
# Multi-scale Deep Tensor Factorization Learns a Latent Representation of the Human Epigenome

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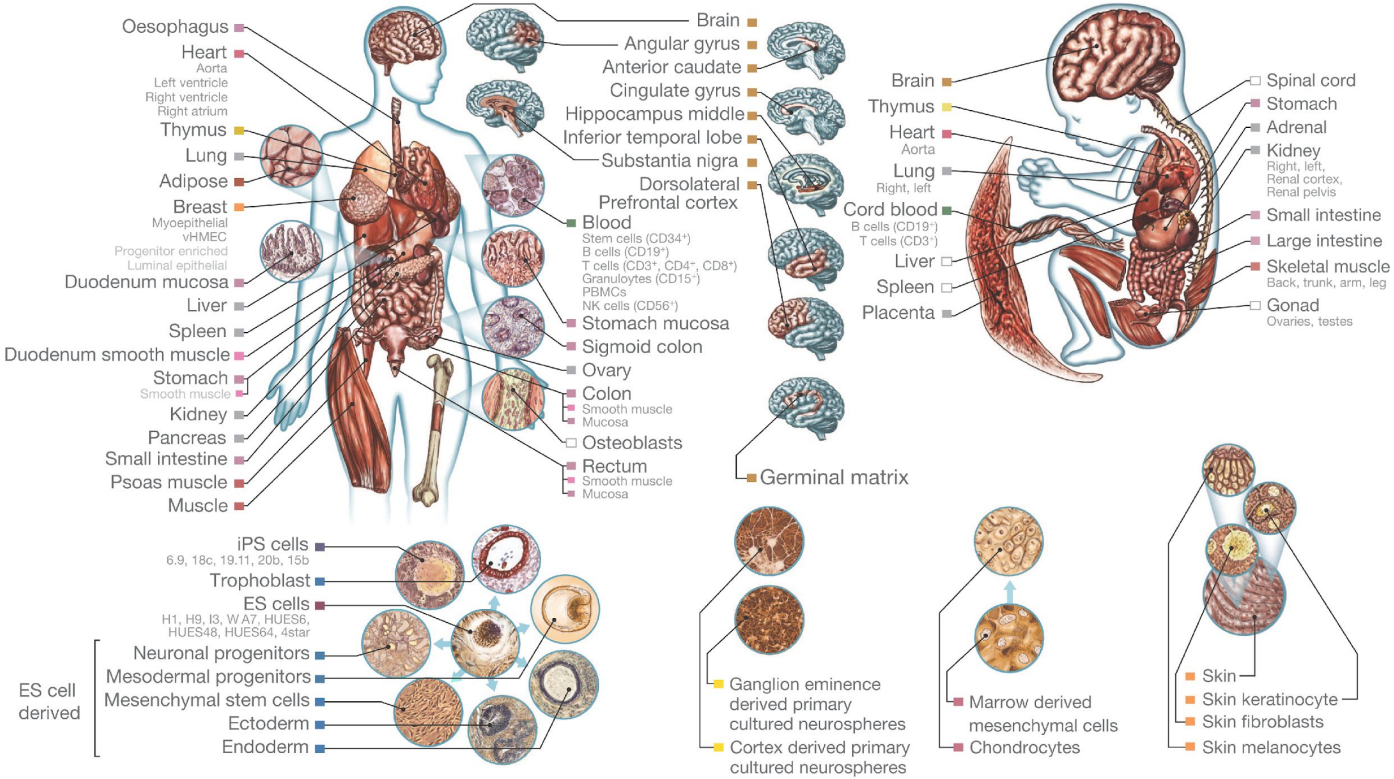
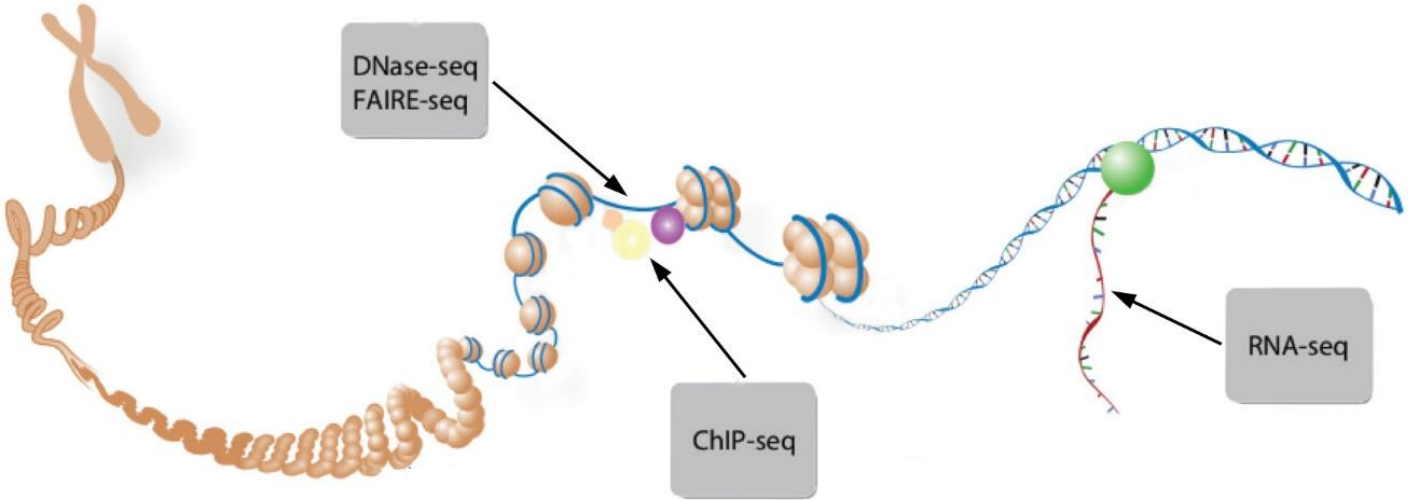
# The sequence of the human genome cannot explain the diversity of human cell types



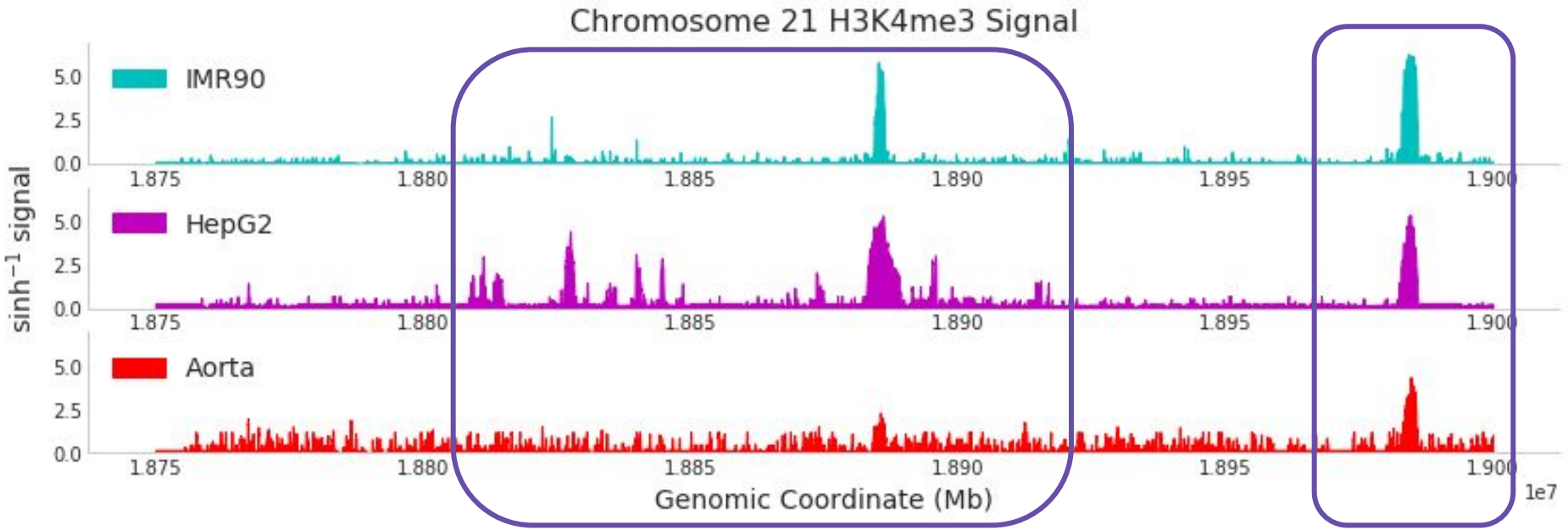

Credits: Roadmap Consortium, Nature (2015)

# Many measurements can be gathered in addition to nucleotide sequence



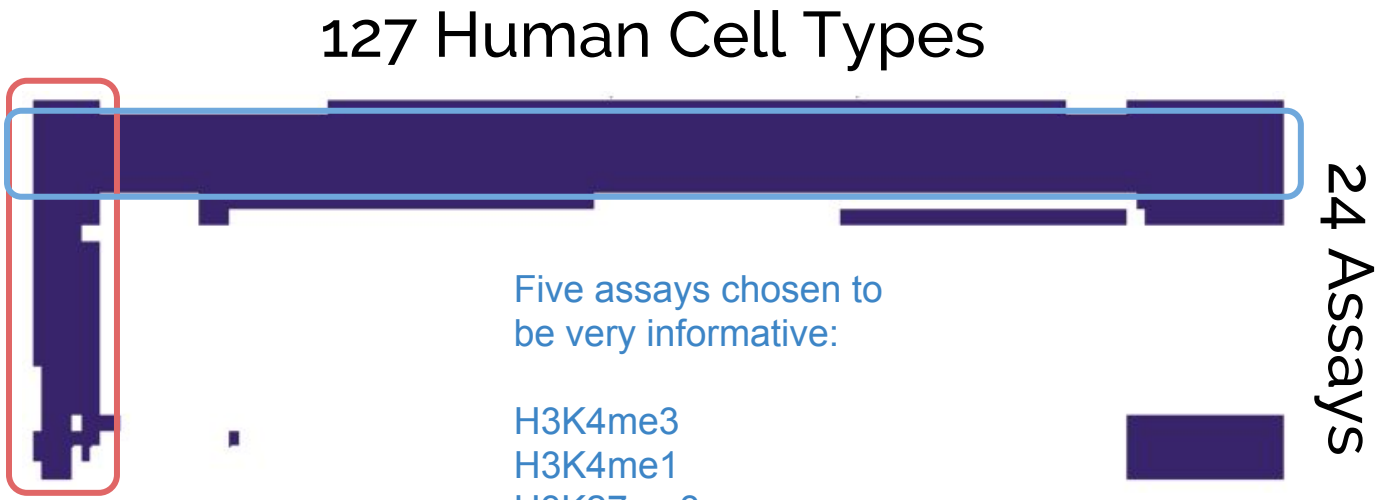

Credits: Darryl Leja (NHGRI), Ian Dunham (EBI)

# The signal of epigenomic assays vary across cell types



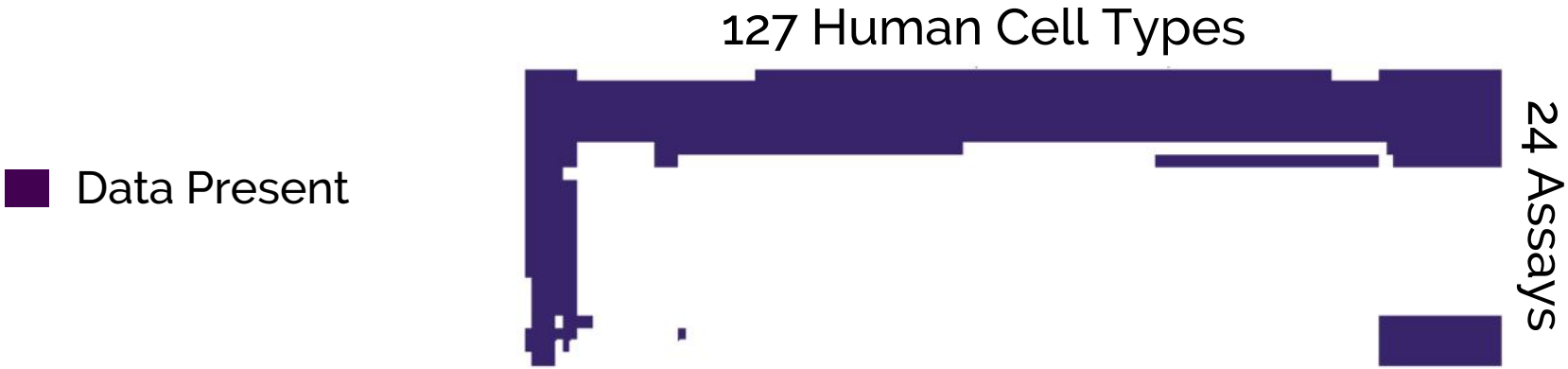
# Many experiments have been performed, but still only a fraction of possible experiments

Data Present




1,014 experiments performed out of a possible 3,048

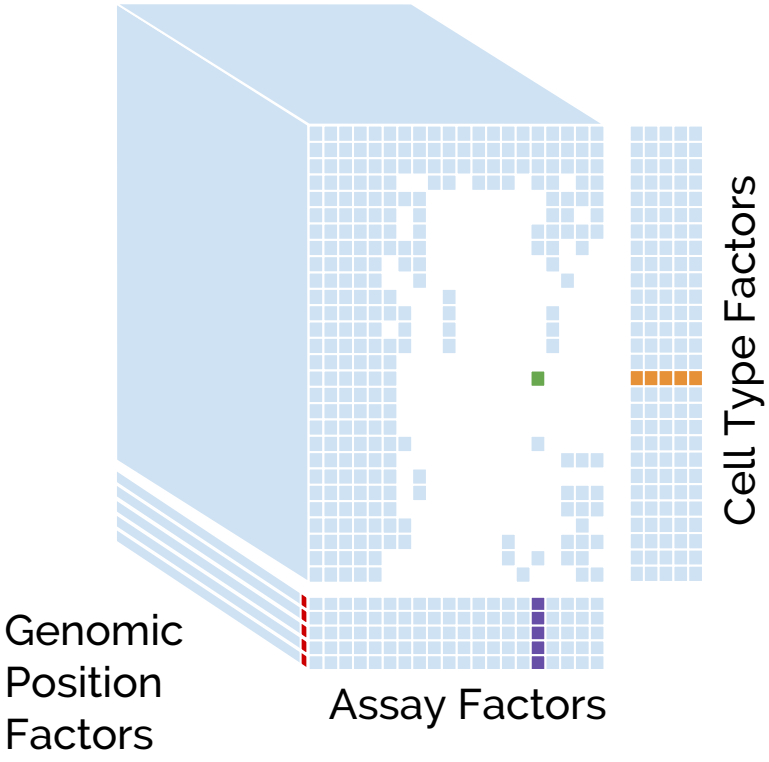
# Have we characterized the human epigenome yet?

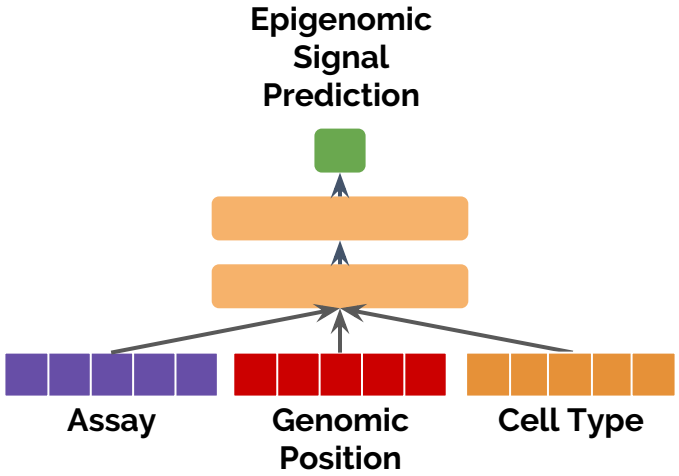



- Previous work sought to fully characterize the epigenome through imputing all potential experiments (ChromImpute[1], PREDICTD[2])
- Can we characterize the epigenome through distilling the available measurements into an informative latent representation?

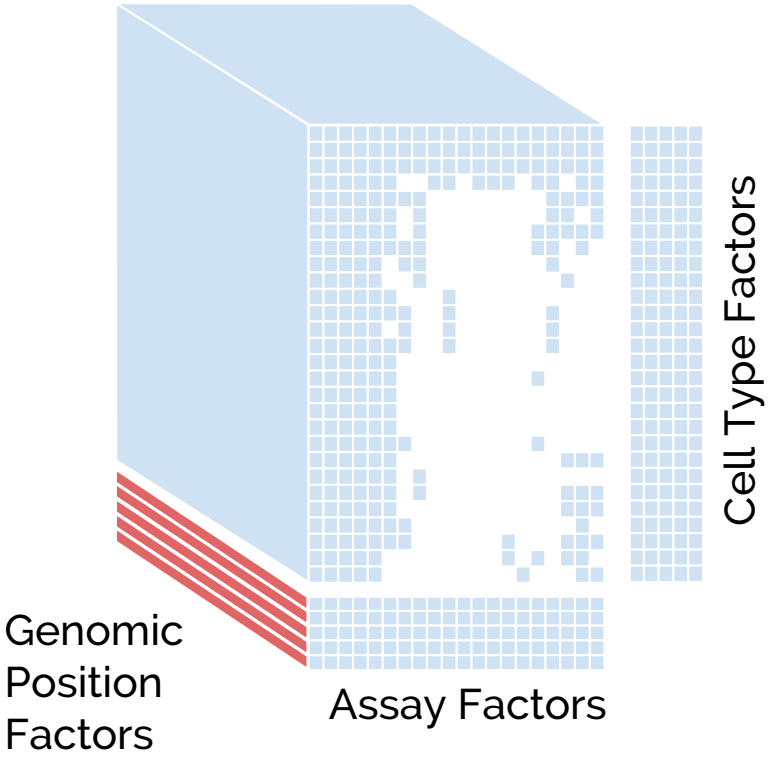
1. Ernst, et al. *Nature Methods, 2015*
2. Durham, et al. *Nature Communications, 2018*

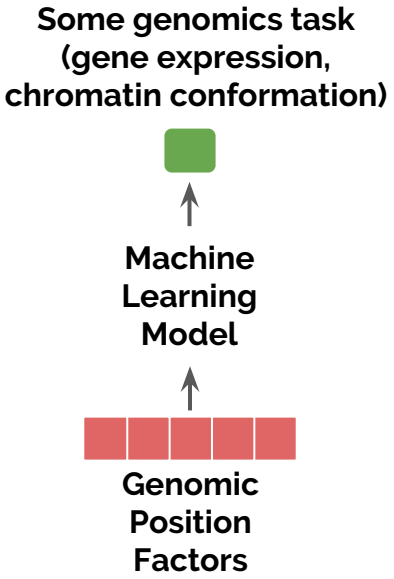
# Avocado is a deep tensor factorization approach



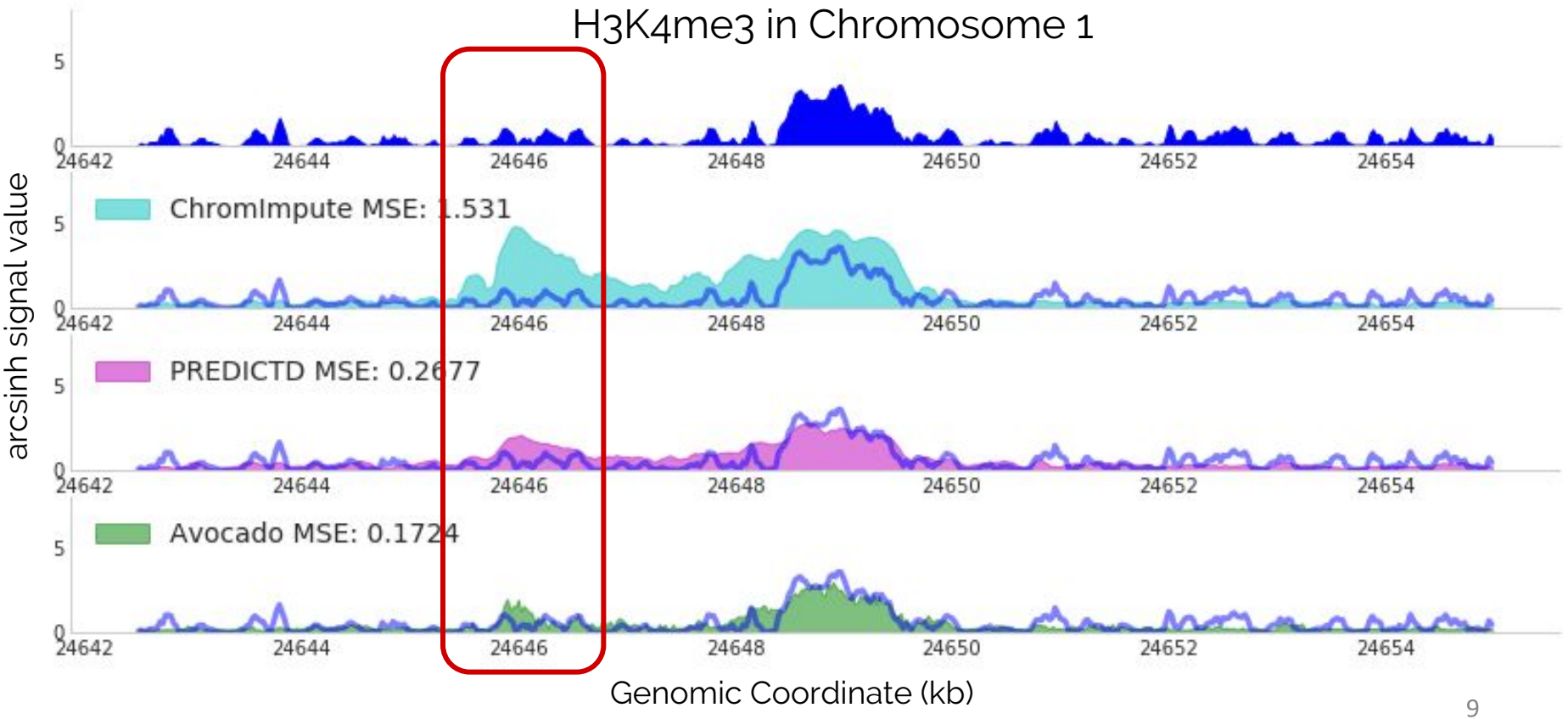



# Our goal is to use the genomic latent factors for other tasks



# Initial inspection of the imputations suggest that Avocado performs well



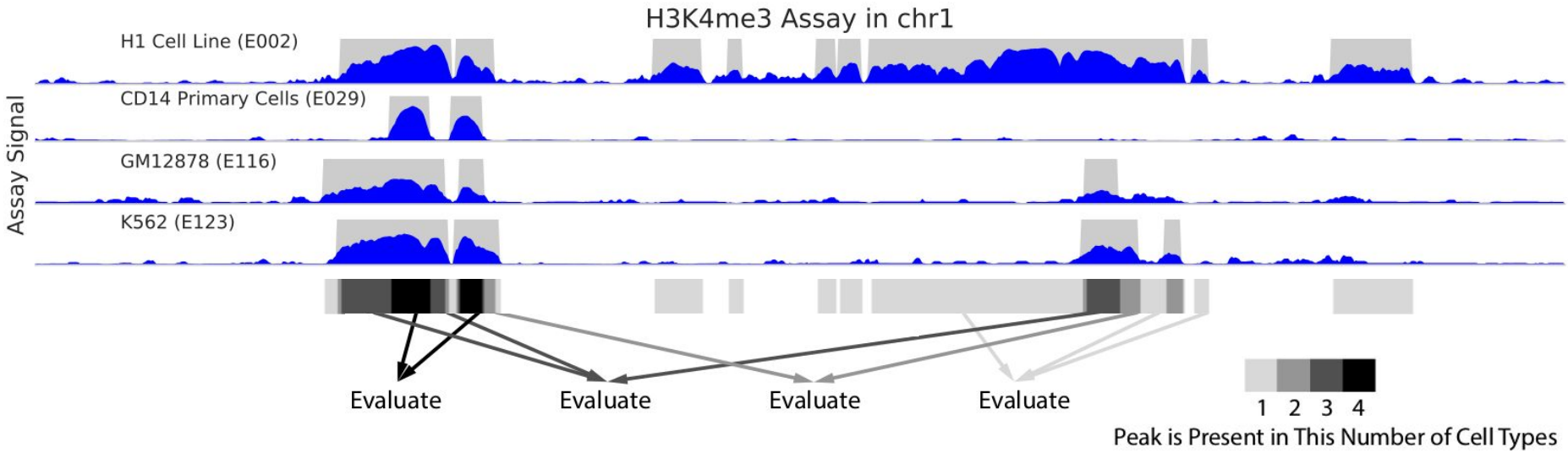
# Avocado continues to perform well genome-wide

???

| MSE- | global | 1obs | 1imp | Prom | Gene | Enh |
|---|---|---|---|---|---|---|
| ChromImpute | 0.113 | **0.941** | 1.09 | 0.3246 | 0.1494 | 0.3164 |
| PREDICTD | **0.1** | 1.76 | 0.897 | 0.2576 | **0.1295** | 0.267 |
| Avocado | **0.1** | 1.66 | **0.845** | **0.249** | **0.1295** | **0.26** |

**MSE-global:** Mean squared error (MSE) across the full length of the genome
**MSE-1obs:** MSE at the top 1% of genomic positions ranked by experimental signal
**MSE-1imp:** MSE at the top 1% of genomic positions ranked by imputed signal
**MSE-Prom:** MSE at promoter regions defined by GENCODE
**MSE-Gene:** MSE at gene bodies defined by GENCODE
**MSE-Enh:** MSE at enhancer regions defined by FANTOM5

# How well can these approaches recover cell type specific peaks?




Evaluate by calculating:

(1) MSE

(2) Recall (thresholding the imputed signal at 1.44)

(3) Precision (thresholding the imputed signal at 1.44)

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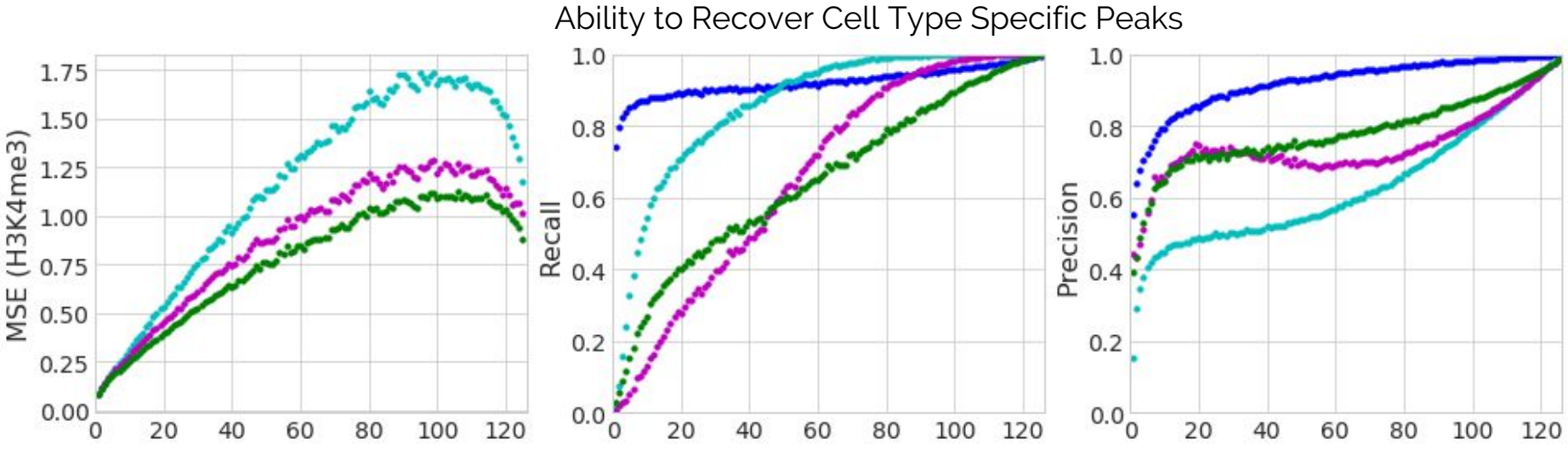

# We evaluated our learned representation in many contexts

**STEP 1:**
Choose a Prediction Task
- Gene Expression
- Promoter-Enhancer Interactions
- Frequently Interacting REgions (FIREs)
- Topologically Associating Domain (TAD) boundaries

**STEP 2:**
Choose a Cell Type
- Task dependant

**STEP 3:**
Choose a Feature Set
- Available epigenomic tracks from the chosen cell type
- Full set of ChromImpute imputed marks for that cell type
- Full set of PREDICTD imputed marks for that cell type
- Full set of Avocado imputed marks for that cell type
- Avocado latent factors
- Full Roadmap compendium

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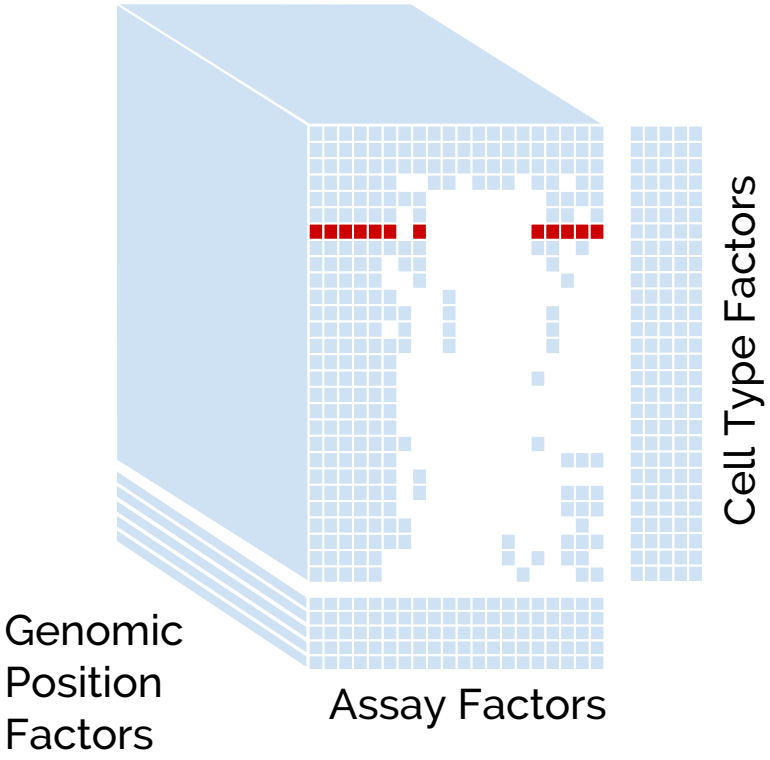


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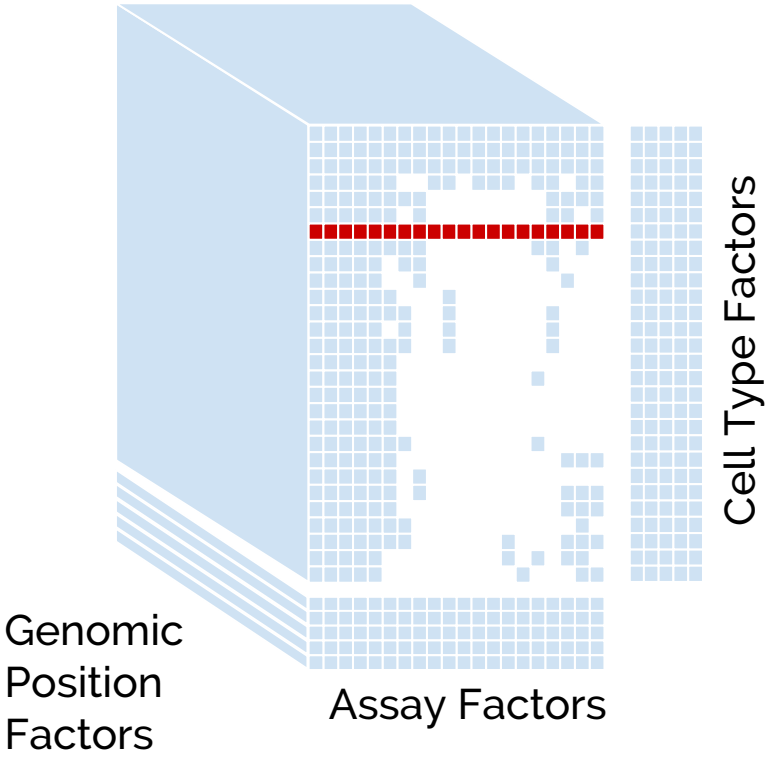


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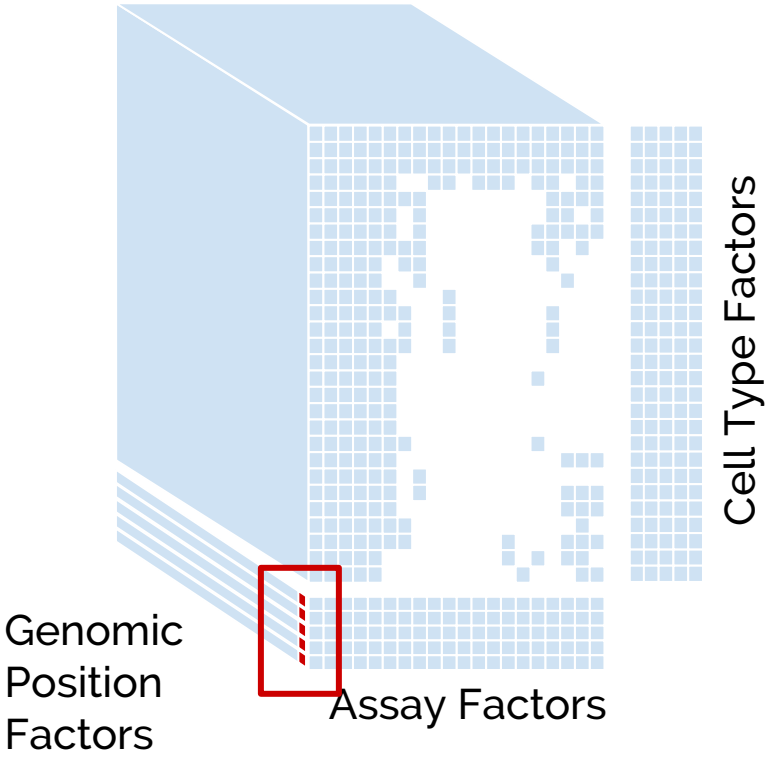


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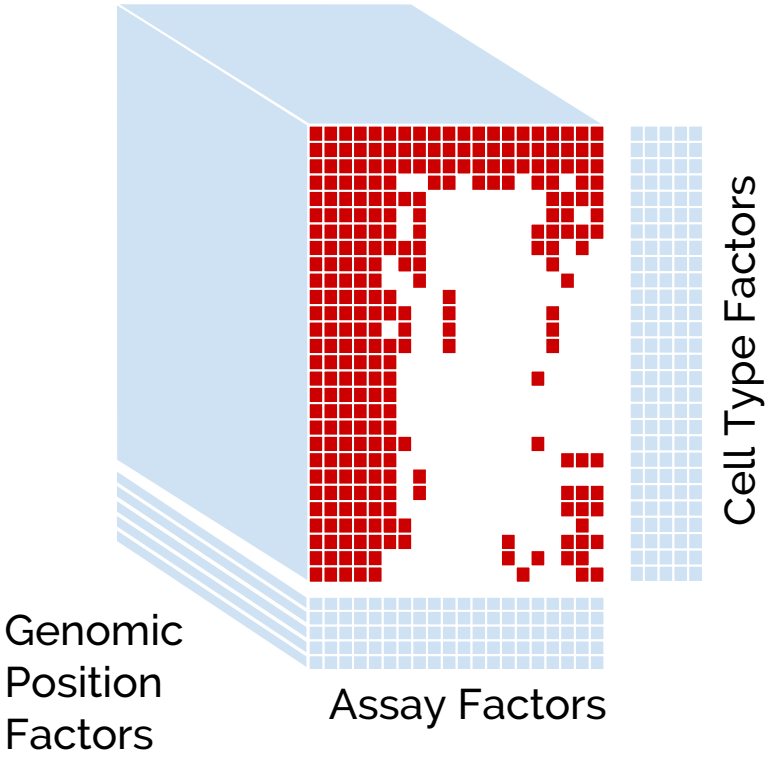


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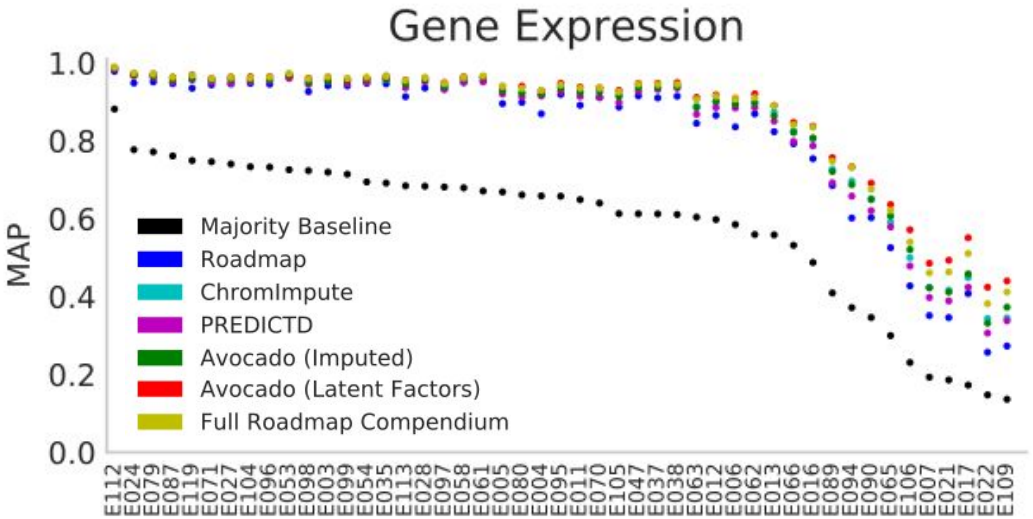
**STEP 4:**
Run 5 fold CV on data set using a gradient boosting machine classifier and calculate the mean average precision (MAP) over all five folds

# Avocado latent factors can predict gene expression



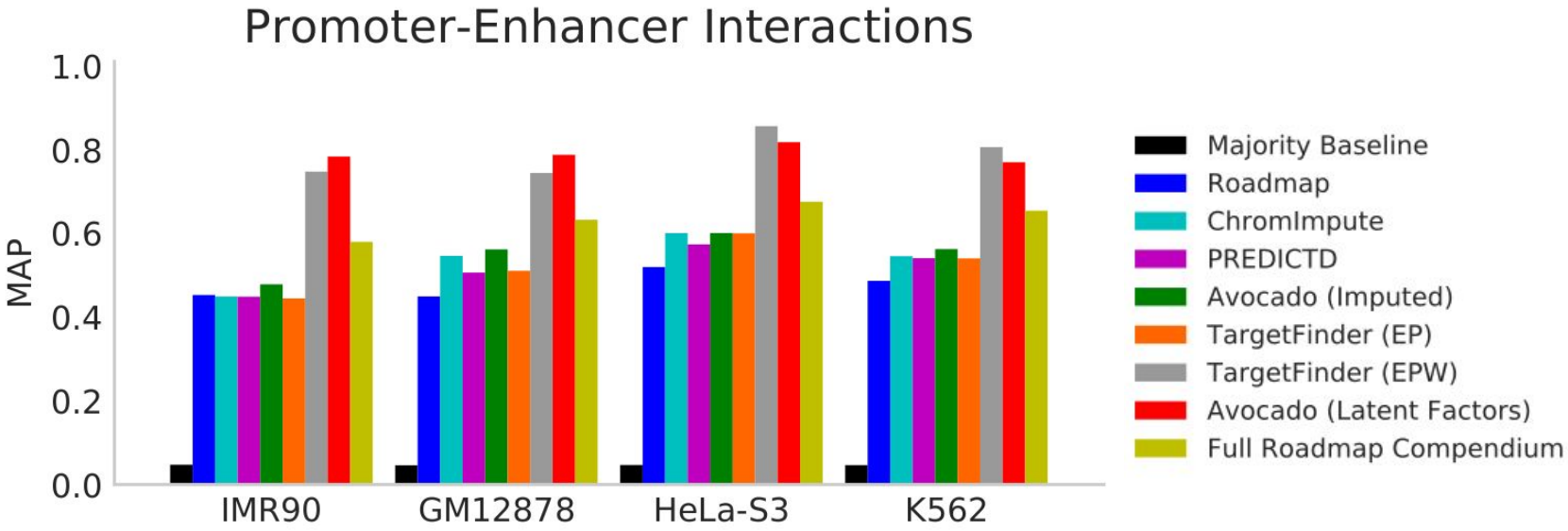

**Avocado > Epigenomic Measurements**

- All cell types
- By an average of 0.144 MAP
- By an average of 0.167 MAP on the 7 most difficult cell types

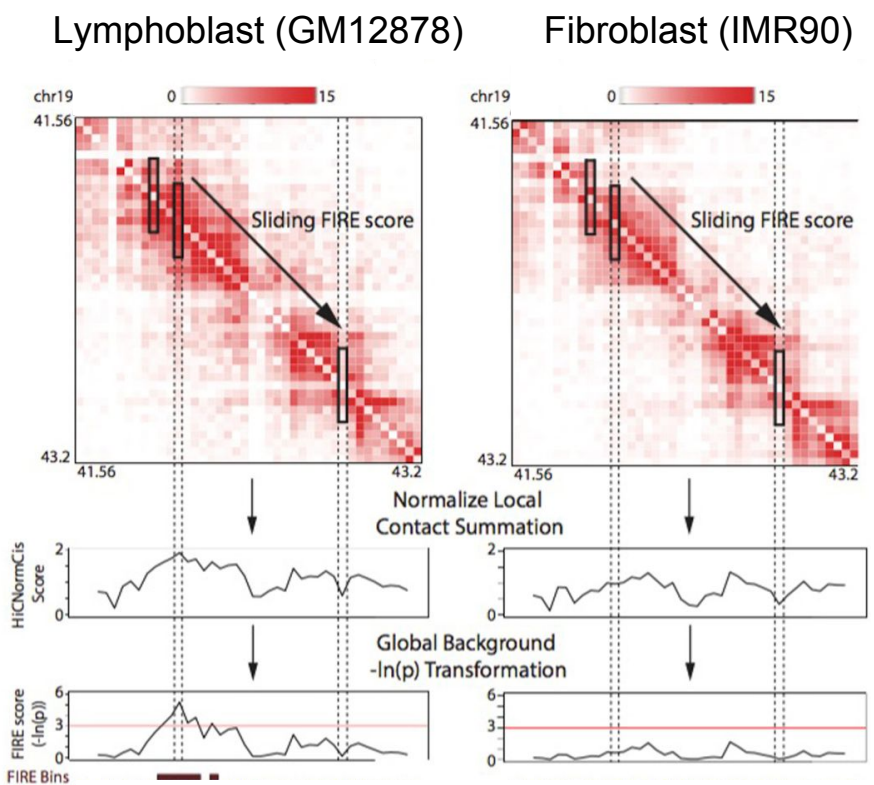
**Avocado > Full Roadmap Compendium**

- 36 / 47 cell types
- By an average of 0.006 MAP
- By an average of 0.03 MAP on the 7 most difficult cell types

# Avocado latent factors can predict promoter-enhancer interactions



# Avocado latent factors can predict FIREs




Schmitt et al, 2016

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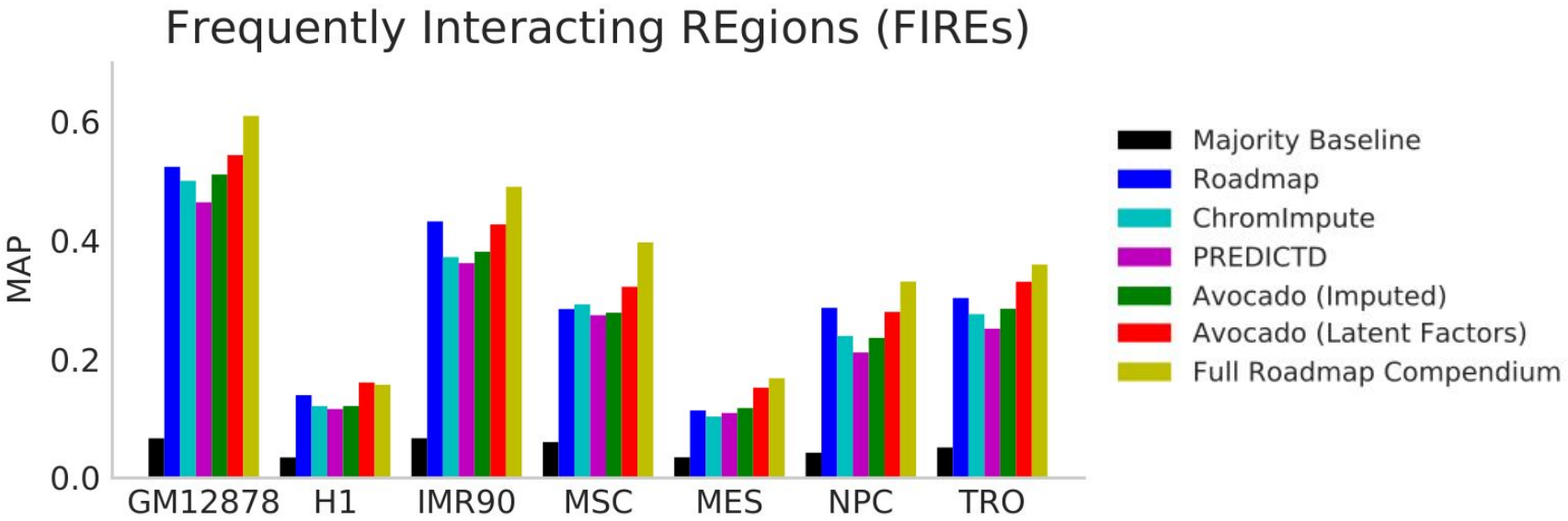
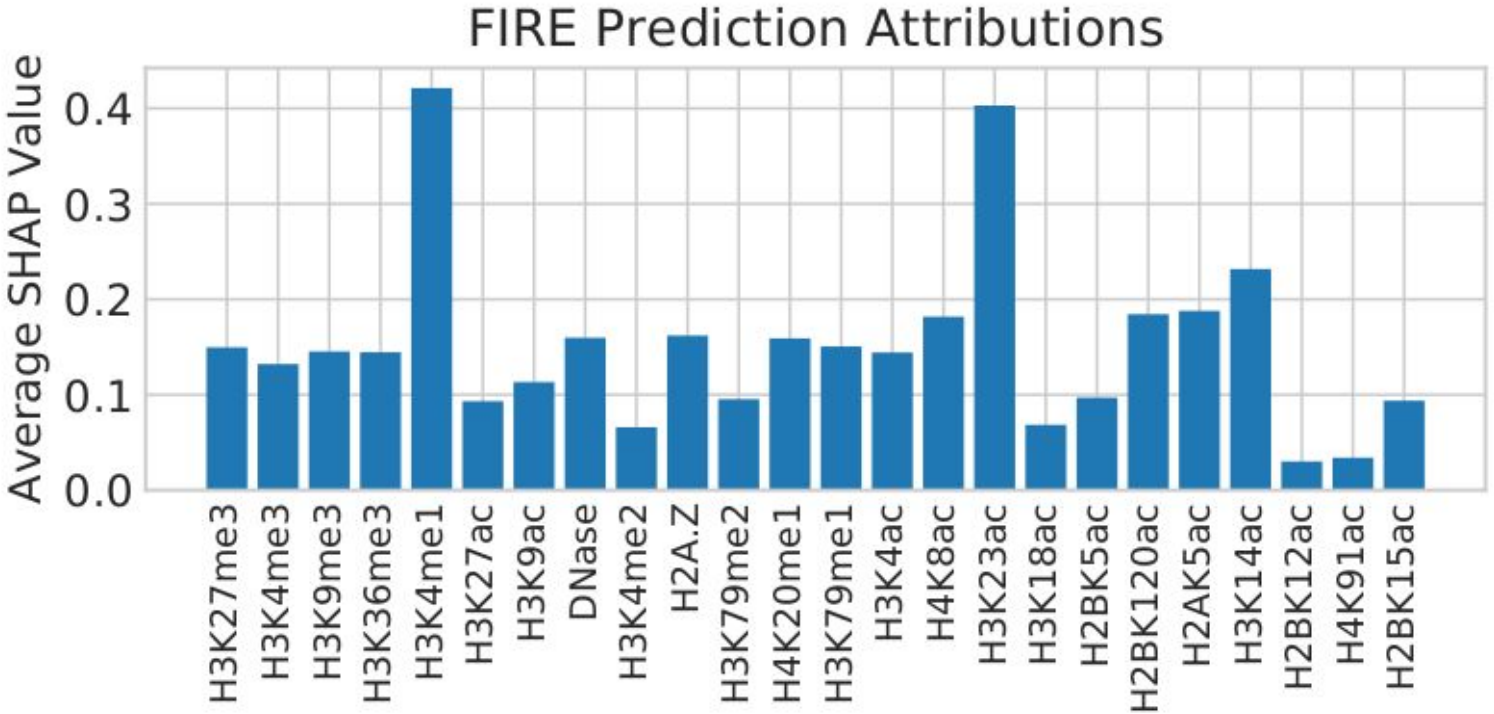


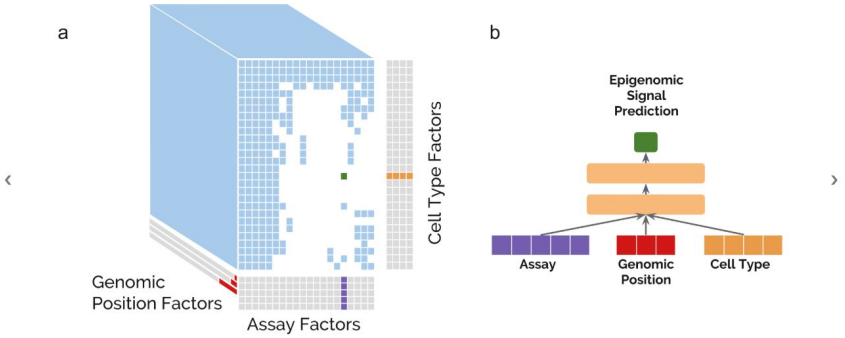
# Feature attribution methods reveal two important marks



# Review

- Avocado is a deep tensor factorization approach for modeling the human epigenome
- After being trained to impute epigenomic marks, it yields more accurate imputations than previous work
- Avocado's genome latent factors serve as a useful input for machine learning models on downstream genomics tasks, outperforming using epigenomic measurements themselves
- Using the entirety of the Roadmap compendium appears to be a stronger baseline than expected suggesting that measurements in many cell types can aid the prediction for a single cell type

# Preprint and model are online now!

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Avocado: Multi-scale Deep Tensor Factorization Learns a Latent Representation of the Human Epigenome

Jacob Schreiber[1], Timothy Durham[2], Jeffrey Bilmes[1, 3], and William Noble[1, 2]

1. Paul G. Allen School of Computer Science and Engineering, University of Washington
2. Department of Genome Science, University of Washington
3. Department of Electrical Engineering, University of Washington

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**doi:** https://doi.org/10.1101/364976

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**Abstract**

The human epigenome has been experimentally characterized by measurements of protein binding, chromatin acessibility, methylation, and histone modification in hundreds of cell types. The result is a huge compendium of data, consisting of thousands of measurements for every basepair in the human genome. These data are difficult to make sense of, not only for humans,

**https://noble.gs.washington.edu/proj/avocado**

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eScience Institute
ADVANCING DATA-INTENSIVE DISCOVERY IN ALL FIELDS

NSF National Science Foundation
WHERE DISCOVERIES BEGIN