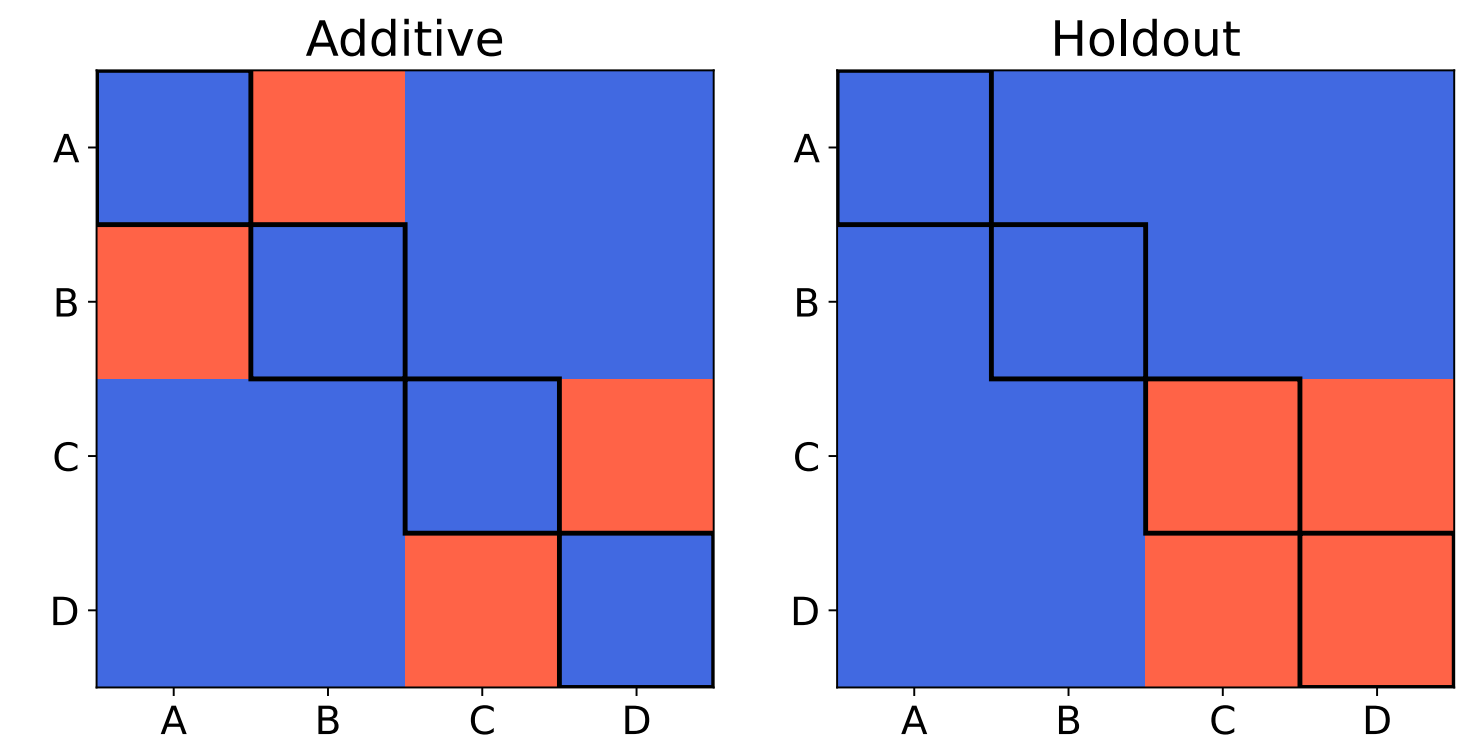
- Norman (CRISPR genetic perturbations; single + double)
- ComboSciPlex (combinatorial drug perturbations)

### Evaluation splits

- Additive: all singles seen; test unseen doubles made from seen singles
- Holdout: remove some singles and all doubles involving them → test unseen singles & doubles

### Split schematic

■ Single (train) ■ Single (test) ■ Double (train) ■ Double (test)

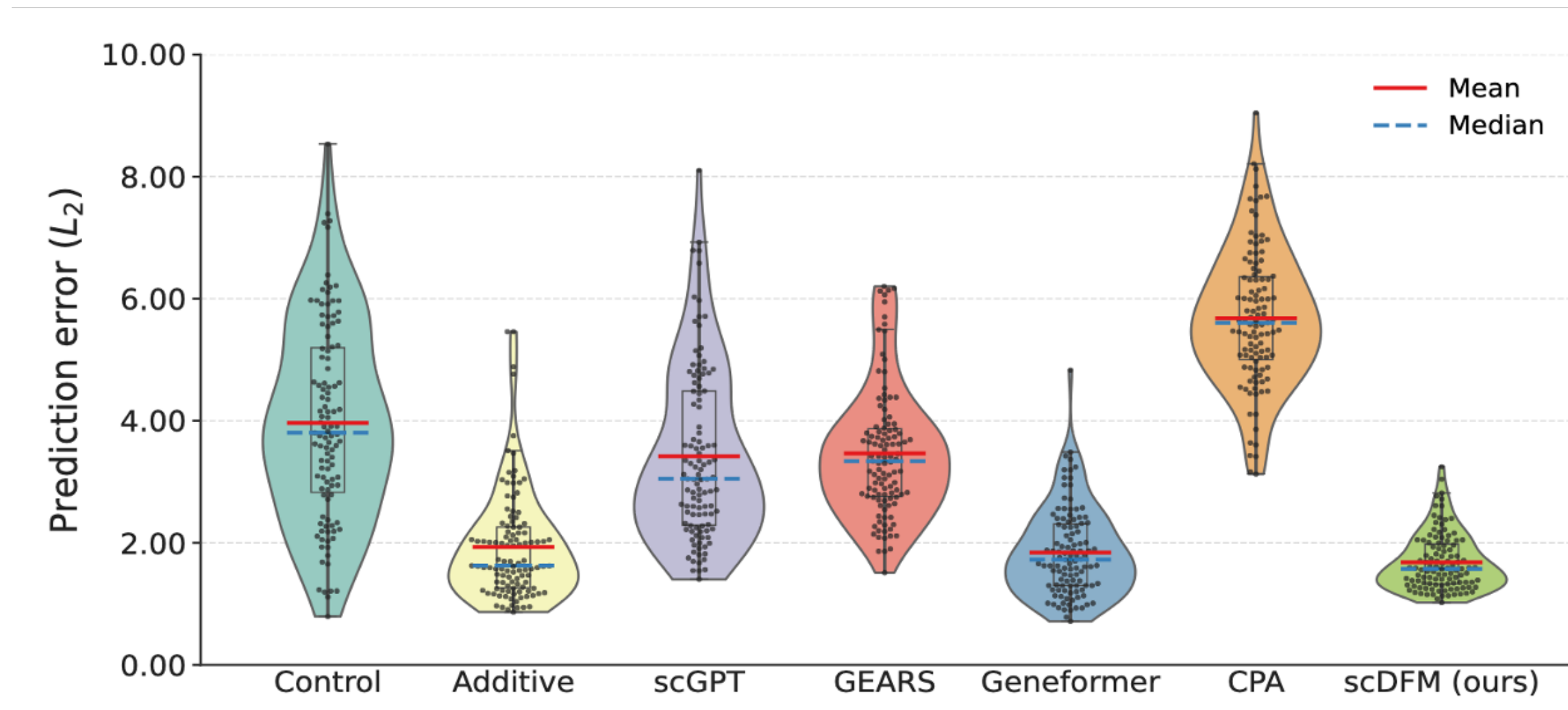


### Metrics

1. Pointwise: MAE / MSE / L2, Pearson  $\Delta$
2. Distribution: DS (discrimination score)
3. Differential expression: DE-Spearman (rank corr. on DE genes)

# Results

## Norman(Additive)



MSE vs best baseline

**-19.6%**

0.00315 vs 0.00392 (CellFlow)

DS

**0.9737**

Higher is better

DE-Spearman

**0.5705**

Captures DE gene ranking

Table 1: Comparison of different methods across evaluation metrics on the Norman additive split.

| Model               | L2 ↓          | MSE ↓          | MAE ↓          | DE-Spearman $\rho$ ↑ | Pearson $\Delta$ ↑ | DS ↑          | Pearson $\hat{\Delta}$ ↑ | Pearson $\hat{\Delta}_{20}$ ↑ |
|---------------------|---------------|----------------|----------------|----------------------|--------------------|---------------|--------------------------|-------------------------------|
| Control             | 3.9937        | 0.01839        | 0.03953        | N.A.                 | N.A.               | 0.5135        | -0.1695                  | -0.1297                       |
| Additive            | 1.9395        | 0.00448        | 0.02276        | 0.5564               | <b>0.9024</b>      | <u>0.9686</u> | <b>0.8584</b>            | <u>0.9244</u>                 |
| scGPT               | 3.4112        | 0.01349        | 0.03796        | 1.07e-5              | 0.5304             | 0.5404        | 0.2165                   | 0.2414                        |
| Geneformer          | 1.9132        | 0.00410        | 0.02360        | 0.3741               | 0.7732             | 0.8241        | -0.0078                  | 0.2239                        |
| GEARS               | 3.5531        | 0.01387        | 0.06624        | <u>0.5624</u>        | 0.7421             | 0.8601        | -0.0089                  | 0.2032                        |
| CPA                 | 5.7629        | 0.03435        | 0.07894        | 0.0713               | 0.3845             | 0.6021        | -0.0039                  | 0.2254                        |
| STATE               | 17.3330       | 0.30059        | 0.24705        | 0.5288               | -0.0108            | 0.5135        | -0.0069                  | 0.2515                        |
| CellFlow            | <u>1.7064</u> | <u>0.00392</u> | <u>0.02207</u> | 0.5503               | 0.8678             | 0.9321        | 0.8395                   | 0.8988                        |
| <b>scDFM (ours)</b> | <b>1.7043</b> | <b>0.00315</b> | <b>0.02155</b> | <b>0.5705</b>        | <u>0.8853</u>      | <b>0.9737</b> | <u>0.8468</u>            | <b>0.9260</b>                 |

# Results

## Norman(Holdout)



| Setting | Model               | L2 ↓          | MSE ↓         | MAE ↓         | DE-Spearman $\rho$ ↑ | Pearson $\Delta$ ↑ | DS ↑          | Pearson $\hat{\Delta}$ ↑ | Pearson $\hat{\Delta}_{20}$ ↑ |
|---------|---------------------|---------------|---------------|---------------|----------------------|--------------------|---------------|--------------------------|-------------------------------|
| Single  | Control             | 2.6834        | 0.0095        | 0.0263        | N.A.                 | N.A.               | 0.5217        | 0.1618                   | 0.1982                        |
|         | scGPT               | 2.5007        | 0.0080        | 0.0259        | -0.1139              | 0.4503             | 0.5680        | 0.0747                   | 0.0798                        |
|         | GEARS               | 2.5641        | 0.0075        | 0.0466        | 0.3569               | 0.6646             | <u>0.8271</u> | <u>0.6356</u>            | <u>0.7914</u>                 |
|         | Geneformer          | 1.6962        | 0.0036        | <u>0.0191</u> | 0.3669               | 0.6955             | 0.8070        | 0.5620                   | 0.6513                        |
|         | CPA                 | 5.8060        | 0.0356        | 0.0853        | 0.1168               | 0.2837             | 0.5796        | -0.0028                  | 0.0802                        |
|         | STATE               | 18.2543       | 0.3333        | 0.2693        | <u>0.6116</u>        | 0.0004             | 0.5236        | 0.0154                   | 0.2386                        |
|         | CellFlow            | <u>1.6758</u> | <u>0.0035</u> | <u>0.0191</u> | 0.2860               | <u>0.7109</u>      | 0.8072        | 0.6138                   | 0.6753                        |
|         | <b>scDFM (ours)</b> | <b>1.6186</b> | <b>0.0030</b> | <b>0.0190</b> | <b>0.6957</b>        | <b>0.7127</b>      | <b>0.8914</b> | <b>0.6659</b>            | <b>0.8116</b>                 |
| Double  | Control             | 4.1882        | 0.0207        | 0.0423        | N.A.                 | N.A.               | 0.5322        | -0.1303                  | -0.0265                       |
|         | scGPT               | 3.5171        | 0.0153        | 0.0362        | -0.0665              | 0.5693             | 0.5578        | 0.2814                   | 0.2652                        |
|         | GEARS               | 3.7458        | 0.0156        | 0.0708        | 0.2543               | 0.7552             | <u>0.8766</u> | 0.6407                   | <u>0.8413</u>                 |
|         | Geneformer          | <u>2.0819</u> | 0.0050        | 0.0237        | 0.3468               | 0.7361             | 0.8067        | 0.6245                   | 0.7261                        |
|         | CPA                 | 5.7891        | 0.0357        | 0.0796        | 0.3652               | 0.4176             | 0.6311        | 0.2432                   | 0.2870                        |
|         | STATE               | 18.4458       | 0.3404        | 0.2733        | 0.4071               | 0.0061             | 0.5289        | -0.0023                  | 0.2580                        |
|         | CellFlow            | 2.1042        | <u>0.0049</u> | <u>0.0236</u> | <u>0.5074</u>        | <u>0.8095</u>      | 0.8622        | <u>0.6780</u>            | 0.7155                        |
|         | <b>scDFM (ours)</b> | <b>2.0309</b> | <b>0.0047</b> | <b>0.0235</b> | <b>0.5676</b>        | <b>0.8357</b>      | <b>0.9189</b> | <b>0.7769</b>            | <b>0.8688</b>                 |

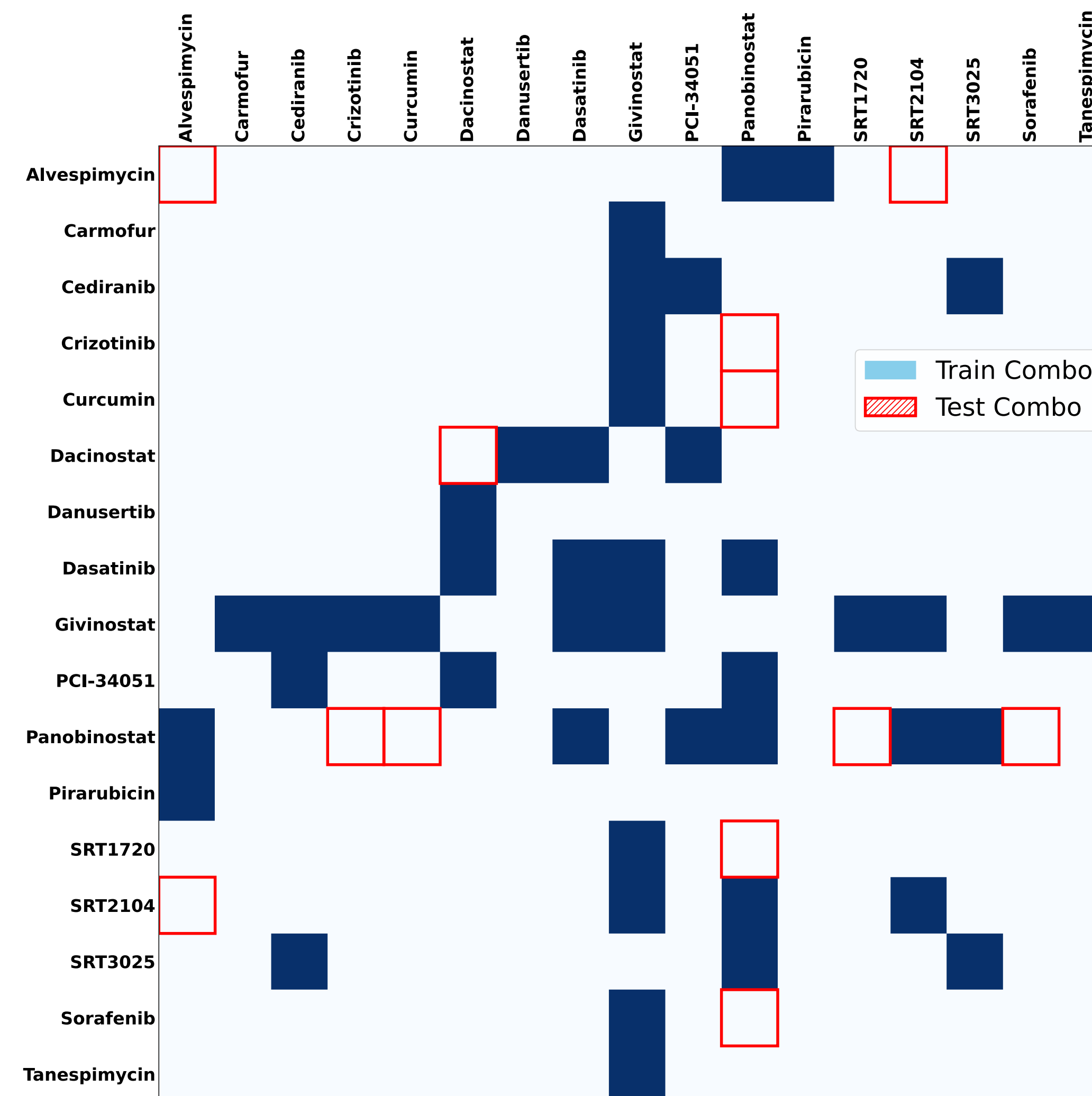
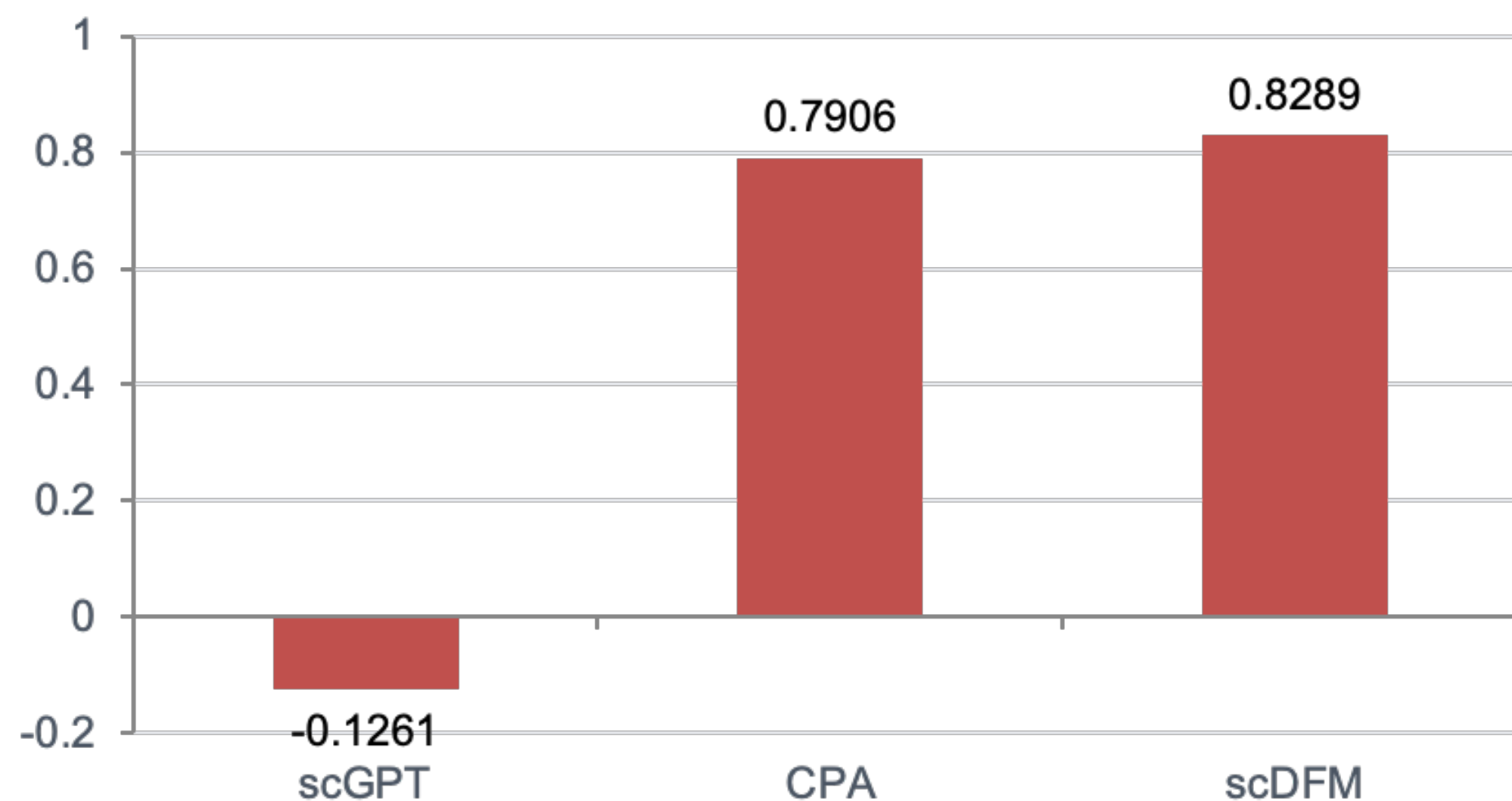
# Results

## ComboSciPlex



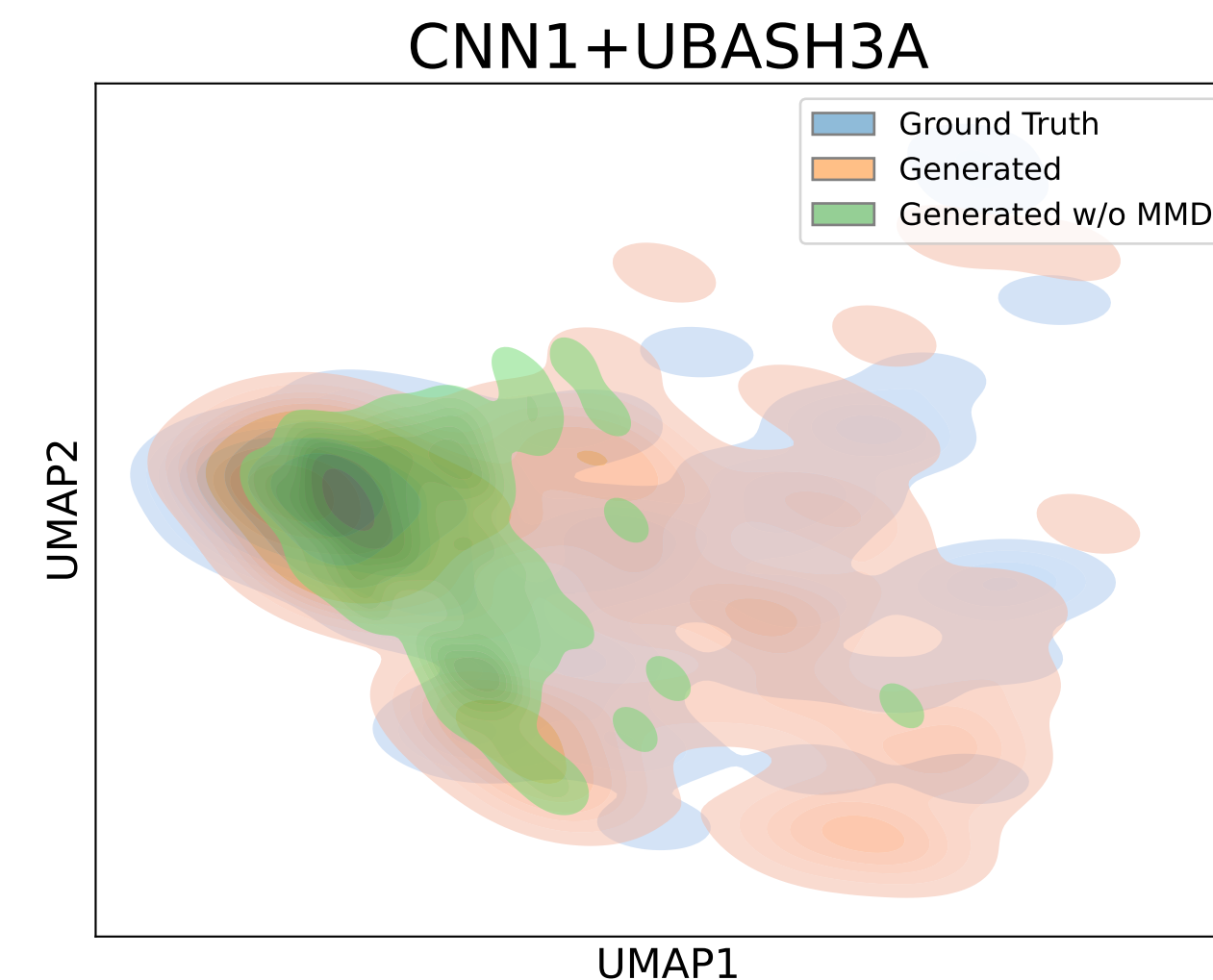
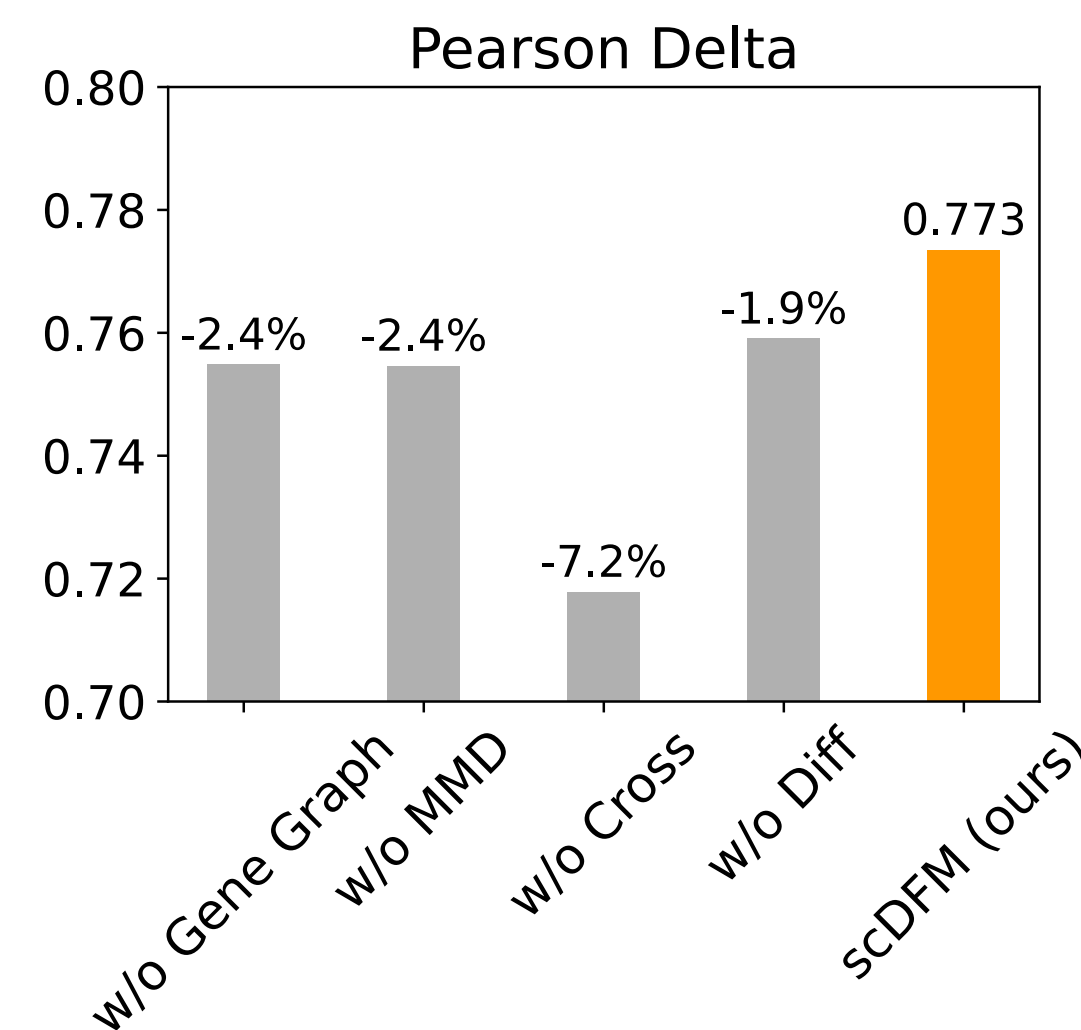
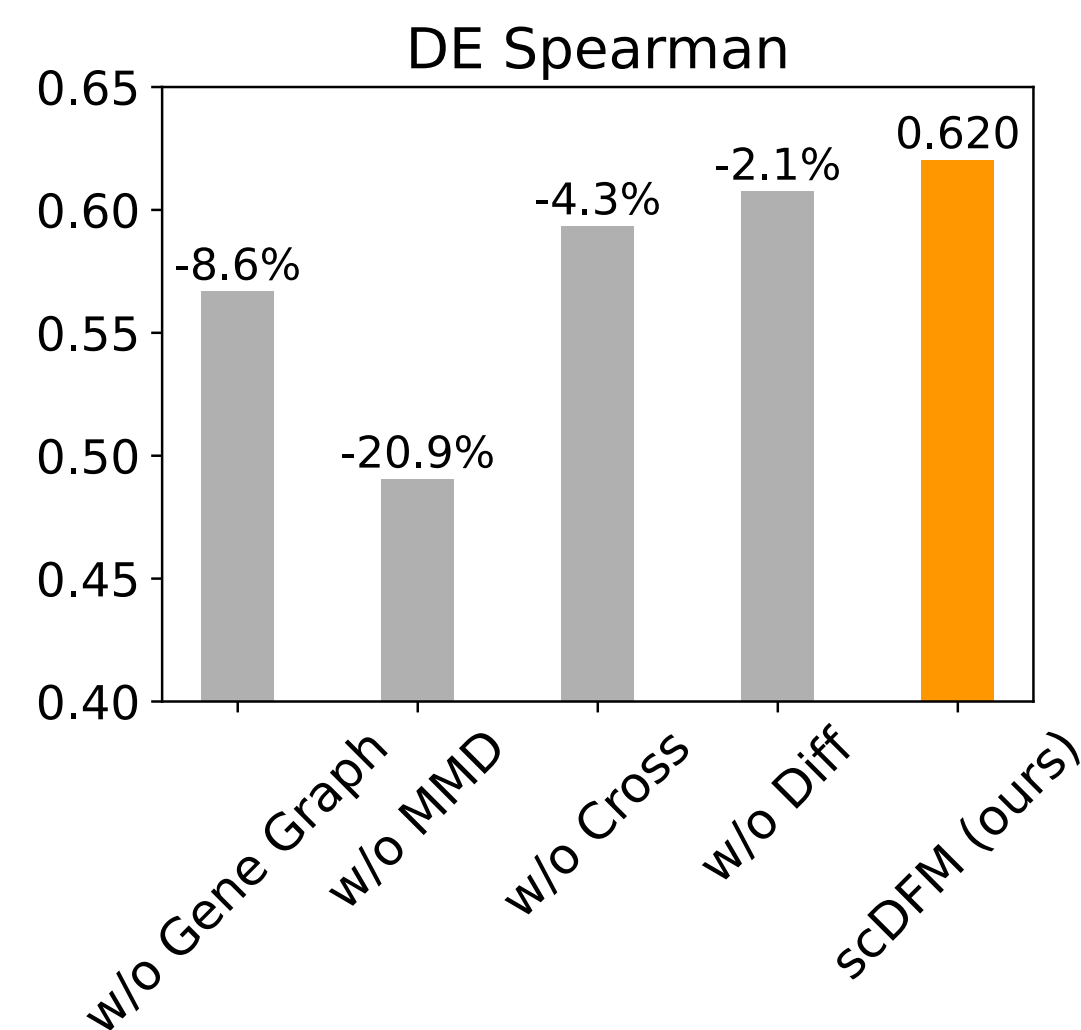
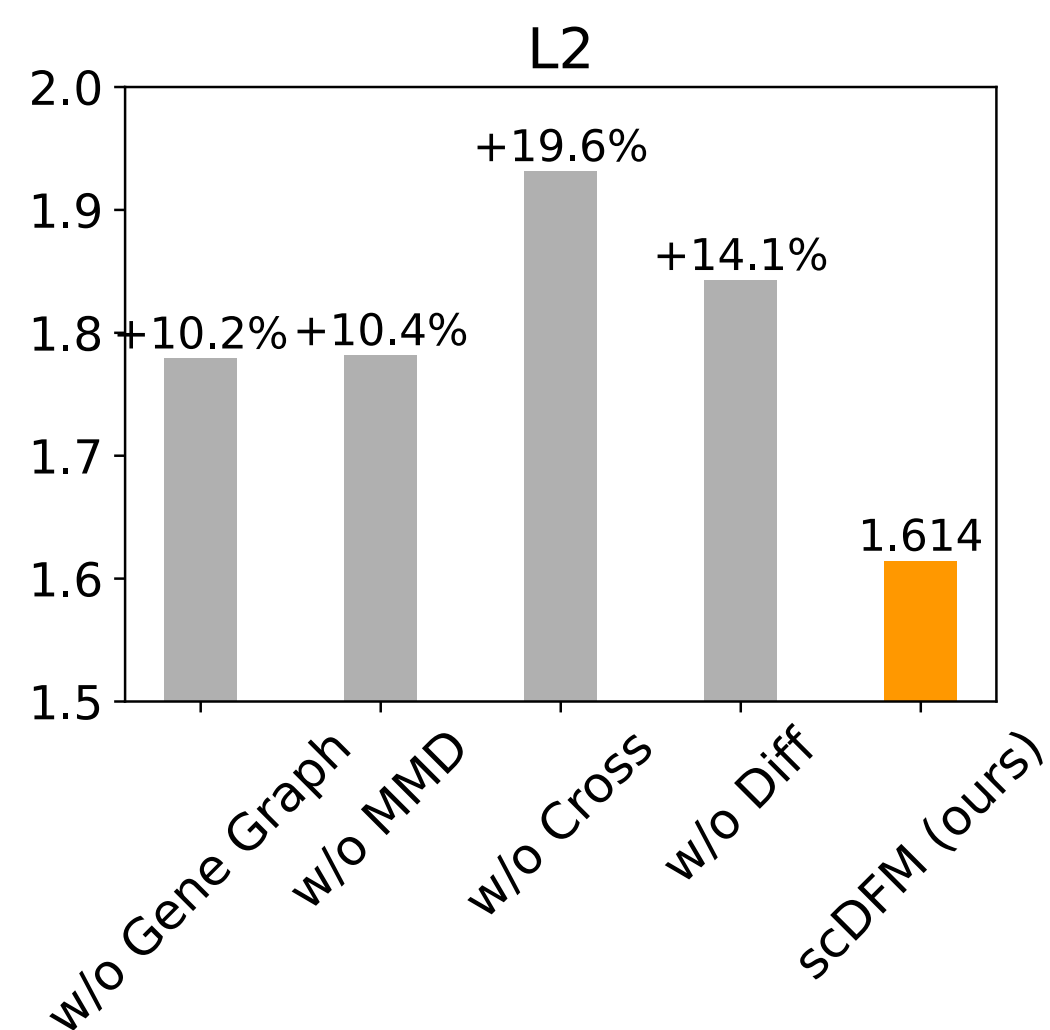
| Model               | L2 ↓          | MSE ↓         | MAE ↓         | DE-Spearman $\rho$ ↑ | Pearson $\Delta$ ↑ | DS ↑          |
|---------------------|---------------|---------------|---------------|----------------------|--------------------|---------------|
| Control             | 5.3716        | 0.0324        | 0.0698        | N.A.                 | N.A.               | 0.5714        |
| scGPT               | 1.6934        | 0.0031        | 0.0251        | -0.1261              | 0.8322             | 0.8571        |
| CPA                 | 1.6592        | 0.0029        | 0.0240        | 0.7906               | 0.8150             | <b>0.8980</b> |
| <b>scDFM (ours)</b> | <b>1.6567</b> | <b>0.0028</b> | <b>0.0220</b> | <b>0.8289</b>        | <b>0.8933</b>      | <u>0.8776</u> |

### DE-Spearman on ComboSciPlex



# Why does it work?

## Ablations + qualitative distribution alignment

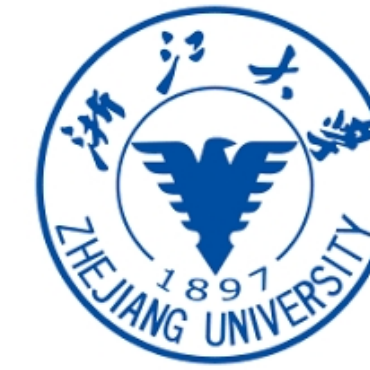


- MMD is critical for endpoint population fidelity
- Gene-graph mask improves robustness to noisy genes
- Differential attention improves DE signal recovery

### Observation

MMD aligns the endpoint distribution → stable, biologically consistent predictions.

# Takeaways



## Distribution-level generative modeling for perturbation prediction

### Main contributions

- Formulate perturbation prediction as conditional distribution generation
- Flow matching in expression space + MMD for endpoint distribution fidelity
- PAD-Transformer: gene-graph mask + differential attention for robustness to noise/sparsity
- Strong generalization to unseen and combinatorial perturbations (genes and drugs)



### Outlook

Towards “digital twins” of cellular response: simulate large perturbation spaces in silico to prioritize experiments.