2024 Datasets and Benchmarks Track

A benchmark for prediction of transcriptomic responses to chemical perturbations across cell types

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openproblems.bio/results/perturbation_prediction

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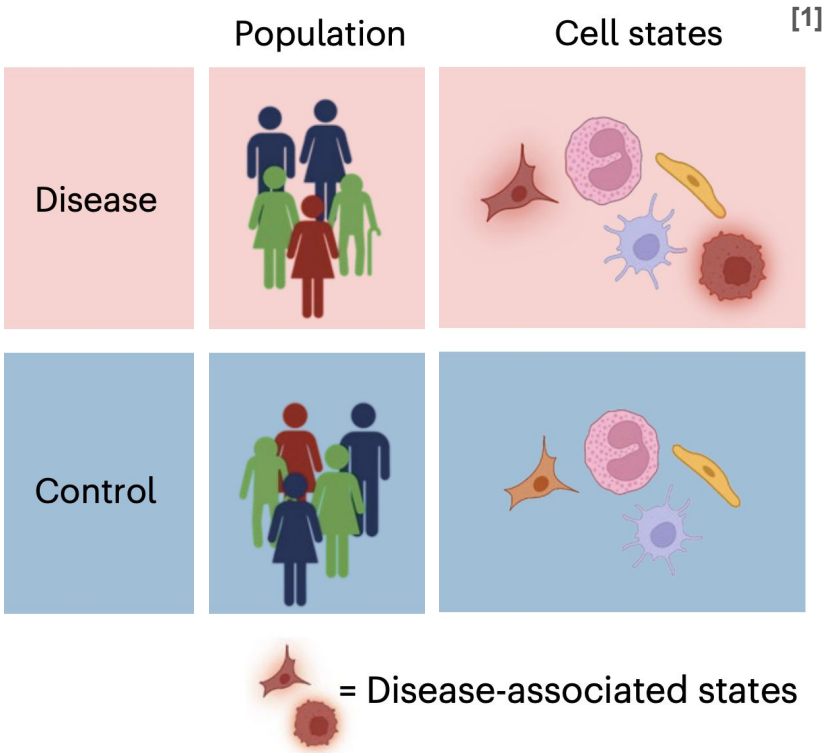
Single-cell RNA sequencing has the potential to unlock novel treatments for complex diseases

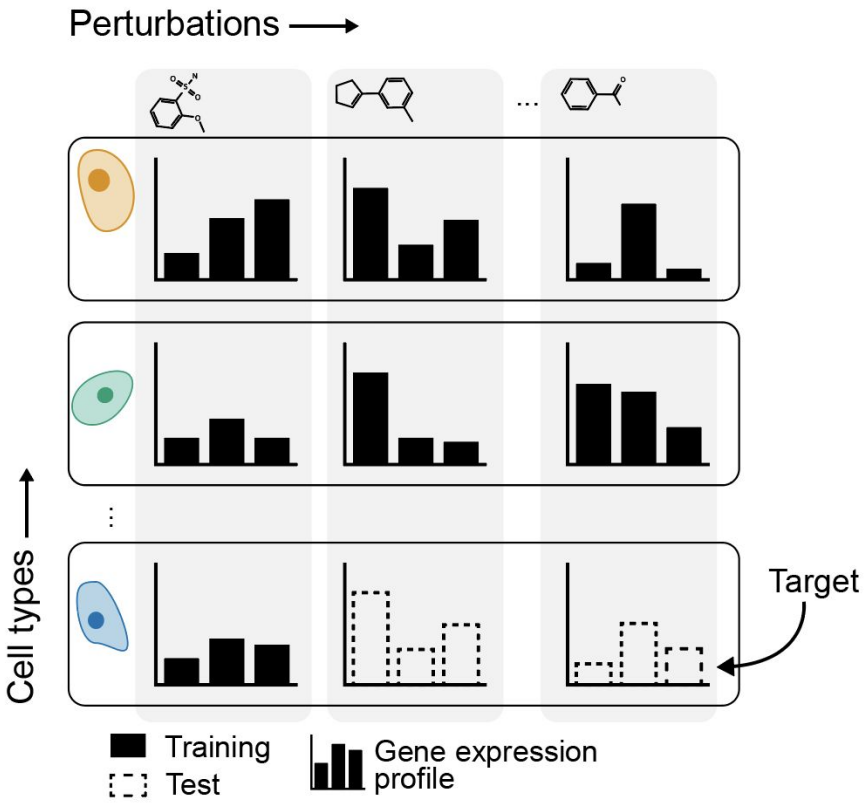
- Identification of transitions from disease to healthy cell states
- This information can be used for drug screening (inducing disease-to-healthy transitions)
- This could treat complex diseases that involve multiple biological pathways



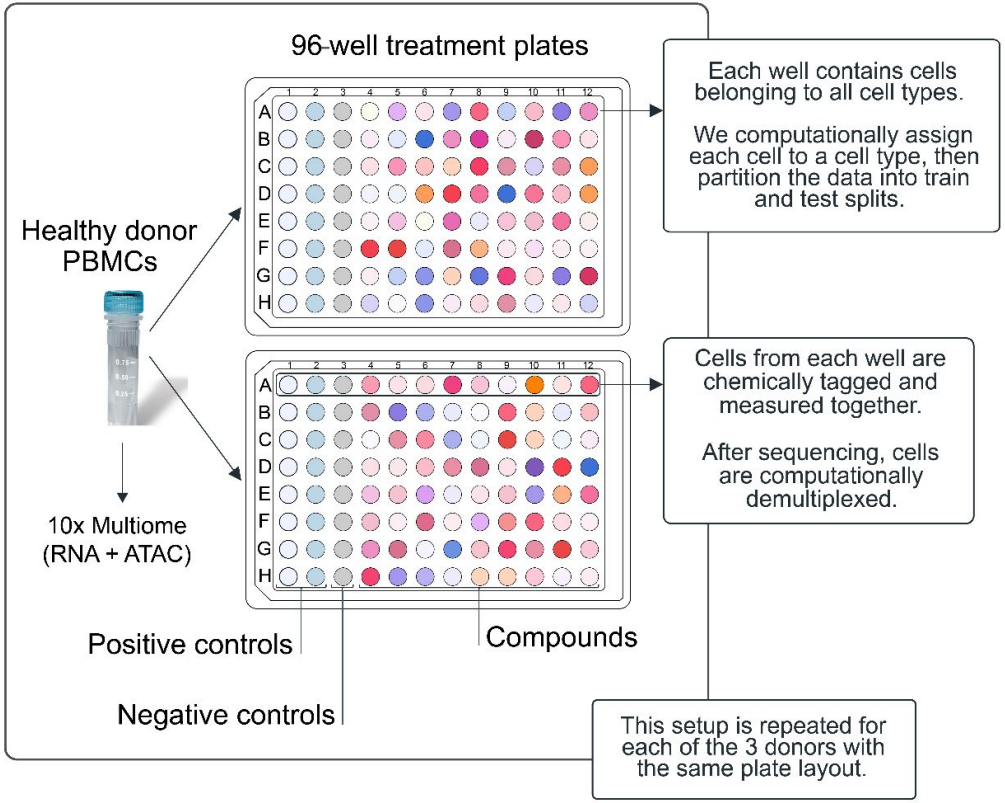
[1] Adapted from: Dann, Emma, et al. "Precise identification of cell states altered in disease using healthy single-cell references." Nature Genetics (2023)

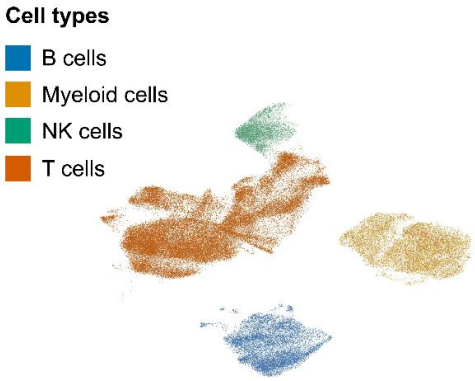
Perturbation prediction makes screening compounds against a change in gene expression tractable

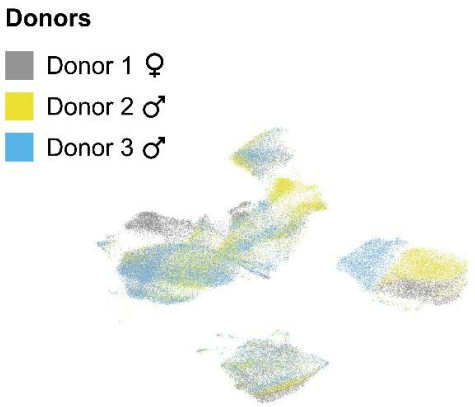
- Goal: understand how chemical perturbations impact gene expression
- Challenge: biological and chemical space are both very large
- Solution: measure a fraction of possible perturbations and infer the rest
- However, existing perturbation datasets are limited by size and data quality issues



A new single-cell dataset: 146 drug perturbations in human peripheral blood cells from 3 donors with 4 distinct cell types

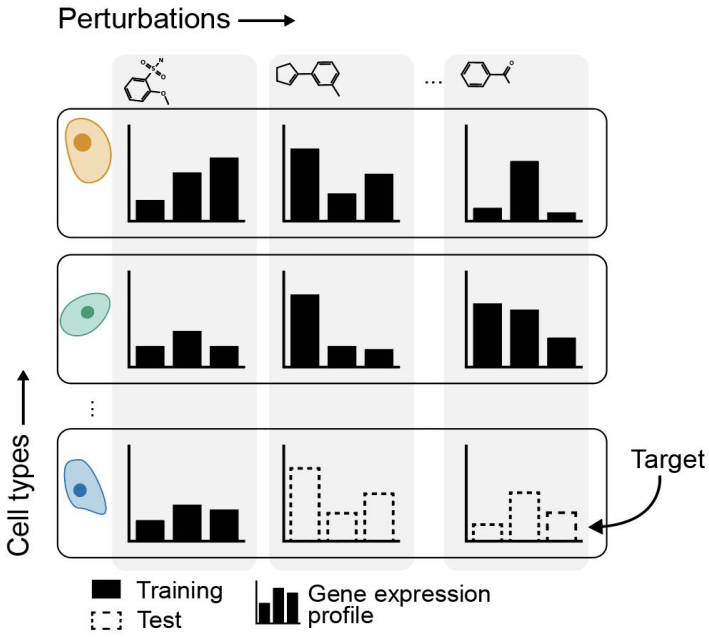






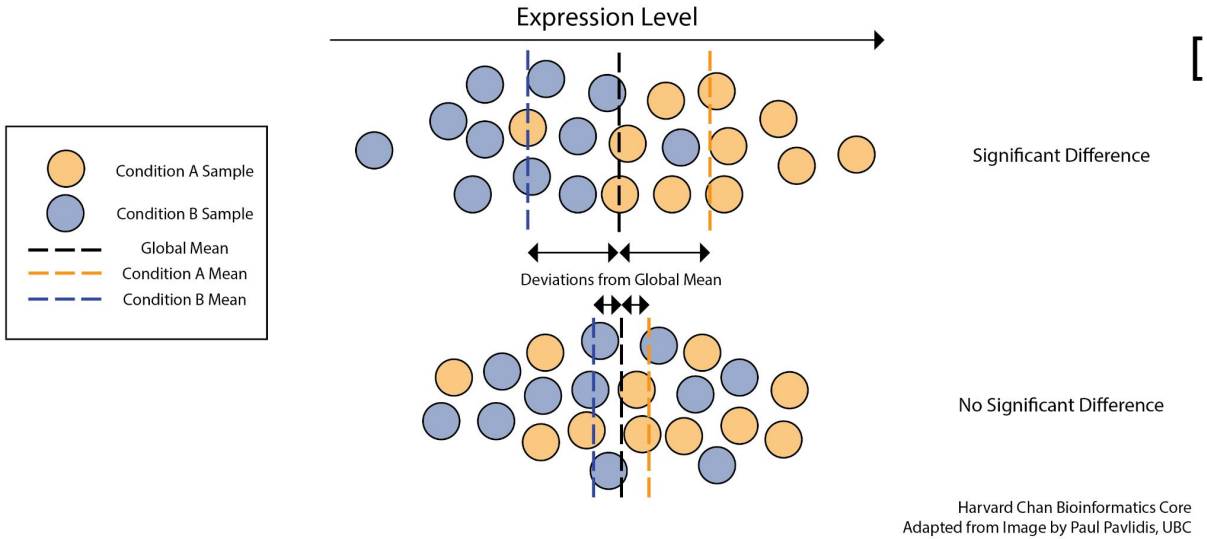
We developed a robust benchmark around this new dataset

- Task: predict perturbation effects for held out (cell type, compound) pairs
- Perturbation effects are derived from a generalized linear model contrasting treatment and control conditions
- p-value: probability that observed effects in treatment vs. control are random
- fold-change: magnitude of effect difference between treatment and control



Perturbation representation

- Perturbation effect is measured with a generalized linear model
- We propose cross-donor retrieval to evaluate the representation of perturbation effects
- Best representation: $-\log_{10}(p\text{-value}) \times \text{sign}(\text{log-fold change})$

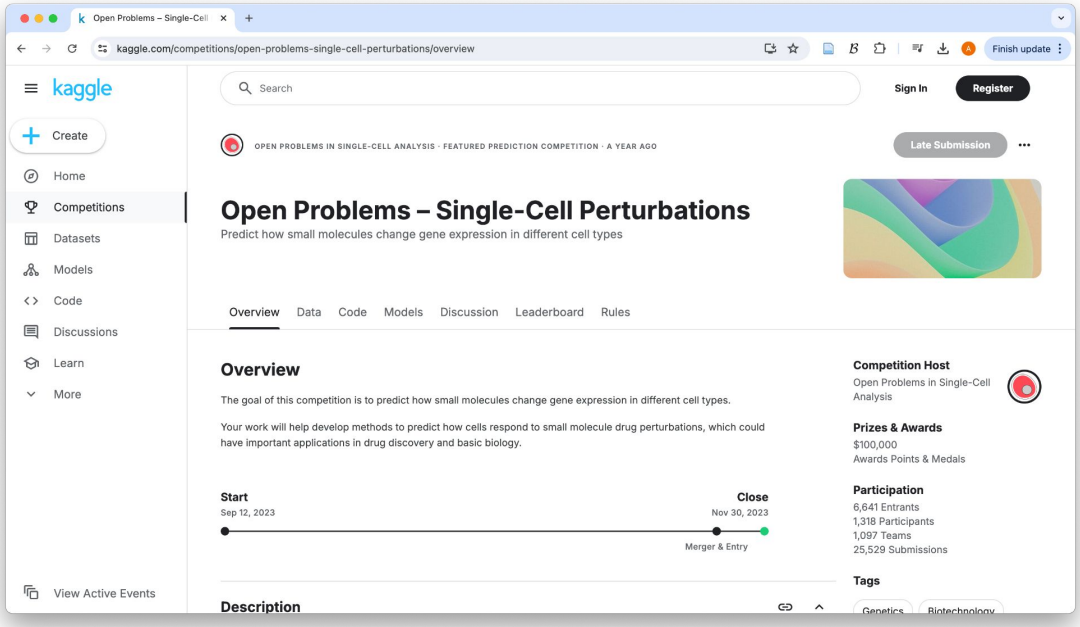


[1]

[1] https://hbctraining.github.io/DGE_workshop_salmon_online/lessons/04a_design_formulas.html

Competition on Kaggle based on this benchmark

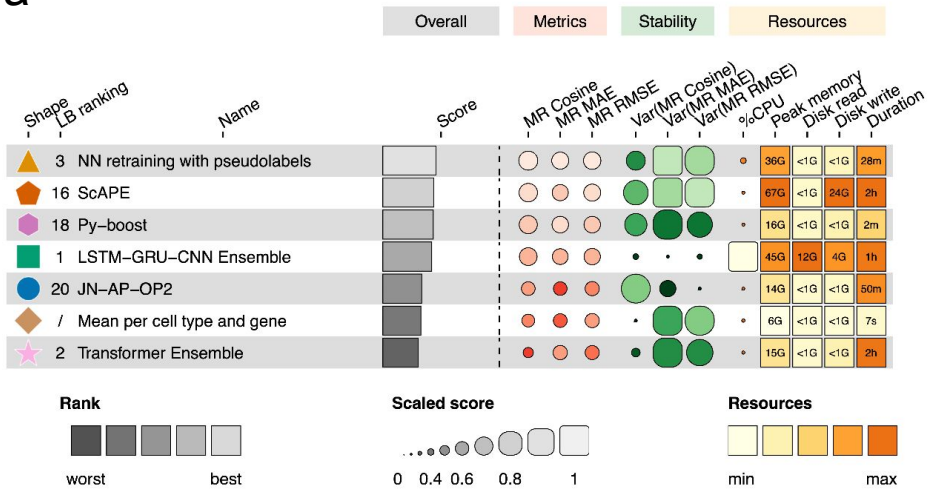
- Sourcing effective models for perturbation prediction from Kaggle competitors
- Improving dataset and benchmark based on competitor feedback



A new benchmarking platform: Open Problems Perturbation Prediction (OP3)

- Top models from Kaggle competition were implemented for benchmark
- Dataset bootstrapping to assess robustness
- Key findings:
  - simple models tend to outperform more complex ones
  - drugs with larger effects are more difficult to predict correctly

a



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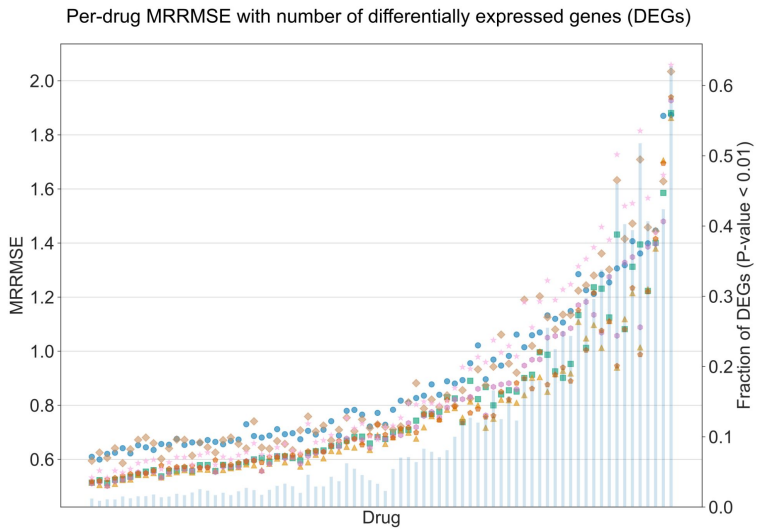
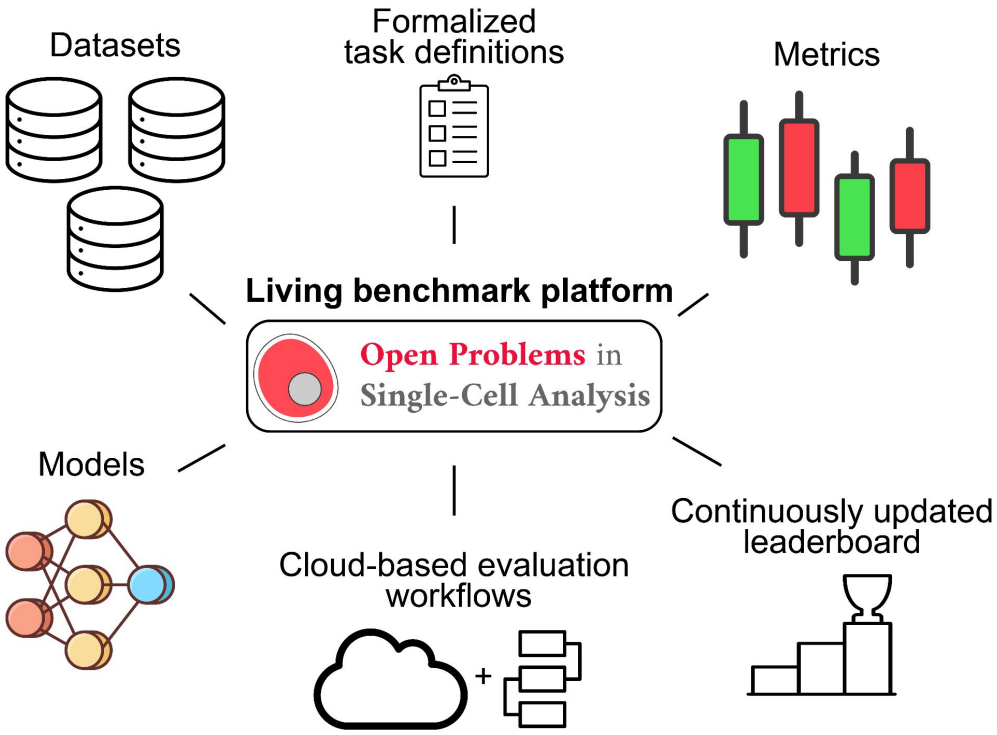


Glossary: Mean Rowwise (MR), Root Mean Squared Error (RMSE), Differentially Expressed Genes (DEGs)

The OP3 benchmarking platform is a first step towards developing successful perturbation prediction models

- Best model predictions are still far from ground truth
- New methods can easily be added to the benchmarking platform via GitHub PRs
- More data is clearly needed, especially for the task of extrapolating across unseen chemical structures



Acknowledgements

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kaggle competitors

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