

In Silico Cellular Perturbation Models: Current Methods, Performance Metrics, and Directions for Future Development

James P. Long

Statistics in Biomedical Research Symposium
UTRGV Brownsville
April 23, 2026

Outline

Cell Perturbation Experiments

In Silico Modeling Approaches

Causal / Mechanistic Modeling

Deep Learning / AI

DE Model Evaluation Metric

Present and Future Research

Outline

Cell Perturbation Experiments

In Silico Modeling Approaches

Causal / Mechanistic Modeling

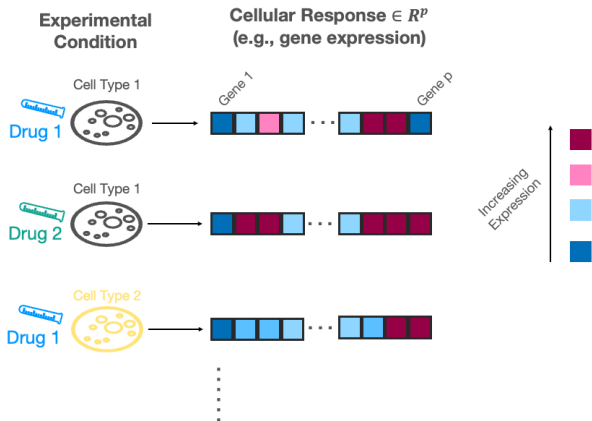
Deep Learning / AI

DE Model Evaluation Metric

Present and Future Research

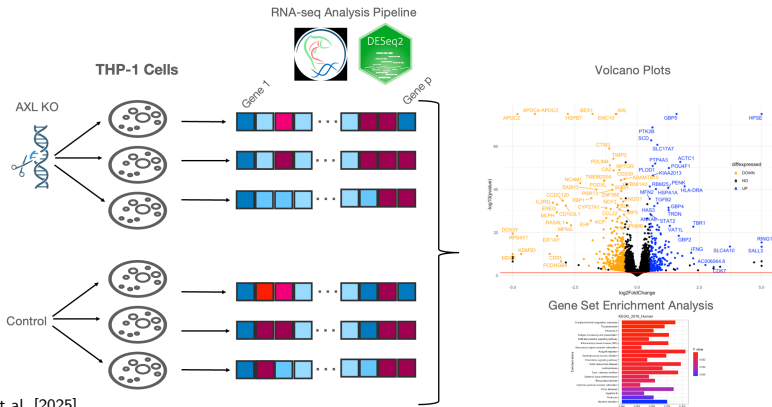
Cell Perturbation Experiments

- Groups of cells are perturbed (e.g. drug applied)
- Responses measured (e.g. gene expression)



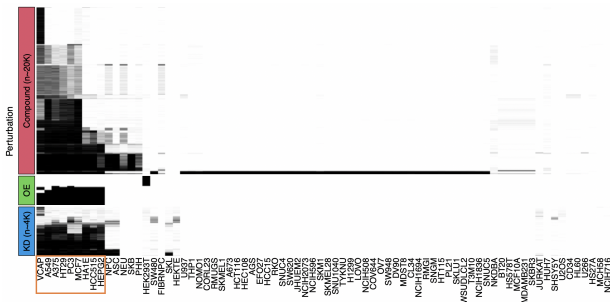
Small Scale Perturbation Studies

- AXL is a therapeutic target in inflammatory breast cancer.
- Tumor microenvironment (TME) plays important role in therapy response
- How does altering AXL affect gene expression in TME macrophages?



Large Scale Perturbation Studies: LINCS L1000

- $\sim 25,000$ perturbations, ~ 70 cell lines
- ~ 1.75 million possible cell line-perturbation combinations
- In vitro tested about 10% of possible combinations
- After perturbation, measure the expression of 1000 genes



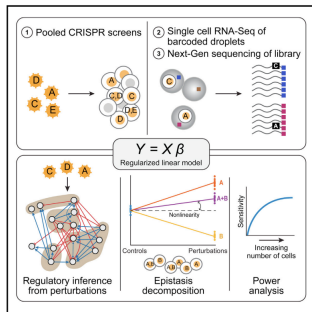
Perturb-seq: CRISPR + Single Cell Sequencing

Resource

Cell

Perturb-Seq: Dissecting Molecular Circuits with Scalable Single-Cell RNA Profiling of Pooled Genetic Screens

Graphical Abstract



Authors

Atray Dixit, Oren Parnas, Biyu Li, ..., Jonathan S. Weissman, Nir Friedman, Aviv Regev

Correspondence

aregev@broadinstitute.org

In Brief

A technology combining single-cell RNA sequencing with CRISPR-based perturbations termed Perturb-seq makes analyzing complex phenotypes at a large scale possible

Perturb-seq enables the profiling of thousands of genetic perturbations with gene expression readouts.

Databases of Perturbation Experiments

Nucleic Acids Research, 2025, 53, D1099–D1111
<https://doi.org/10.1093/nar/gkaf058>
Advance access publication date: 8 October 2024
Database issue



PerturbBase: a comprehensive database for single-cell perturbation data analysis and visualization

Zhiting Wei^{1,2,†}, Duanmiao Si^{1,2,†}, Bin Duan^{1,2,†}, Yicheng Gao^{1,2,†}, Qian Yu³, Zhenbo Zhang^{2,*},
Ling Guo^{3,*} and Qi Liu^{1,2,3,4,*}

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nature methods

Resource

<https://doi.org/10.1038/s41592-023-02164-y>

scPerturb: harmonized single-cell perturbation data

Received: 28 January 2023

Accepted: 4 December 2023

Published online: 26 January 2024

Check for updates

Stefan Peidli^{1,3,†}, Tessa D. Green^{1,3}, Ciyue Shen^{1,3,4}, Torsten Gross²,
Joseph Min¹, Samuele Garda^{2,4}, Bo Yuan^{1,3,5}, Linus J. Schumacher¹,
Jake P. Taylor-King¹, Debora S. Marks^{1,3,5}, Augustin Luna^{1,3,4,5},
Nils Blüthgen^{1,3,5} & Chris Sander^{1,3,4,5,†}

scBaseCount: an AI agent-curated, uniformly processed, and autonomously updated single cell data repository

Nicholas D. Youngblut^{1,†}, Christopher Carpenter^{1,†}, Arshia Nayebnazar^{1,2}, Abhinav Adduri¹,
Rohan Shah^{1,3}, Chiara Ricci-Tam¹, Jaanak Prashar^{1,4}, Rajesh Ilango¹, Noam Teysstier¹,
Silvana Konermann^{1,1,4}, Patrick D. Hsu^{1,1,2}, Alexander Dobin^{1,1}, Dave P. Burke^{1,1},
Hani Goodarzi^{1,1,1,5}, Yusuf H. Roohani^{1,1}

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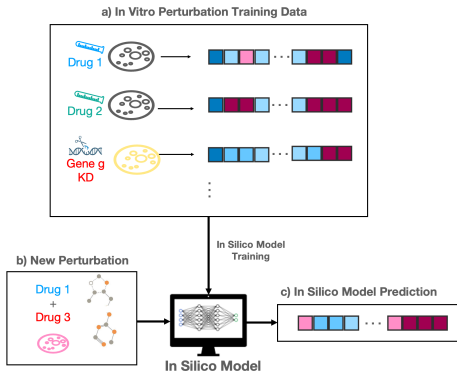
⁴Stanford University; ⁵University of California, San Francisco

In Silico Perturbation Modeling

- **Challenge:**

- In vitro experimental resources are limited (time, money)
- Many perturbations of interest:
With 10,000 genes, $\sim 50M$ 2-gene perturbations

- **Solution:** In silico (computational) models are used to predict the responses to perturbations.



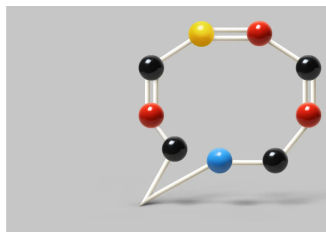
Recent In Silico Models

Method Name	Model Type	Year	Evaluation Metrics
scGen [Lotfollahi et al., 2019a]	DL/Autoencoder	2019	R^2
XGBoost [Li and Li, 2019]	Boosting	2019	MAE
trVAE [Lotfollahi et al., 2020]	DL/Autoencoder	2020	R^2
CellBox [Yuan et al., 2021]	ODE/Causal	2021	R^2
CPA [Lotfollahi et al., 2023]	DL/Autoencoder	2021	R^2
ENformer [Avsec et al., 2021]	DL/Transformer	2021	R^2
SI-A [Squires et al., 2022b]	Causal	2022	R^2 , RMSE
Ensemble [Al Taweraqi and King, 2022]	Ensemble	2022	R^2
GEARS [Roohani et al., 2024]	DL/GNN	2022	R^2 , MSE
CellOT [Bunne et al., 2023]	Optimal Transport	2023	MMD
scGPT [Cui et al., 2024]	DL/Transformer	2024	R^2
Bicycle [Rohbeck et al., 2024]	ODE/Causal	2024	I-MAE
scFoundation [Hao et al., 2024]	DL/Transformer	2024	R^2 , PCC
SAMS-VAE [Bereket and Karaletsos, 2024]	DL/Autoencoder	2024	R^2
scPRAM [Jiang et al., 2024]	DL/Attention+OT	2024	R^2
GenePert [Chen and Zou, 2024]	Regression/LLM Embed.	2024	R^2 , RMSE
scLAMBDA [Wang et al., 2024]	DL/Autoencoder	2024	R^2 , Diff. Exp. Concordance
LPM [Brbić et al., 2025]	DL/Transformer	2025	R^2
CellFlow [Klein et al., 2025]	DL/Flow Matching	2025	R^2 + Others
scREPA [Li et al., 2025]	DL/Autoencoder	2025	R^2 , WD
scDFM [Yu et al., 2026]	DL/Flow Matching	2025	R^2 + Distance Metrics

Excitement Surrounding Models in Popular Press

A.I. Is Learning What It Means to Be Alive

Given troves of data about genes and cells, A.I. models have made some surprising discoveries. What could they teach us someday?



“ ‘That’s going to be hugely revolutionary for the field of biology,’ said Bo Wang, a computational biologist at the University of Toronto and the creator of scGPT. With this virtual cell, he speculated, it would be possible to predict what a real cell would do in any situation. Scientists could run entire experiments on their computers rather than in petri dishes.”

Carl Zimmer, New York Times, March 10, 2024

<https://www.nytimes.com/2024/03/10/science/ai-learning-biology.html>

Prediction Competitions

2023

kaggle

Open Problems – Single-Cell Perturbations

Predict how small molecules change gene expression in different cell types

December 2025

HOSTED BY

Arc Institute

Virtual Cell Challenge

Join us in shaping the future of cellular biology through predictive modeling.

Ongoing



**Obesity ML Competition: Tackling
Metabolic Diseases - Part 1**

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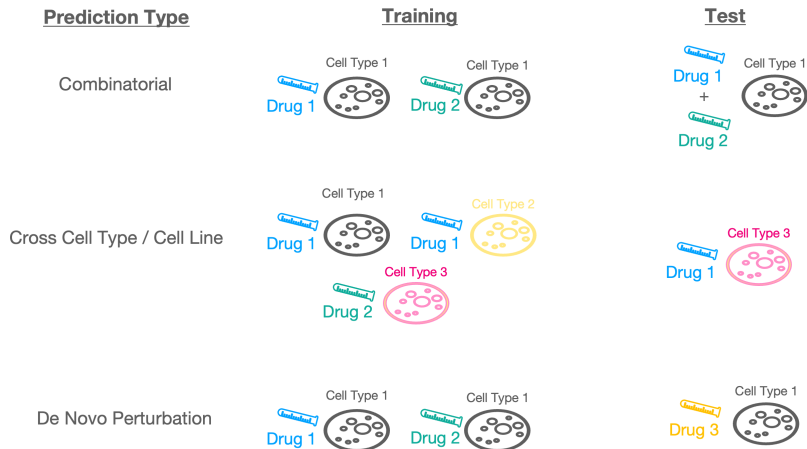
Causal / Mechanistic Modeling

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DE Model Evaluation Metric

Present and Future Research

Targets of In Silico Models



- Drug perturbation versus genetic perturbations.
- Experimental readouts: gene expression, protein expression

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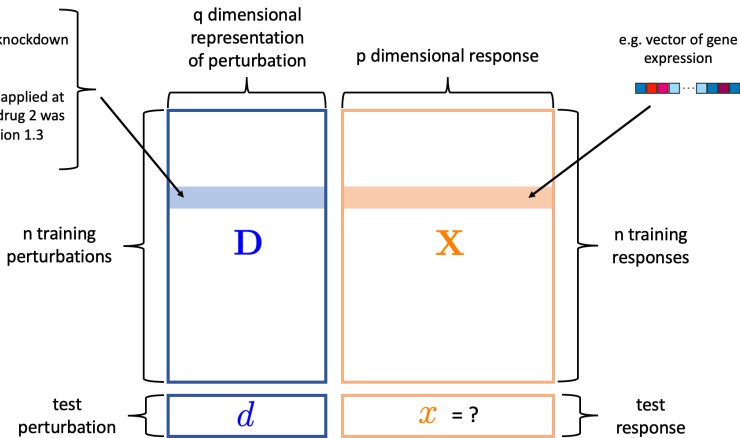
Notation

Genetic Perturbation

$(0,0,0,1,0)$ = gene g_4 knockdown

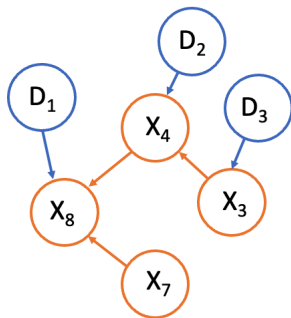
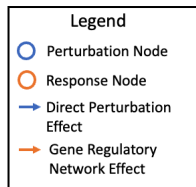
Drug Perturbation

$(3,1.3,0,0,0)$ = drug 1 applied at concentration 3 and drug 2 was applied at concentration 1.3



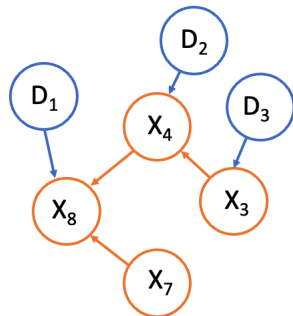
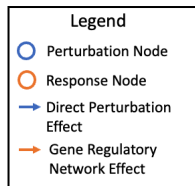
Perturbations and Regulatory Networks

- Perturbations have direct effects on response variables
 - Example: Knockdown of PTEN (D_3) gene directly effects gene expression of PTEN (X_3)
- Genes regulate expression of other genes via regulatory networks.
 - Genes X_4 and X_8 are downstream of PTEN and will be affected by PTEN KD



Causal Approach to In Silico Modeling

1. **Causal Discovery:** Use training data to learn causal structure (orange arrows)
2. **Prediction:** Assume direct effect perturbation known and propagate effect of perturbation through the inferred causal structure.



Implementation of Idea

Linear Causal Structure (GRN) + Linear Interventions:

$$\mathbf{X} = \mathbf{X}A + \mathbf{D}B^T + \epsilon$$

- $\mathbf{X} \in \mathbb{R}^{n \times p}$ training responses
 - $\mathbf{D} \in \mathbb{R}^{n \times q}$ training predictors
 - A_{ij} = causal effect of X_i on X_j (GRN)
 - B_{il} = direct intervention effect of D_l on response X_i
 - ϵ = unmeasured experimental factors (independent of \mathbf{D})
- Causal Structure Learning (CSL) with B Known:

$$\hat{A} = \underset{\{A: I-A \succ 0\}}{\operatorname{argmin}} \quad \|\mathbf{X} - \mathbf{D}B^T(I - A)^{-1}\|_F^2 + \lambda\|A\|_1$$

- Predict response

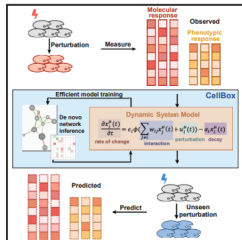
$$\hat{x} = d^T B^T (I - \hat{A})^{-1}.$$

Cell Systems

Article

CellBox: Interpretable Machine Learning for Perturbation Biology with Application to the Design of Cancer Combination Therapy

Graphical Abstract



Highlights

- CellBox includes explicit models of cell dynamics in a machine-learning framework
- CellBox enables the prediction of system responses to unseen perturbations
- CellBox-derived molecular interactions generally agree with known biological pathways
- CellBox is an example of interpretable scientific machine learning in cell biology

Authors

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Correspondence

boyuan@g.harvard.edu (B.Y.), c_shen@g.harvard.edu (C. Shen), mathcellbox@gmail.com (C. Sander)

In Brief

The ability to accurately predict cell behavior to previously untested perturbations would benefit the discovery of combination therapies in cancer. To overcome the lack of interpretability of black-box machine-learning models, we developed a hybrid approach called CellBox that combines explicit mathematical models of molecular interactions with efficient parameter inference algorithms adapted from deep learning. The models are data driven and do not require prior knowledge, and their predictive scope scales well with the availability of high-throughput data.

nature

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Article | Open access | Published: 08 February 2023

Dissecting cell identity via network inference and in silico gene perturbation

Kenji Kamimoto, Berta Stringa, Christy M. Hoffmann, Kunal Jindal, Liliana Solnica-Krezel & Samantha A. Morris

Nature 614, 742–751 (2023) | Cite this article

182k Accesses | 588 Citations | 337 Altmetric | Metrics

Proceedings of Machine Learning Research vol 236:209–242, 2024

3rd Conference on Causal Learning and Reasoning

Bicycle: Intervention-Based Causal Discovery with Cycles

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Brian Clarke

German Cancer Research Center

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Methods for causal inference from gene perturbation experiments and validation

Nicolai Meinshausen*, Alain Hauser*, Joris M. Mooij[†], Jonas Peters[‡], Philip Versteeg[§], and Peter Bühlmann[¶]

*Seminar for Statistics, Eidgenössische Technische Hochschule (ETH) Zurich, CH 8092 Zurich, Switzerland; [†]Department of Engineering and Information Technology, Bern University of Applied Sciences, CH-3400 Burgdorf, Switzerland; [‡]Informatics Institute, University of Amsterdam, 1098 GH Amsterdam, The Netherlands; and [§]Max Planck Institute for Intelligent Systems, D-72076 Tübingen, Germany

Edited by Richard M. Shiffrin, Indiana University, Bloomington, IN, and approved April 5, 2016 (received for review June 5, 2015)

Infering causal effects from observational and interventional data is a non-trivial task. The system of structural equations is

Note on Regression Approach

- Least squares regression fit:

$$\hat{R} = \operatorname{argmin}_R \|\mathbf{X} - \mathbf{D}R\|_F^2$$

- Predict response:

$$\hat{x} = d^T \hat{R}.$$

- Compare prediction \hat{x} with ground truth x

Problem: \hat{R} not defined for denovo prediction (new perturbation never applied in training data).

For details: Long, J.P., Yang, Y., Shimizu, S., Pham, T. and Do, K.A., 2025. Causal models and prediction in cell line perturbation experiments. BMC Bioinformatics, 26(1), p.4.

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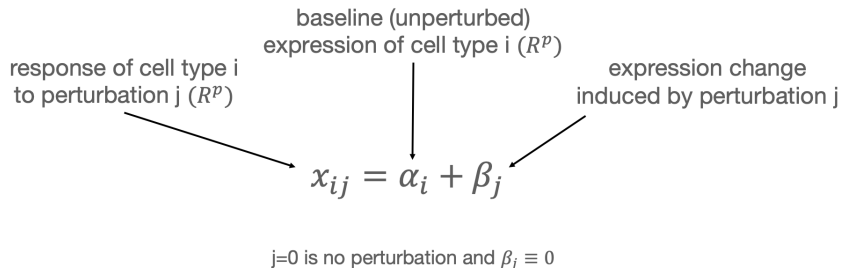
DE Model Evaluation Metric

Present and Future Research

Overview of DL / AI Approaches

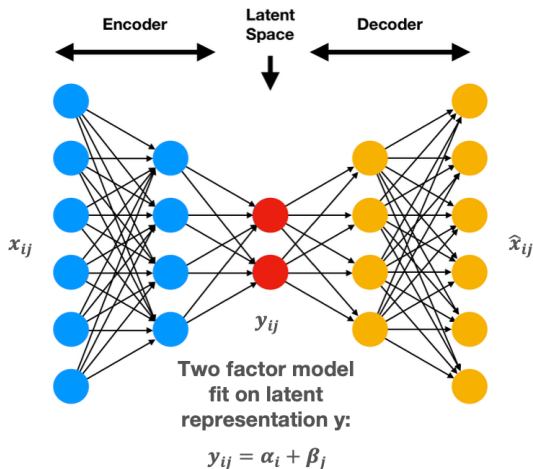
- General idea: Adapt AI/DL modeling strategies to biology
- Broad set of methods
 - Auto-encoders
 - Generative modeling
 - Foundation models
 - Fine tuning
- Often less interpretable than causal approaches
- Scalability: By leveraging AI/DL computing strategies, can model huge data sets

Benchmark Two Factor Model



Unrealistic Assumption: Perturbations have same effect across cell lines / cell types.

Autoencoders



Idea: Learn two factor model on latent space where invariance assumption is better approximation.

Examples

scgen (2019)

nature methods

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Article | Published: 29 July 2019

scGen predicts single-cell perturbation responses

[Mohammad Lotfollahi](#), [F. Alexander Wolf](#)  & [Fabian J. Theis](#) 

[Nature Methods](#) **16**, 715–721 (2019) | [Cite this article](#)

58k Accesses | **653** Citations | **216** Altmetric | [Metrics](#)

trVAE (2020)

[Bioinformatics](#), 2020, 2020, 410–417
doi: 10.1093/bioinformatics/btaa000
ECCB2020

OXFORD

Genes

Conditional out-of-distribution generation for unpaired data using transfer VAE

[Mohammad Lotfollahi](#)^{1,2}, [Mohsen Naghipourfar](#)¹, [Fabian J. Theis](#)^{1,2,3,*} and [F. Alexander Wolf](#)^{1,*}

¹Institute of Computational Biology, Helmholtz Center Munich, Neuherberg, Germany, ²School of Life Sciences Weihenstephan, Technical University of Munich, Munich, Germany and ³Department of Mathematics, Technische Universität München, Munich, Germany







CPA (2023)

Article



molecular
systems
biology

Predicting cellular responses to complex perturbations in high-throughput screens

[Mohammad Lotfollahi](#)^{1,2,3}, [Anna Klimovskaia Susmelj](#)^{3,4,5} , [Carlo De Donno](#)^{3,5,6} , [Leon Hetzel](#)^{1,4} , [Yuge Ji](#)^{1,5}, [Ignacio L Ibarra](#)¹ , [Sanjay R Srivatsan](#)⁷, [Mohsen Naghipourfar](#)⁸, [Riza M Daza](#)⁷ , [Beth Martin](#)⁷, [Jay Shendure](#)^{7,9,10,11}, [Jose L McFaline-Figueroa](#)¹² , [Pierre Boyeau](#)¹³, [F. Alexander Wolf](#)^{1,4}, [Nafissa Yakubova](#)³, [Stephan Günemann](#)¹⁴, [Cole Trapnell](#)^{7,10,11}, [David Lopez-Paz](#)² & [Fabian J Theis](#)^{1,2,3,6,*} 

Foundation Models

- Trained on huge datasets
 - scGen (non-foundation): $\sim 14,000$ cells
 - scGPT (foundation model): 33 million cells
- Model architecture:
 - BERT (e.g. scBERT)
 - GPT (e.g. scGPT)
- General models which can be fine tuned to specific tasks
 - Cell type annotation
 - Multi-batch integration
 - Multi-omic integration
 - Perturbation response prediction

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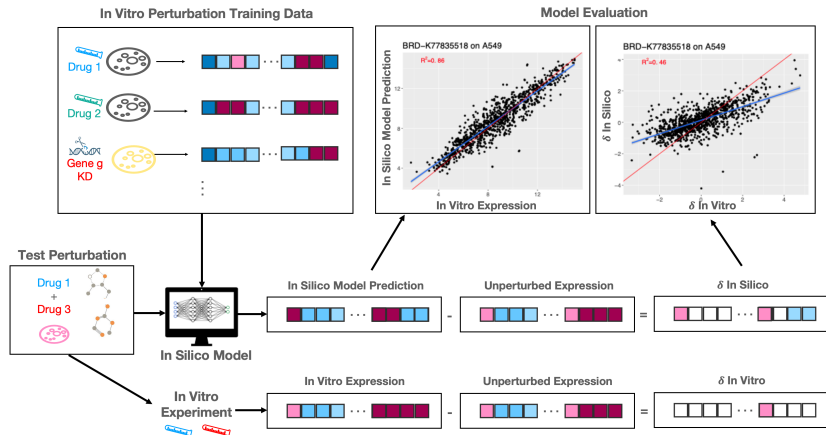
Causal / Mechanistic Modeling

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DE Model Evaluation Metric

Present and Future Research

Model Evaluation: Standard Strategy



Evaluation metrics may be computed for each test perturbation.

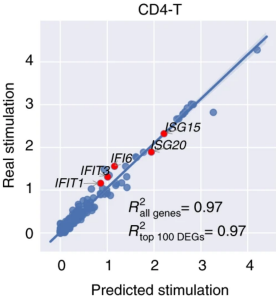
Example: scGen Lotfollahi et al. [2019b]

Perturbation

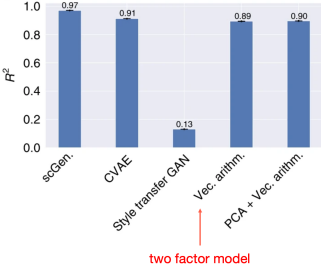
Cell Type

	CD14-Mono	CD4-T	CD8-T	DC	F-Mono	NK
Control	α_1	α_2	α_3	α_4	α_5	α_6
INF-g	$\alpha_1 + \beta_1$	$\alpha_2 + \beta_1$	$\alpha_3 + \beta_1$	$\alpha_4 + \beta_1$	$\alpha_5 + \beta_1$	$\alpha_6 + \beta_1$

■ = training conditions, with 100s-1000s of cells ■ = test condition with 100s-1000s of cells

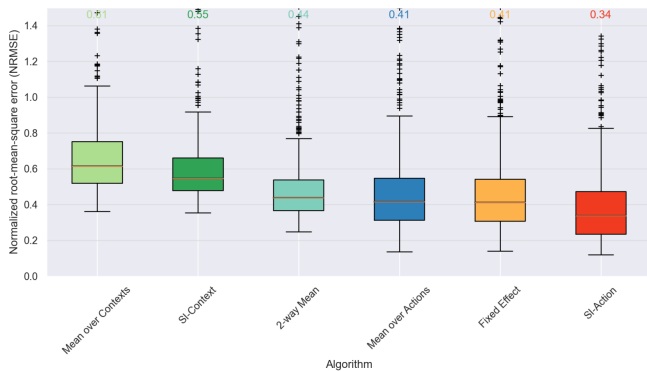


scGen prediction



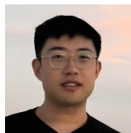
Example: SI-A Squires et al. [2022a]

- 100 cell line-drug pair
- Predict expression of 1000 genes for each pair
- Compute normalized MSE for each pair



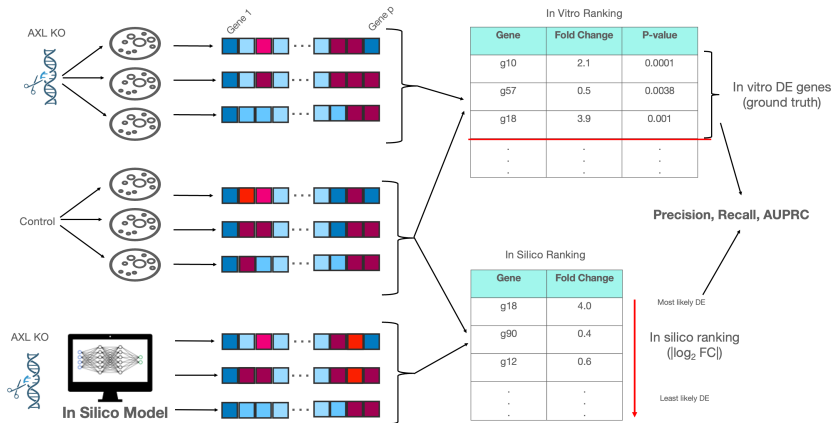
Limitations of Metrics

- Sparse Perturbation Effects: Perturbations typically affect only a small subset of genes. R^2 / MSE metrics may be dominated by the large number of unaffected genes.
- Biological Relevance: Unclear at what R^2 level in silico model can replace in vitro experiment.



Hongxu Zhu

Proposal: Evaluate Quality of In Silico DE Analysis



Precision, Recall, and AUPRC

- $R_g = |\log_2(\text{In Silico FC of gene } g)|$
- $Z_g = \begin{cases} 1 & \text{if gene } g \text{ is DE in vitro} \\ 0 & \text{otherwise} \end{cases}$
- At threshold r :

$$\text{Precision} = \frac{\sum_g 1_{Z_g=1, R_g > r}}{\sum_g 1_{R_g > r}}$$

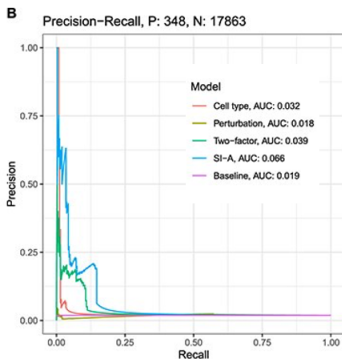
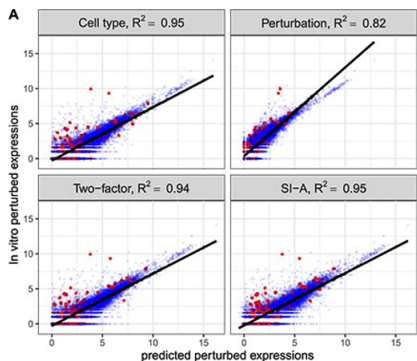
$$\text{Recall} = \frac{\sum_g 1_{Z_g=1, R_g > r}}{\sum_g 1_{Z_g=1}}$$

- AUPRC: Area under precision recall curve

Kaggle Competition Example

- **Goal:** Predict gene expression of CD4+ T cells following perturbation with Perhexiline
 - Part of Kaggle 2023 competition
- In silico models tested:
 - Benchmark: Perturbation, Cell type, Two Factor
 - Synthetic Intervention - Action (SI-A) [Squires et al., 2022a]
- In vitro DE analysis detects 348 differentially expressed genes

Kaggle Competition Example




At recall of 25%, precision is less than 10% for all methods.

PBMC Example

Cell Type	Method	Precision		
		at 25% Recall	at 50% Recall	at 75% Recall
CD4-T	scGen	1	0.44	0.38
	Two-factor	0.89	0.75	0.34
B	scGen	0.41	0.39	0.18
	Two-factor	1	0.67	0.49
CD8-T	scGen	0.73	0.37	0.22
	Two-factor	0.8	0.65	0.5
CD14+Mono	scGen	0.93	0.91	0.88
	Two-factor	1	0.82	0.66
NK	scGen	0.73	0.48	0.4
	Two-factor	0.89	0.62	0.47
Dendritic	scGen	0.76	0.8	0.78
	Two-factor	1	0.88	0.73
FCGR3A+Mono	scGen	0.93	0.83	0.67
	Two-factor	1	0.82	0.57

- At recall of 25%, precision generally $> 80\%$
- Low precision if you seek most diff expressed genes.
- scgen and Two-factor have similar overall performance.

AUPRC: a metric for evaluating the performance of *in-silico* perturbation methods in identifying differentially expressed genes

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Abstract

In silico perturbation models, computational methods that can predict cellular responses to perturbations, present an opportunity to reduce the need for costly and time-intensive *in vitro* experiments. Many recently proposed models predict high-dimensional cellular responses, such as gene or protein expression to perturbations such as gene knockout or drugs. However, evaluating *in silico*

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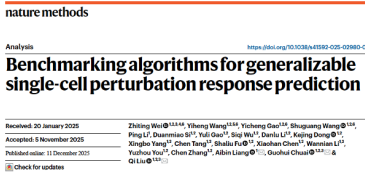
Deep Learning / AI

DE Model Evaluation Metric

Present and Future Research

Benchmarking

- Over-investment in new methods
- Under-investment in benchmarking (pre-2025)
 - Recent benchmarking studies are cautionary



Csendes et al. *BMC Genomics* (2025) 26:293
<https://doi.org/10.1186/s12864-025-11600-2>

BMC Genomics



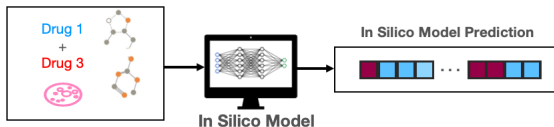
Abstract

Accurately predicting cellular responses to perturbations is essential for understanding cell behaviour in both healthy and diseased states. While perturbation data is ideal for building such predictive models, its availability is considerably lower than baseline (non-perturbed) cellular data. To address this limitation, several foundation cell models have been developed using large-scale single-cell gene expression data. These models are fine-tuned after pre-training for specific tasks, such as predicting post-perturbation gene expression profiles, and are considered state-of-the-art for these tasks. However, because various implementations of these models exist in the open-source ecosystem,

Reverse (or Inverse) Problem

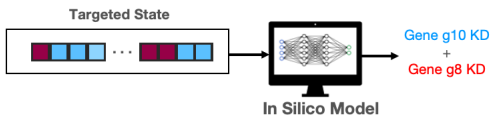
Forward Problem

Given perturbation, predict transcriptional state



Reverse / Inverse Problem

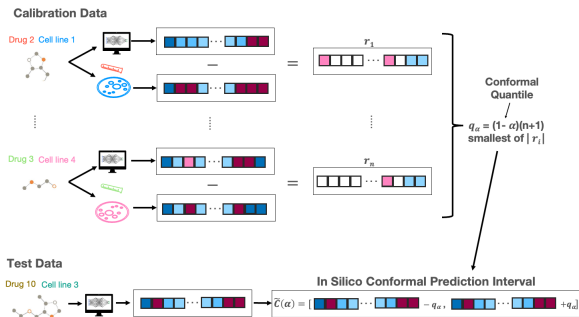
Find perturbation which reaches targeted transcription state



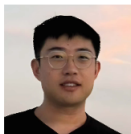
Gonzalez, G., Lin, X., Herath, I., Veselkov, K., Bronstein, M. and Zitnik, M., 2025. Combinatorial prediction of therapeutic perturbations using causally inspired neural networks. Nature Biomedical Engineering, pp.1-18.

Uncertainty Quantification on Predictions

- In silico model may have:
 - high confidence about how perturbation A changes expression.
 - low confidence about how perturbation B changes expression.
- Current models do not report uncertainty.
- One Approach: **Conformal Prediction**



Collaboration



Hongxu Zhu
(on job market)



Summer Yang



Kim-Anh Do



Ehsan Irajizad



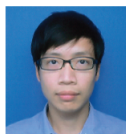
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Thong Pham



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