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

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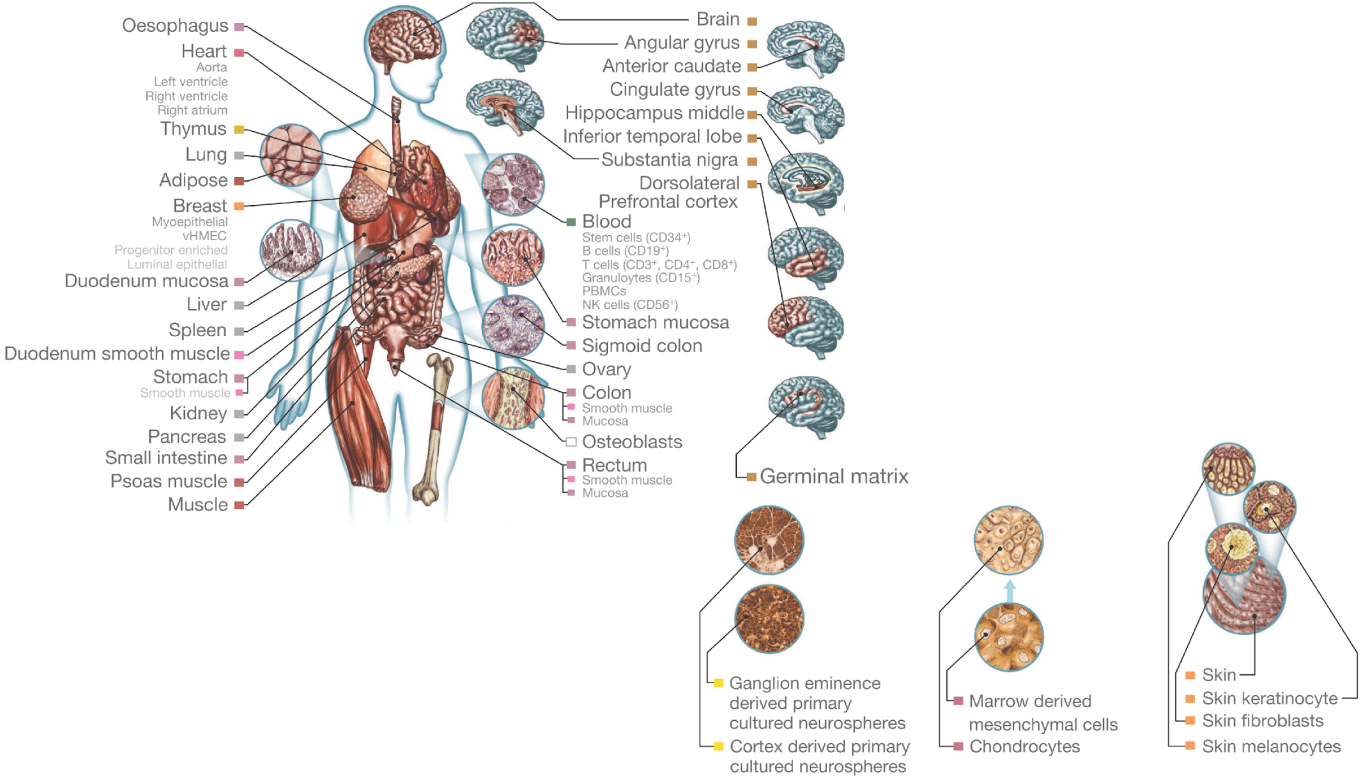
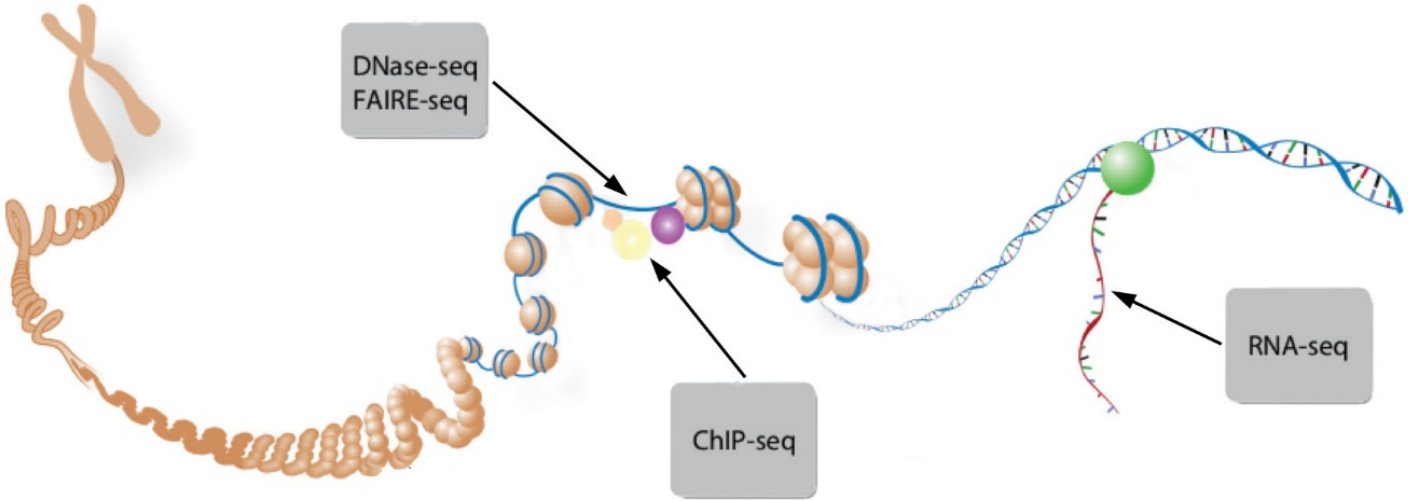
The sequence of the human genome cannot explain the diversity of human cell types



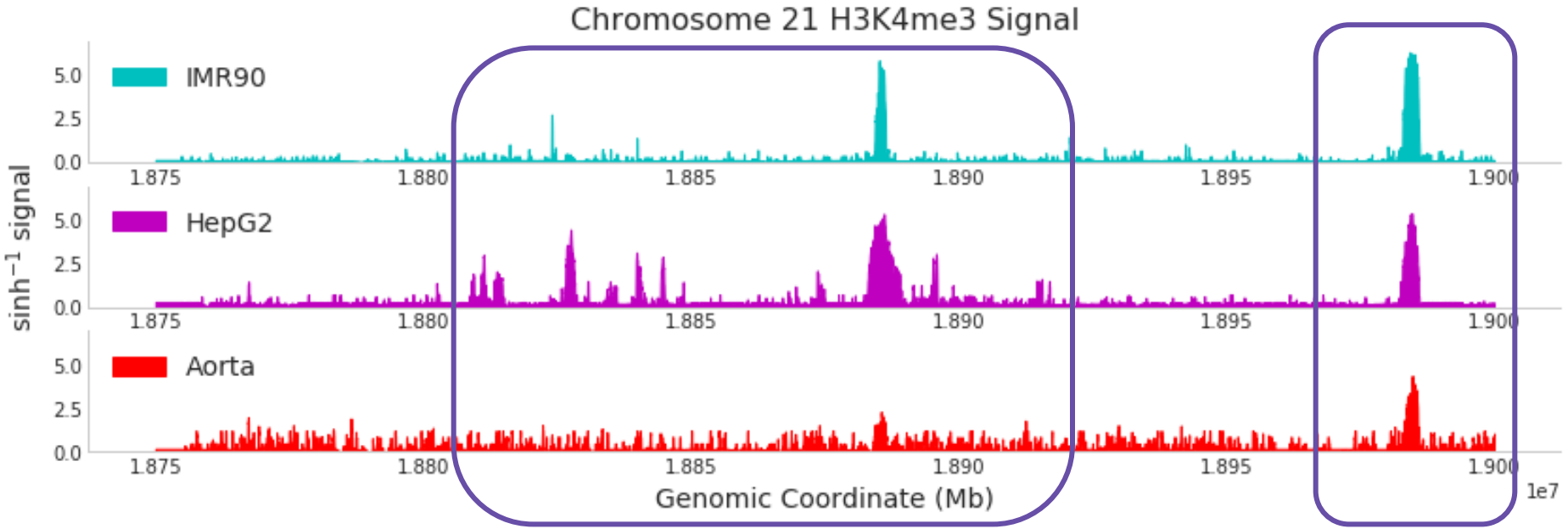
Credits: Roadmap Consortium, Nature (2015)

Many measurements can be gathered in addition to nucleotide sequence



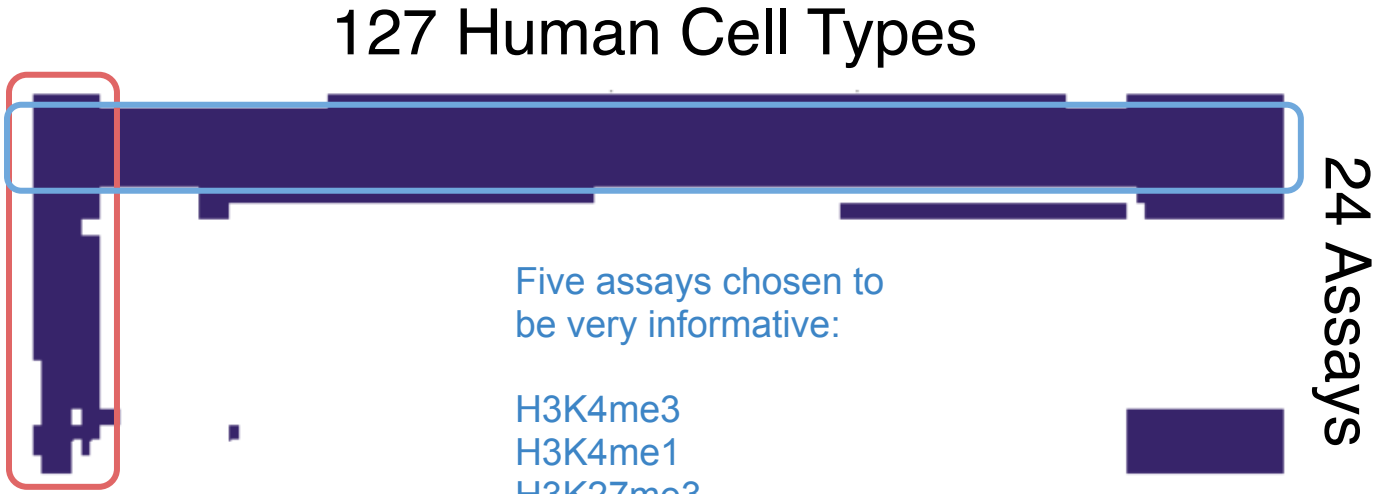
Credits: Darryl Leja (NHGRI), Ian Dunham (EBI)

The signal of epigenomic assays vary across cell types



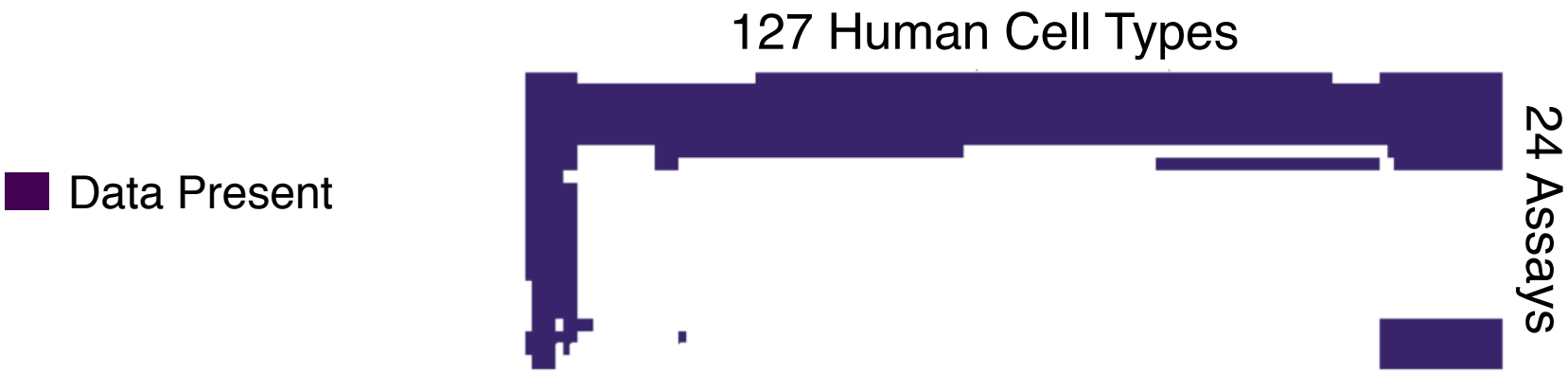
Many experiments have been performed, but still only a fraction of possible experiments

Data Present



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

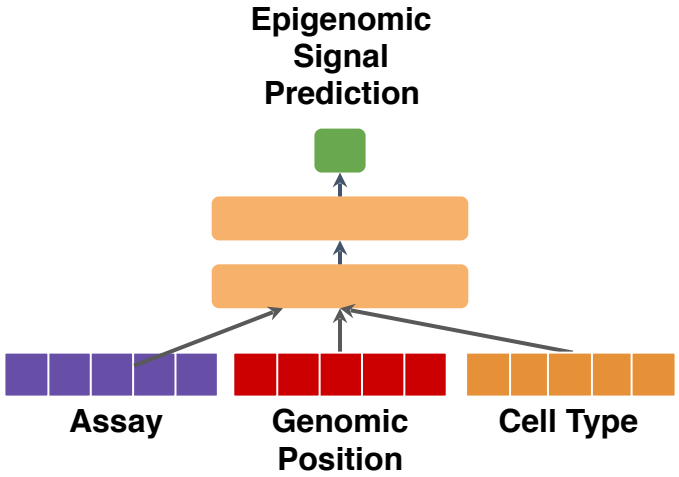
Have we characterized the human epigenome yet?



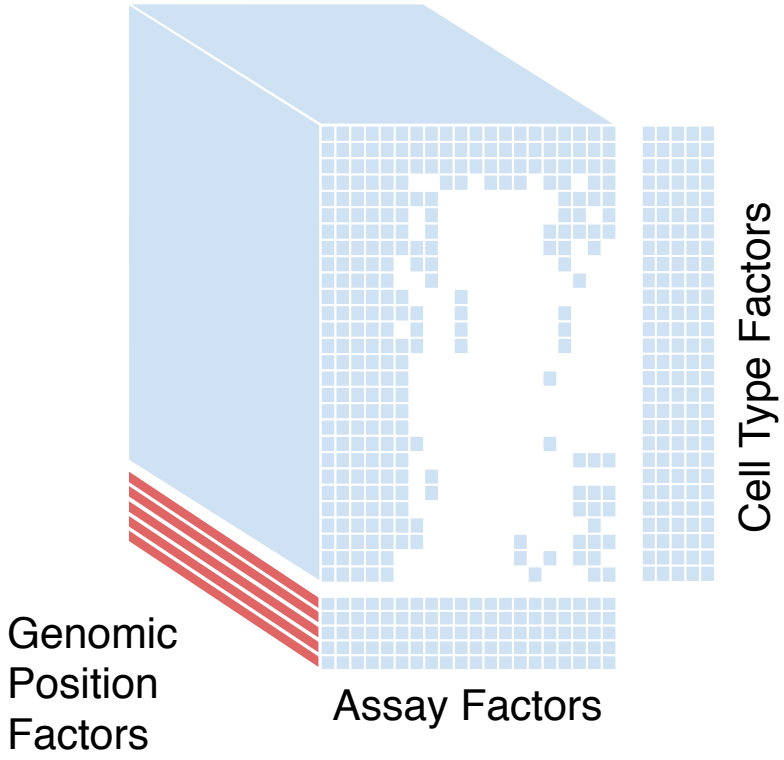
- Previous work sought to fully characterize the epigenome through imputing all potential experiments (ChromImpute[1], PREDICTD[2])
- Can we characterize the epigenome through distilling the available measurements into an informative latent representation?

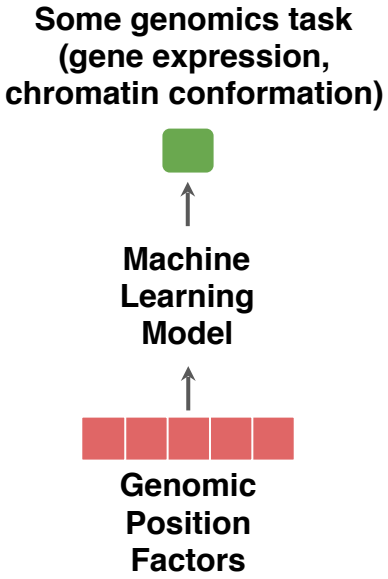
1. Ernst, et al. *Nature Methods, 2015*
2. Durham, et al. *Nature Communications, 2018*

Avocado is a deep tensor factorization approach

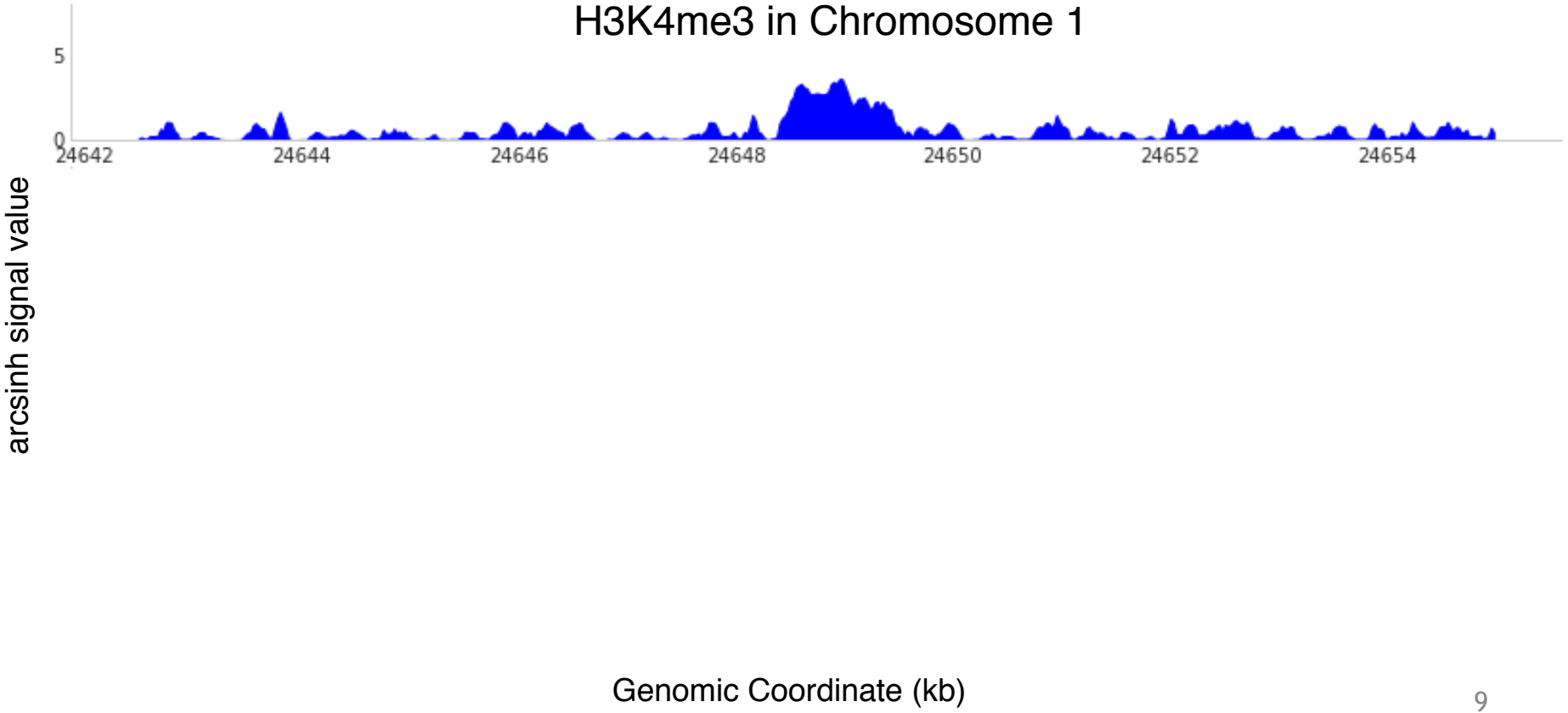


Our goal is to use the genomic latent factors for other tasks





Initial inspection of the imputations suggest that Avocado performs well



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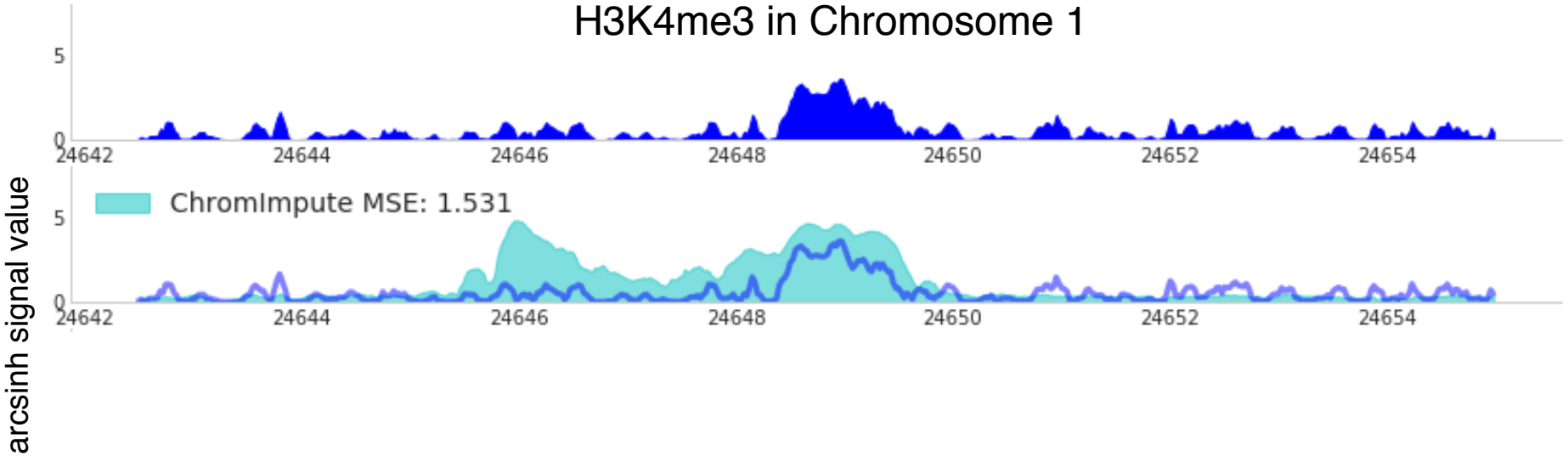

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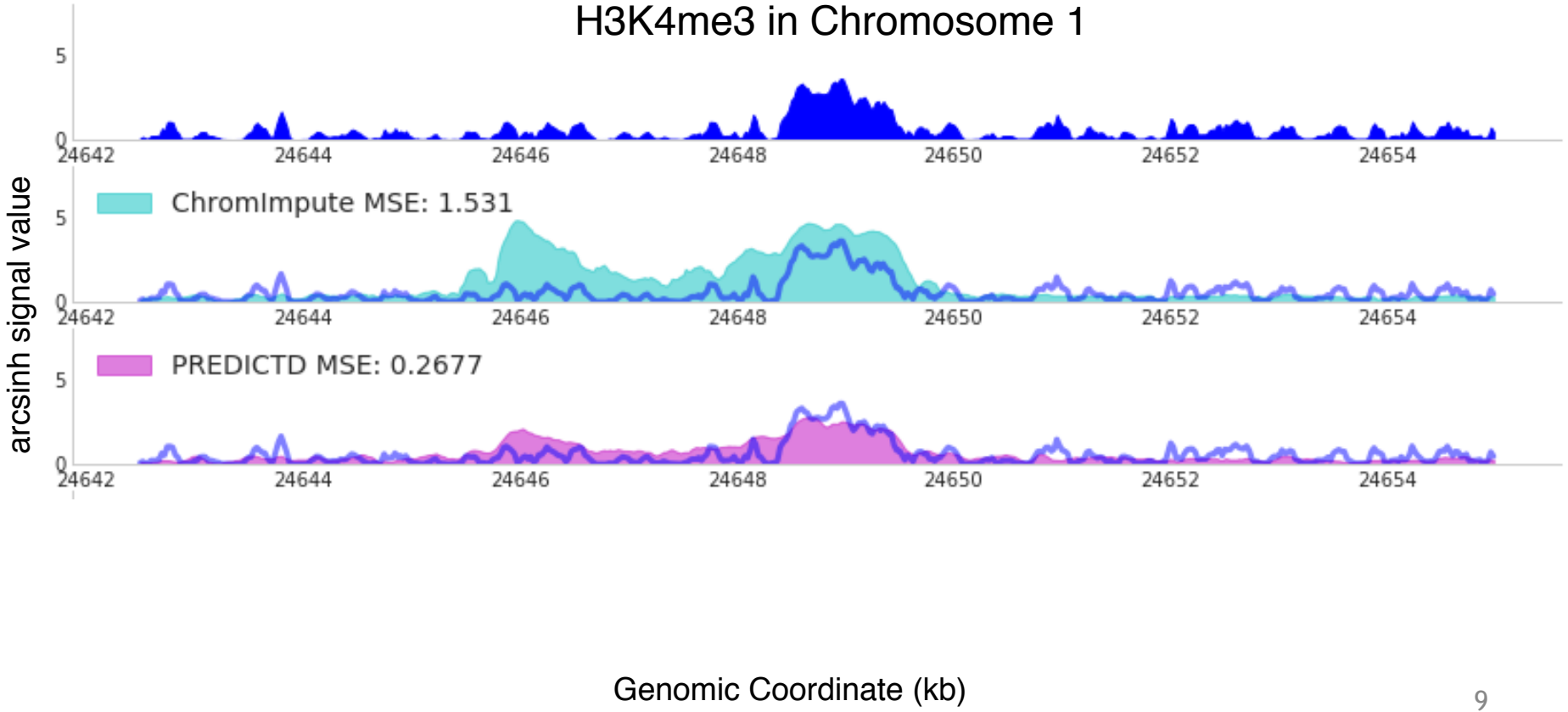

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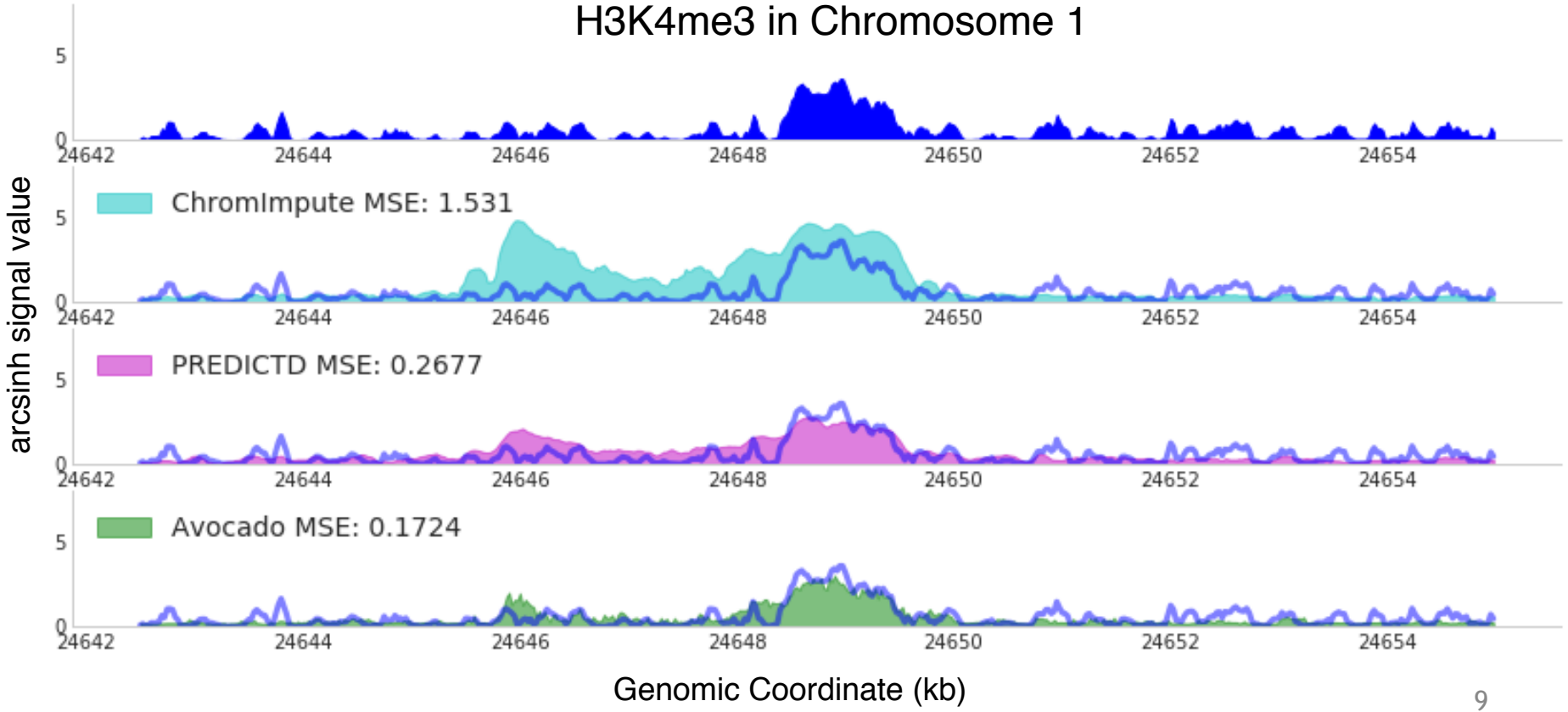

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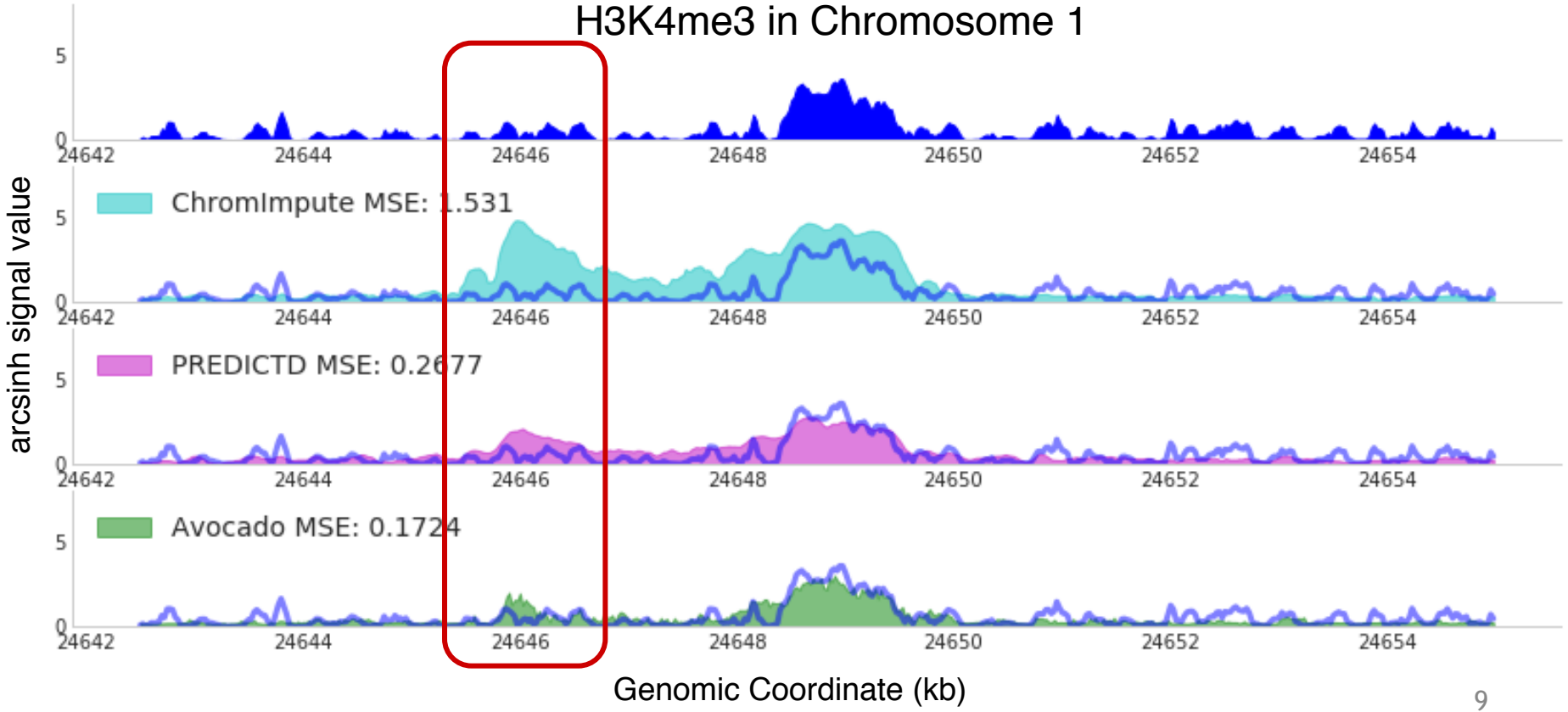

Avocado continues to perform well genome-wide

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

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???

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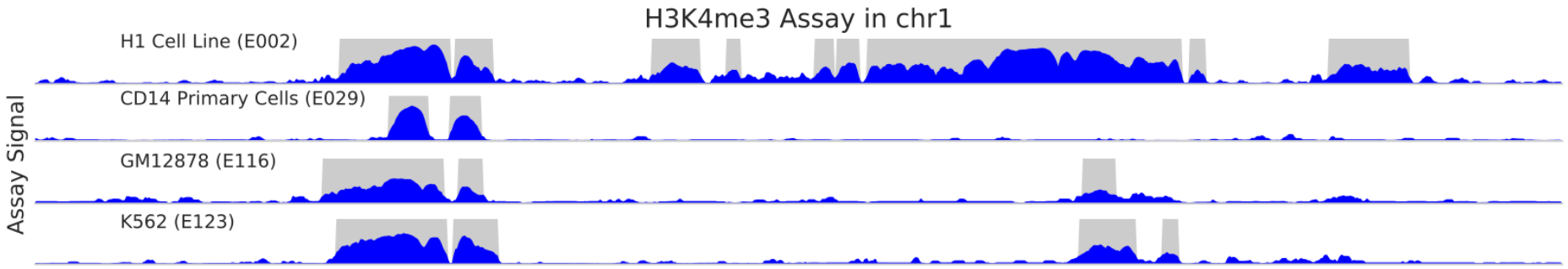
How well can these approaches recover cell type specific peaks?



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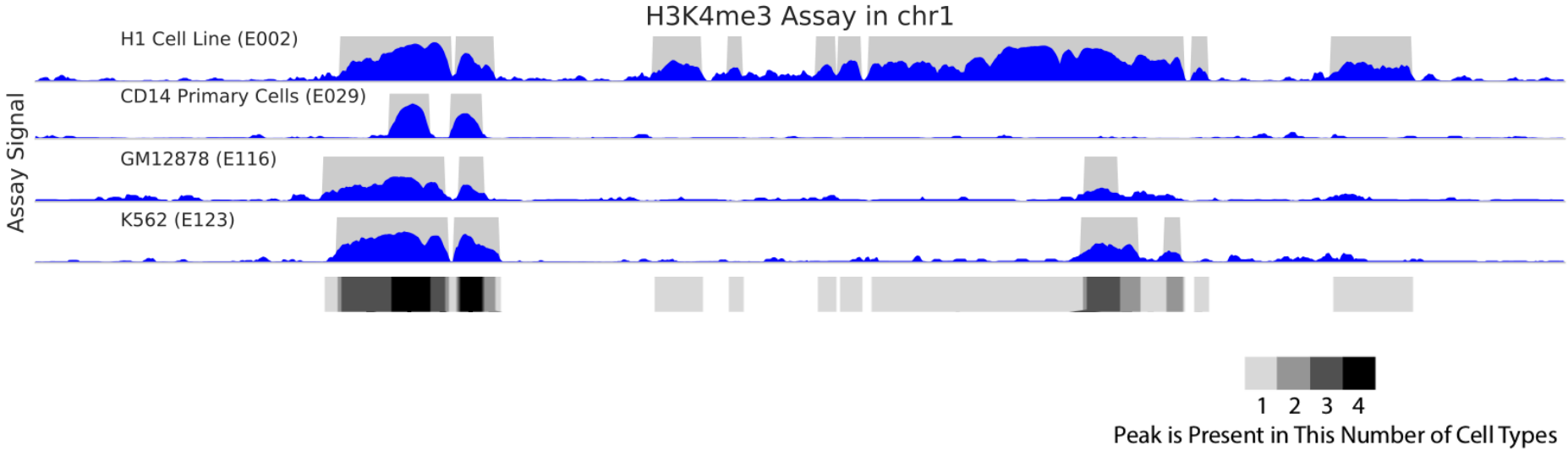

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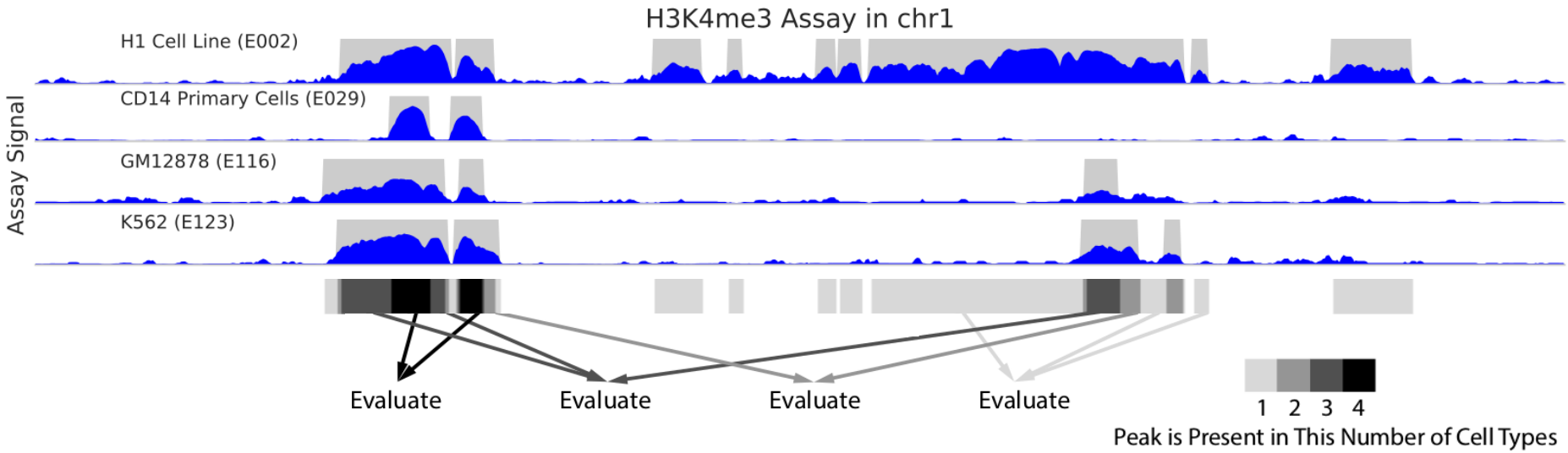

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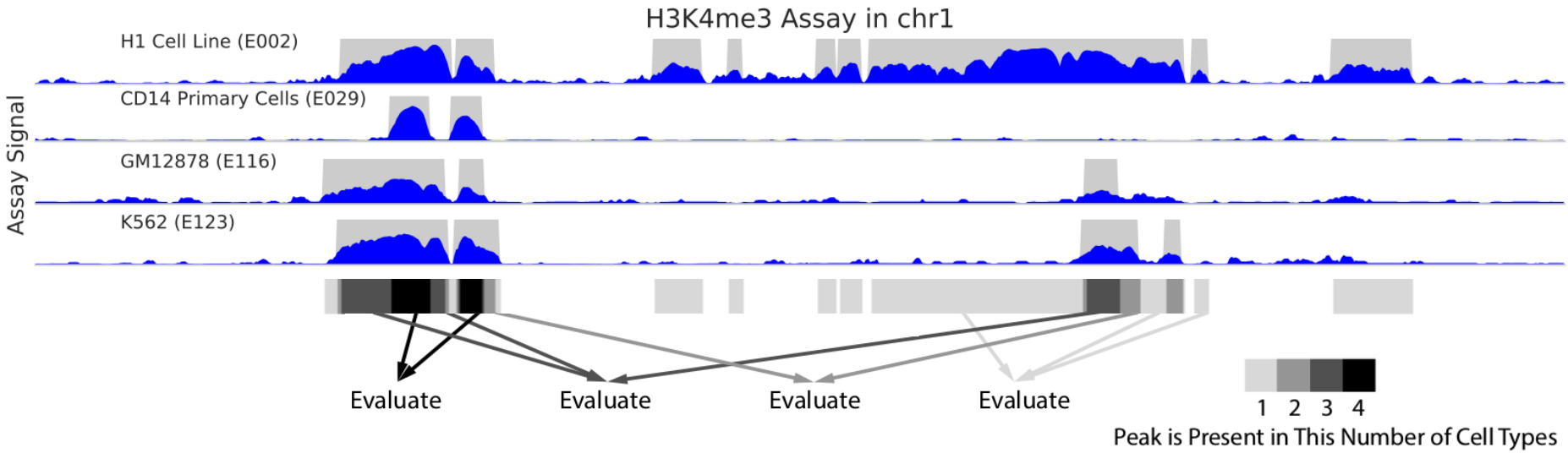

Evaluate by calculating:

(1) MSE

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

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

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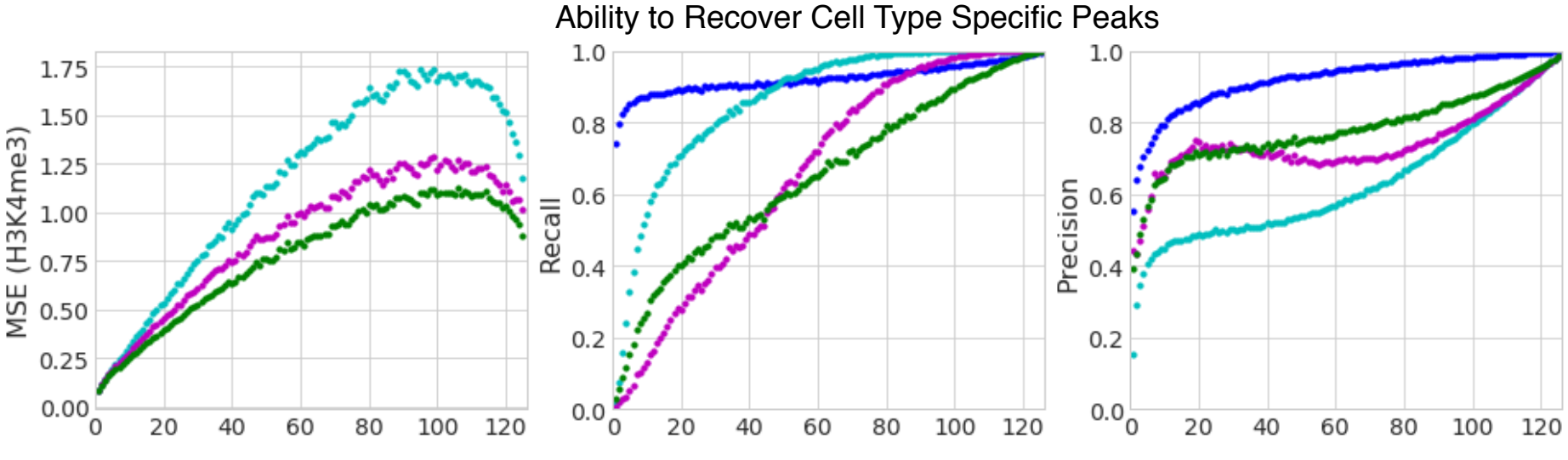

We evaluated our learned representation in many contexts

STEP 1:
Choose a Prediction Task

- Gene Expression
- Promoter-Enhancer Interactions
- Frequently Interacting REgions (FIREs)
- Topologically Associating Domain (TAD) boundaries

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- Task dependant

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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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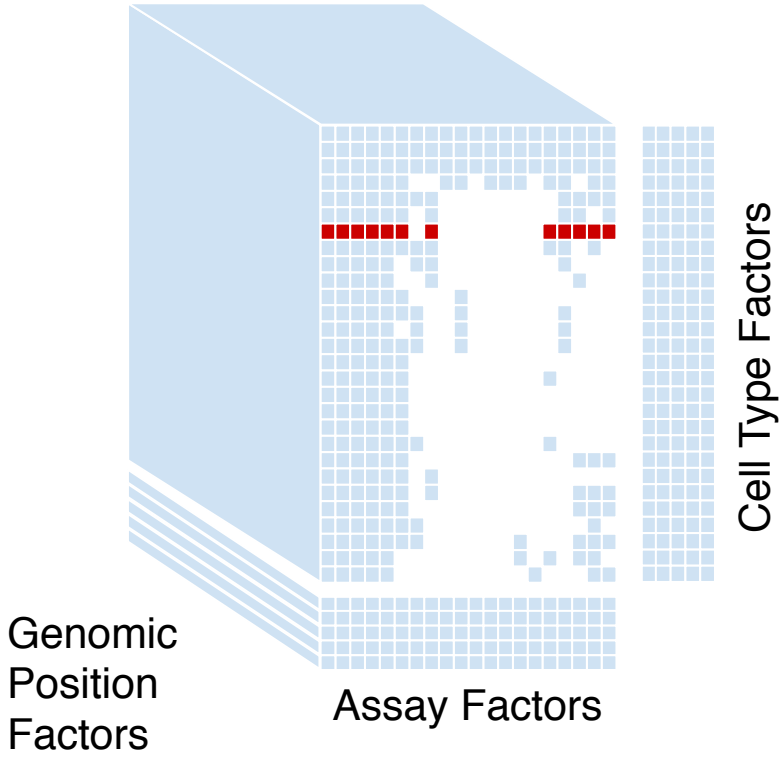

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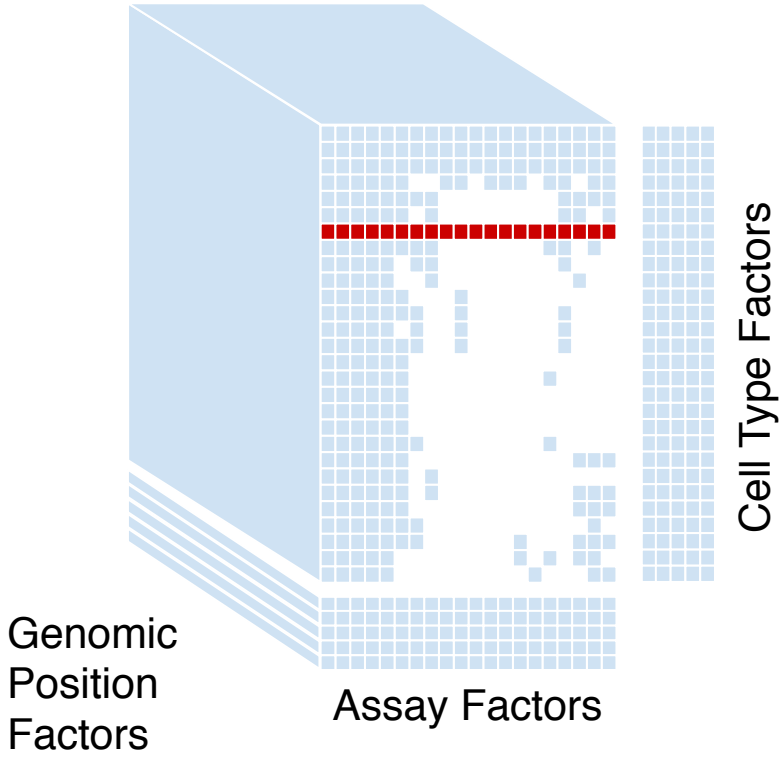

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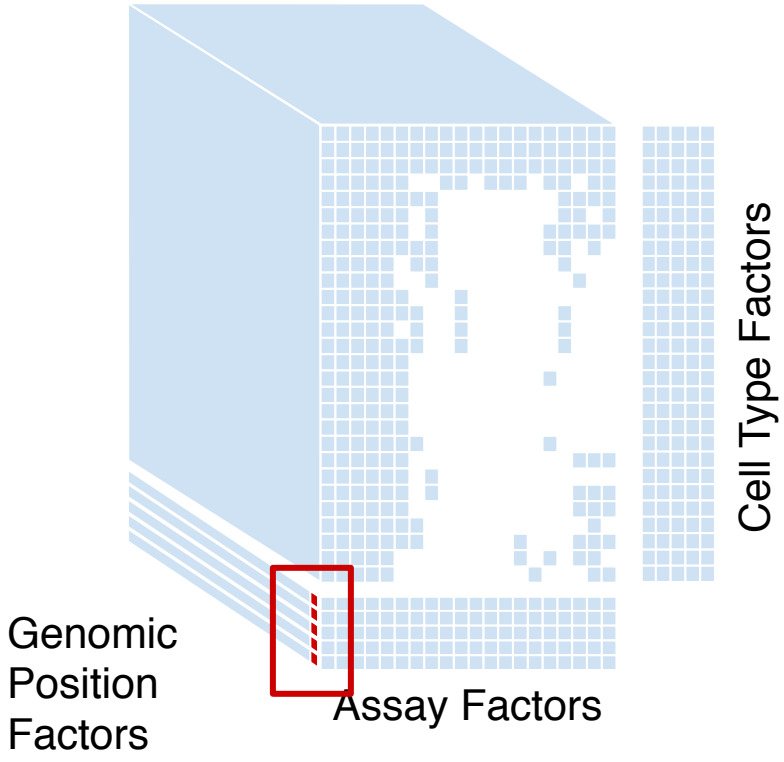

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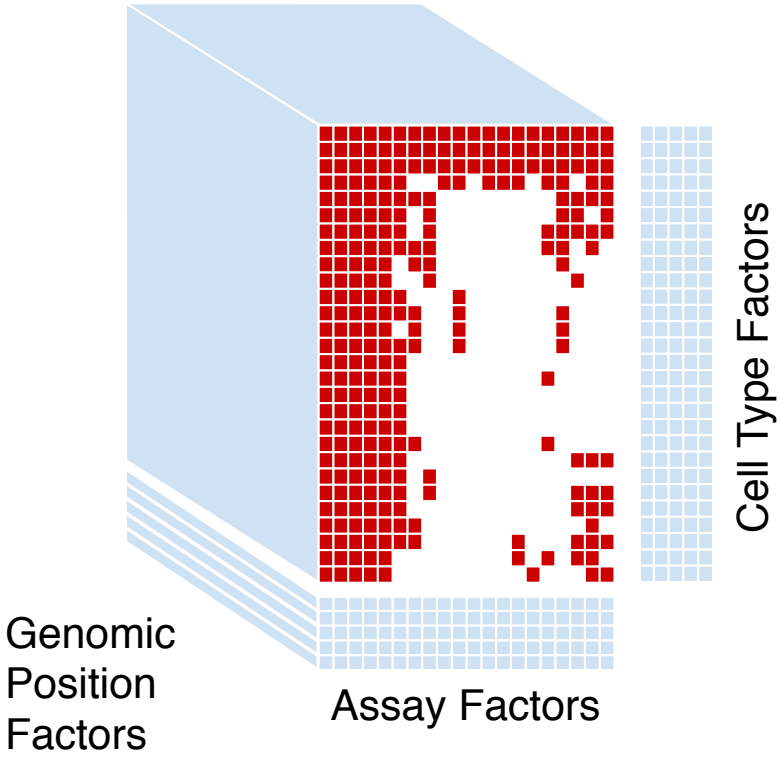

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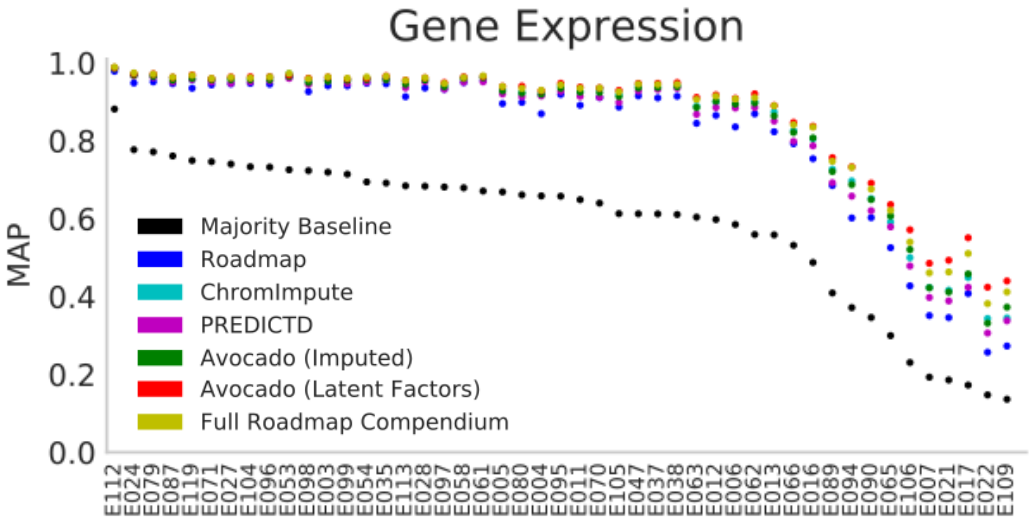
STEP 4:
Run 5 fold CV on data set using a gradient boosting machine classifier and calculate the mean average precision (MAP) over all five folds

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

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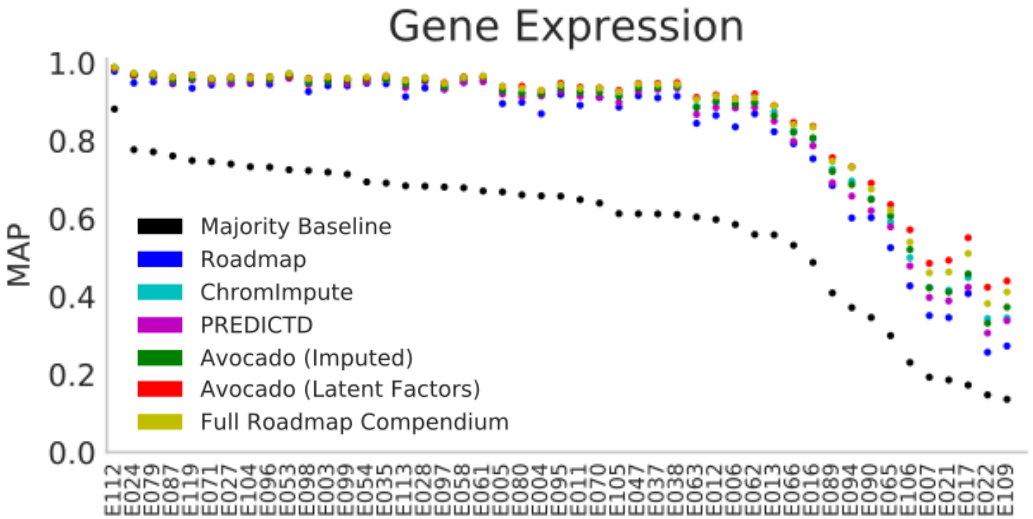
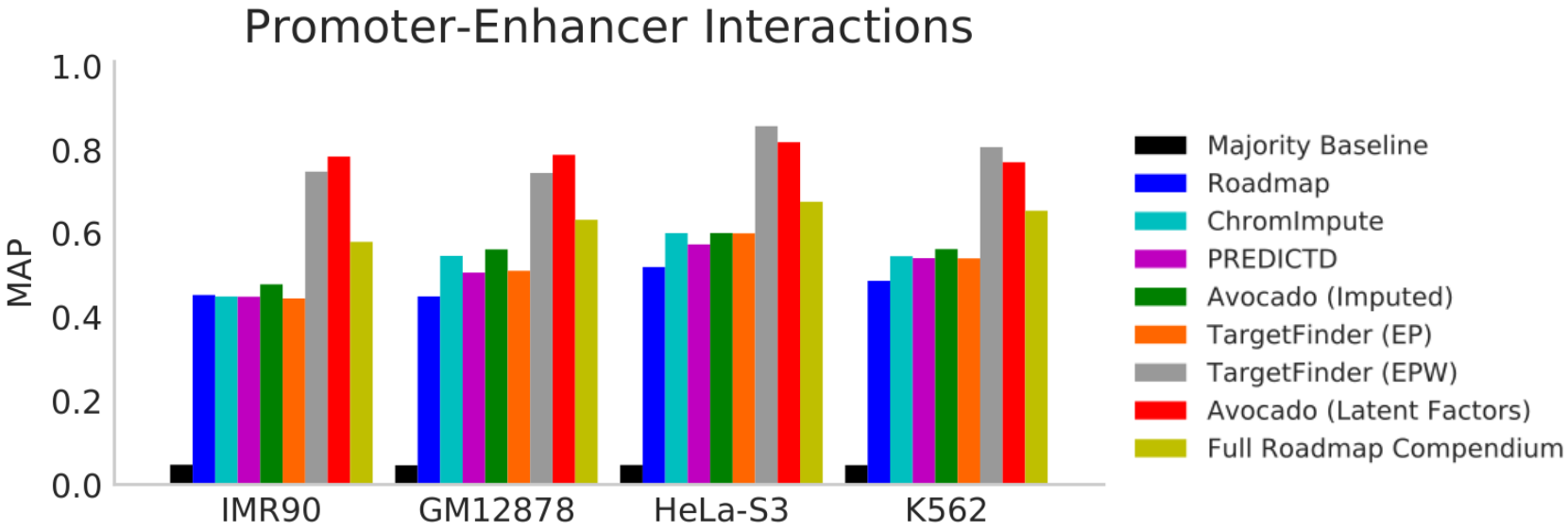


Avocado > Epigenomic Measurements
- All cell types
- By an average of 0.144 MAP
- By an average of 0.167 MAP on the 7 most difficult cell types

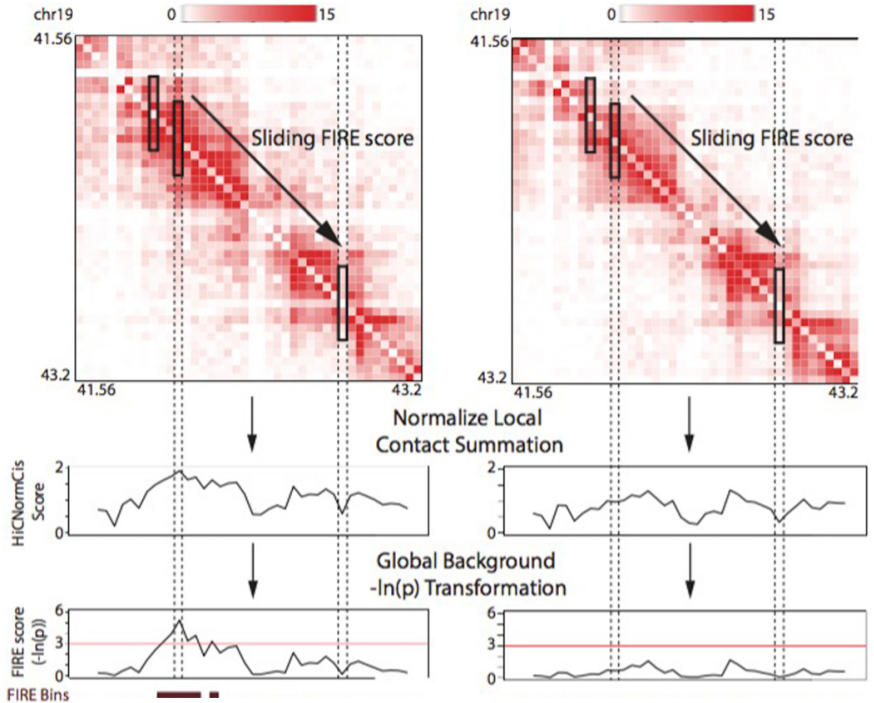
Avocado > Full Roadmap Compendium
- 36 / 47 cell types
- By an average of 0.006 MAP
- By an average of 0.03 MAP on the 7 most difficult cell types

Avocado latent factors can predict promoter-enhancer interactions



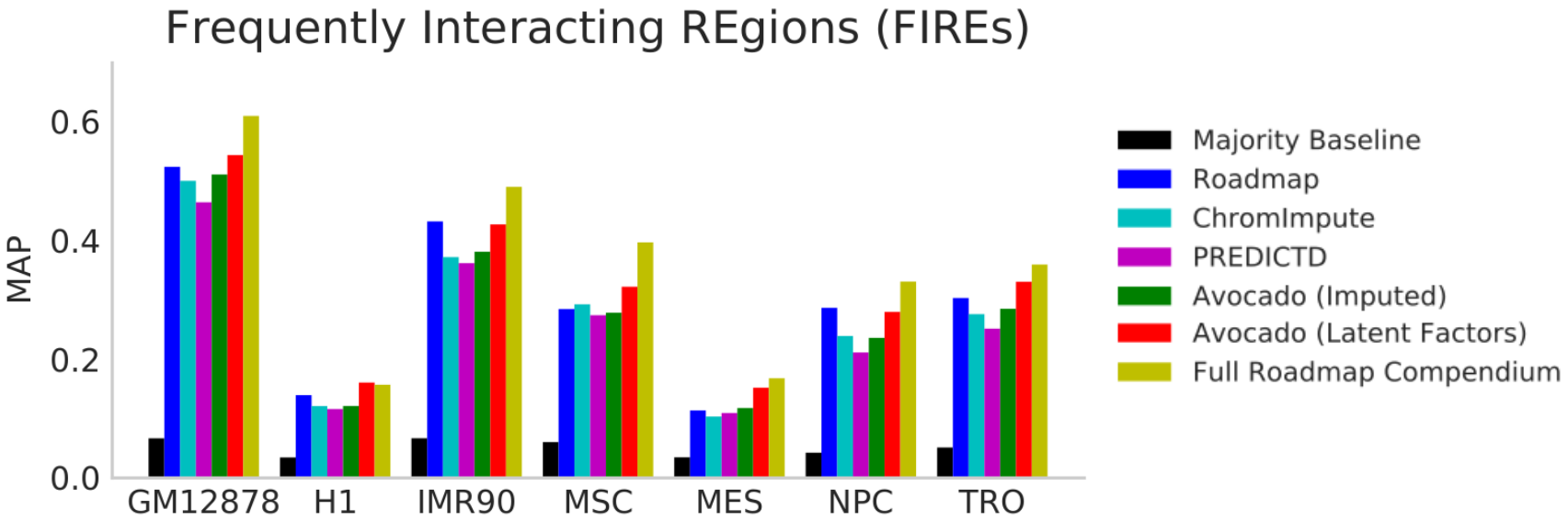
Avocado latent factors can predict FIREs

Lymphoblast (GM12878) Fibroblast (IMR90)

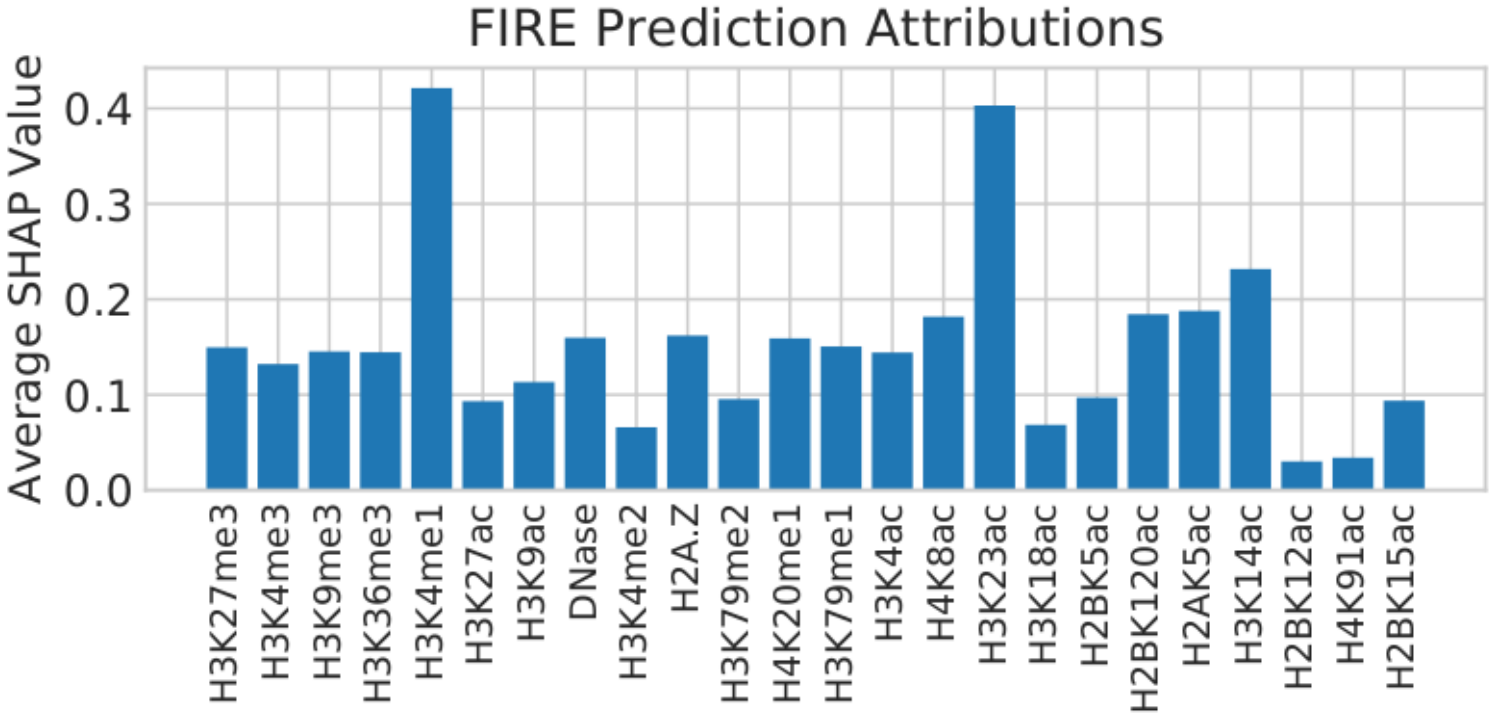


Schmitt et al, 2016

Avocado latent factors can predict FIREs



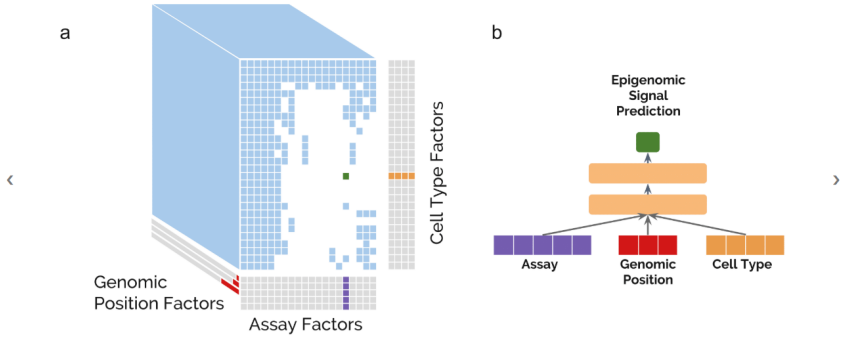
Feature attribution methods reveal two important marks



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

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Jacob Schreiber, Timothy J Durham, Jeffrey Bilmes, William Stafford Noble

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

Abstract | Info/History | Metrics | Supplementary material | Preview PDF

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,

Acknowledgements

eScience Institute
ADVANCING DATA-INTENSIVE DISCOVERY IN ALL FIELDS

NSF National Science Foundation
WHERE DISCOVERIES BEGIN