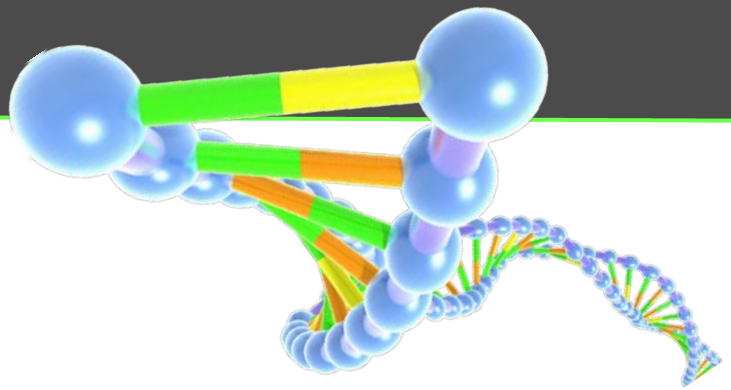
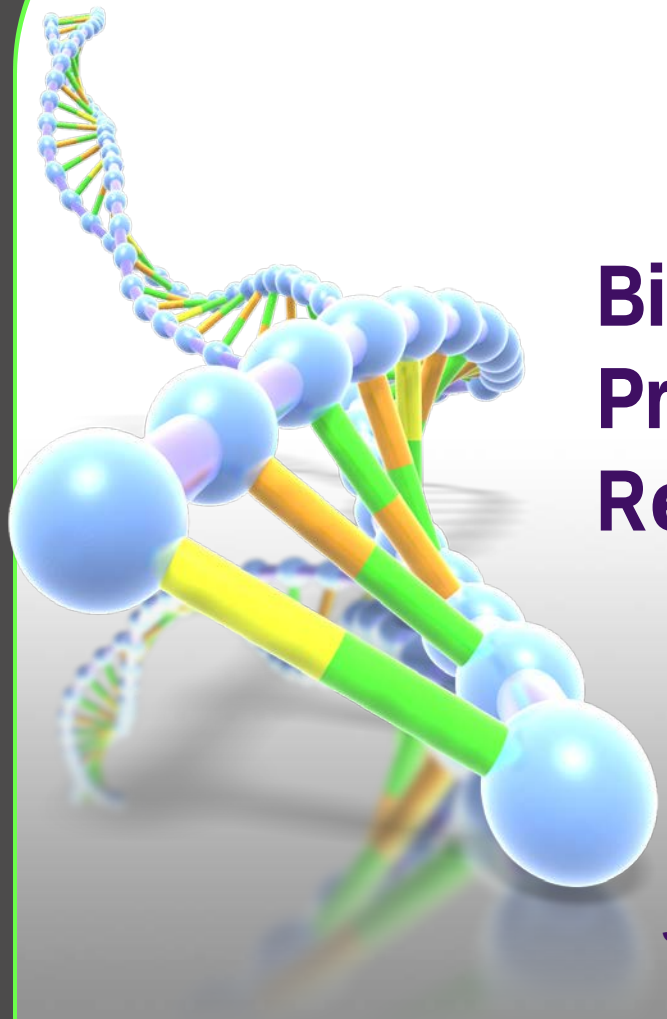




Big Data Regression for Predicting Genome-wide Regulatory Element Activities

Hongkai Ji
Department of Biostatistics
Johns Hopkins Bloomberg School of Public Health
Email: hji@jhu.edu

Big Data Prediction and Regression

X_{px1} → Y_{qx1}

$p = 10^4 - 10^9$

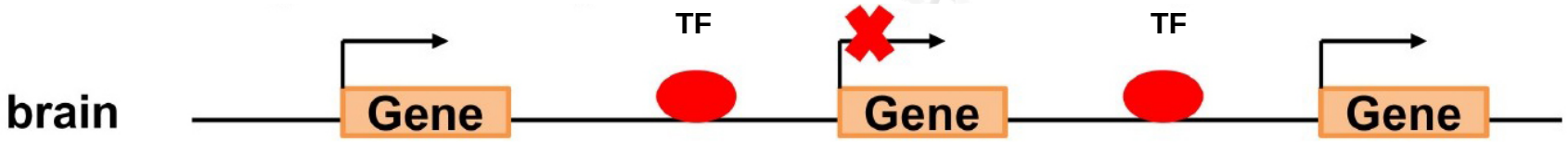
$q = 10^4 - 10^9$

- **Genotype**
- **Gene Expression**
- **Histone modification**
- **DNA methylation**

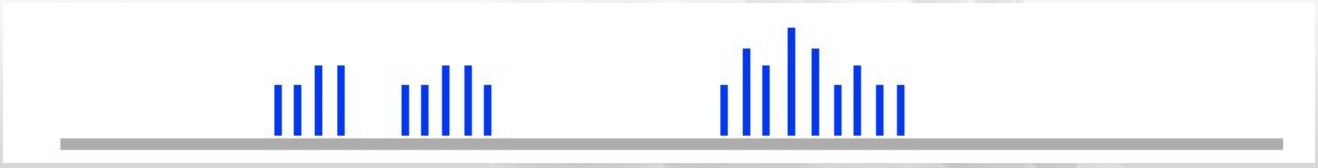
→

- **Chromatin states**
- **Transcription factor binding sites**
- **3D chromatin interaction**

Gene Regulation, Transcription Factor (TF), Cis-regulatory Elements

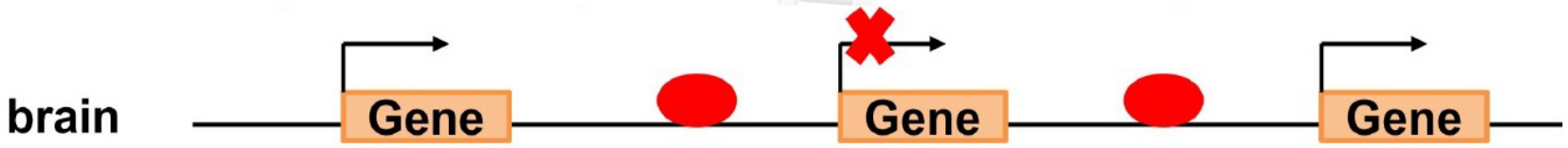


ChIP-seq/ChIP-chip

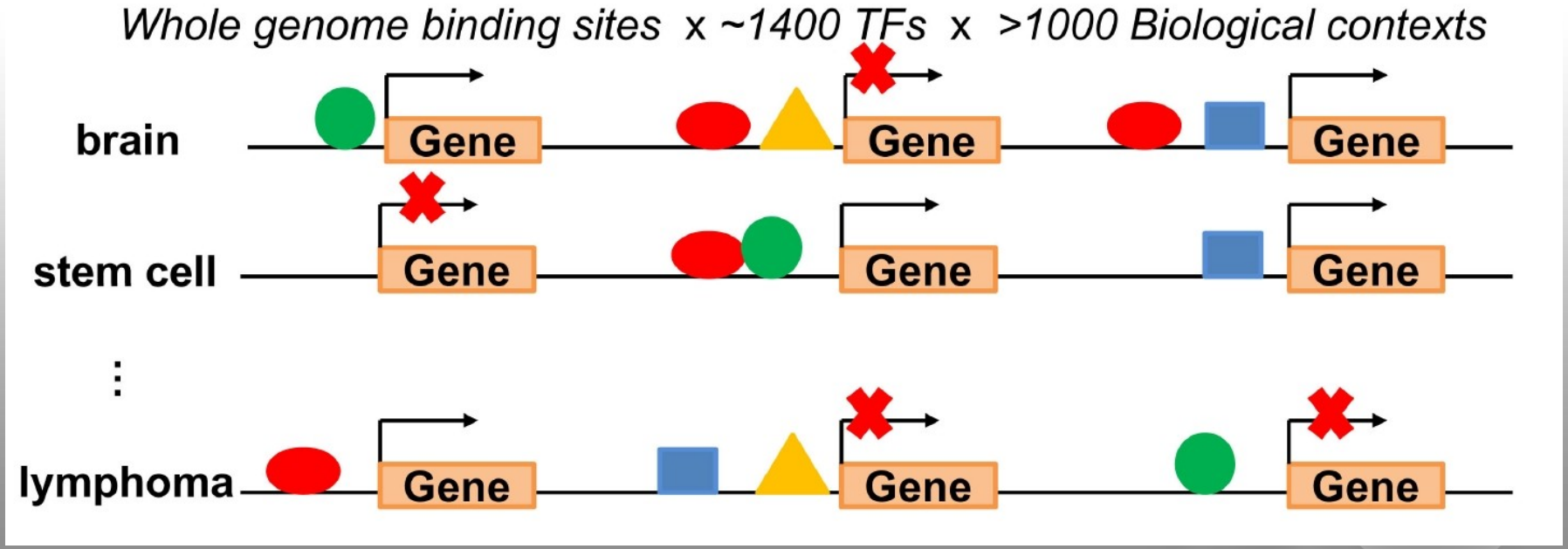


Problems with ChIP-seq

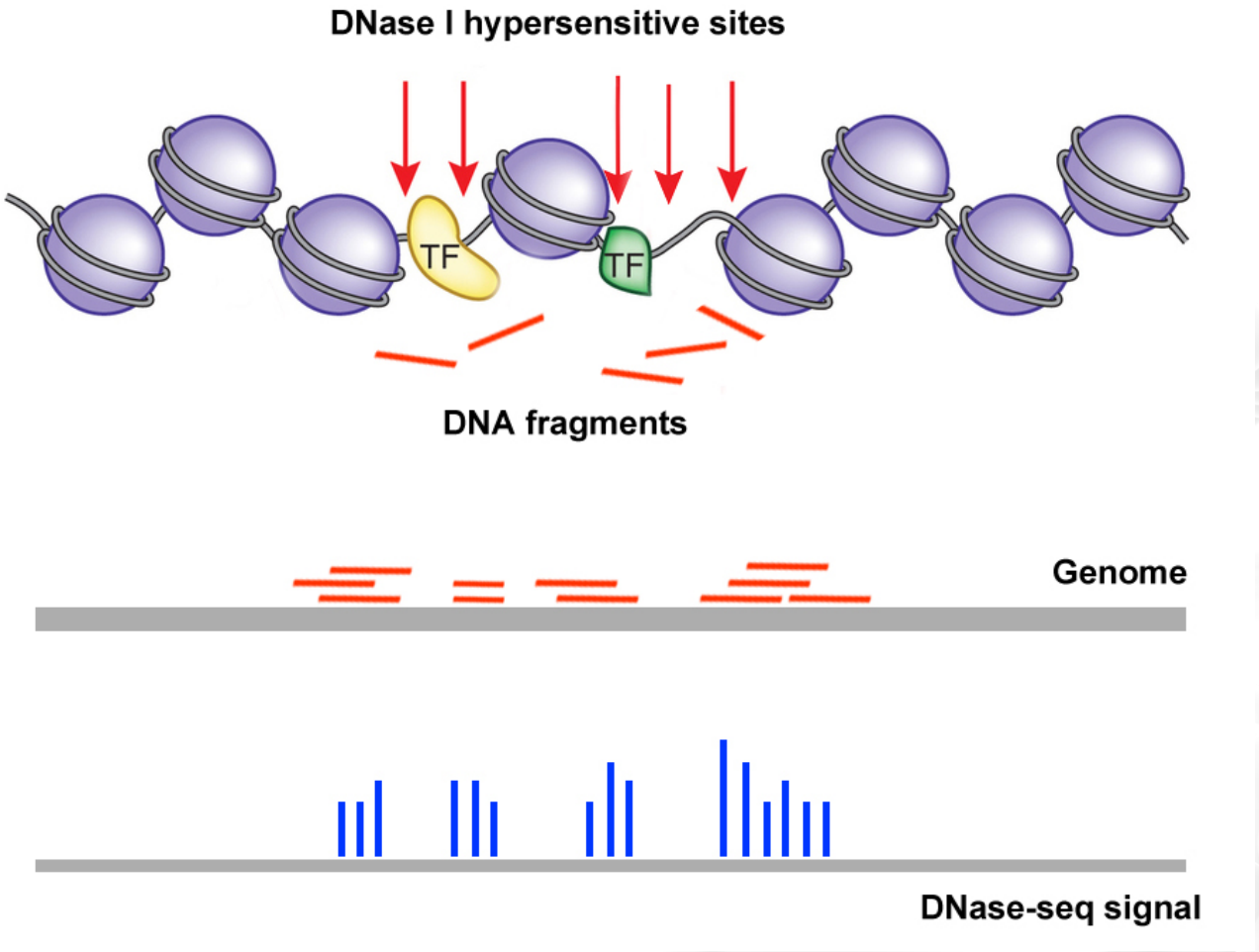
What ChIP-seq can do:



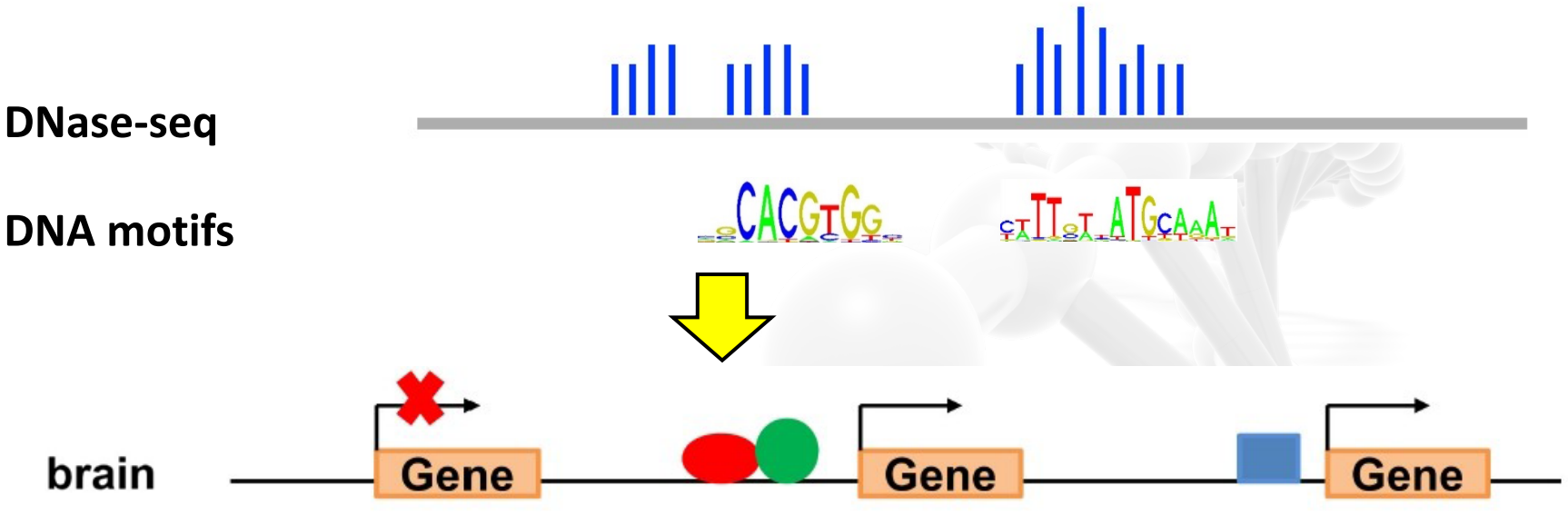
What we want to have:



DNase I Hypersensitivity (DHS) & DNase-seq

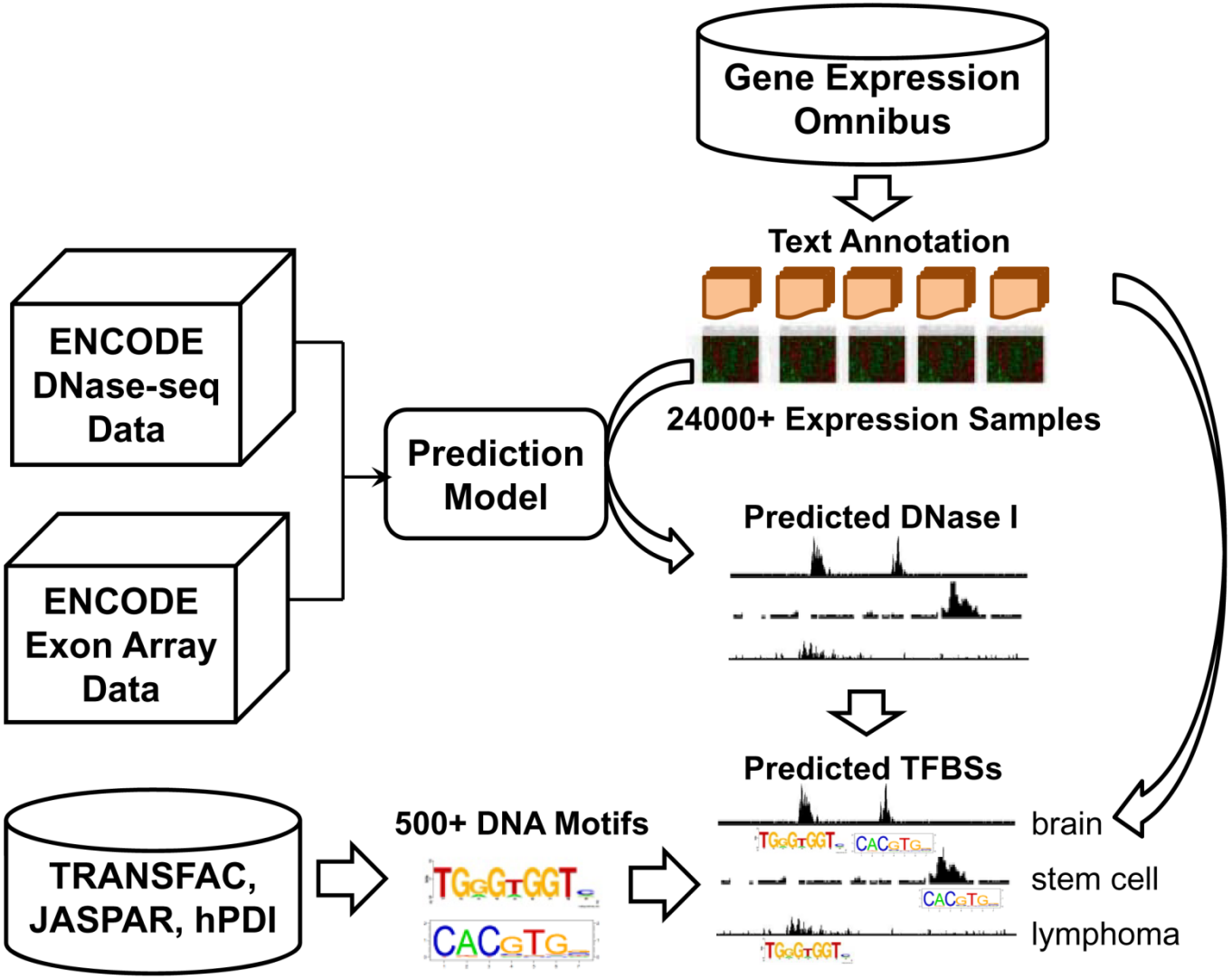


Predict Transcription Factor Binding Sites (TFBS) Based on DNase-seq



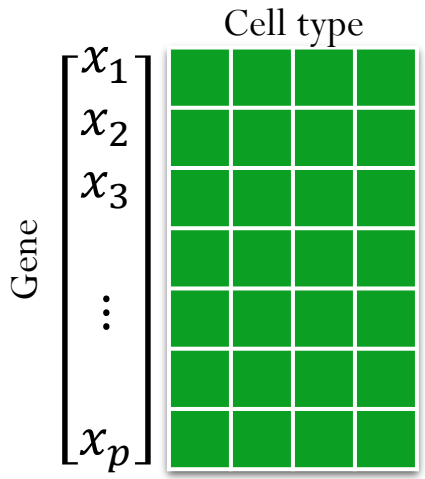
Pique-Regi et al. Genome Res. 2011. 21:447-455

Our Approach: A Solution Based on Big Data

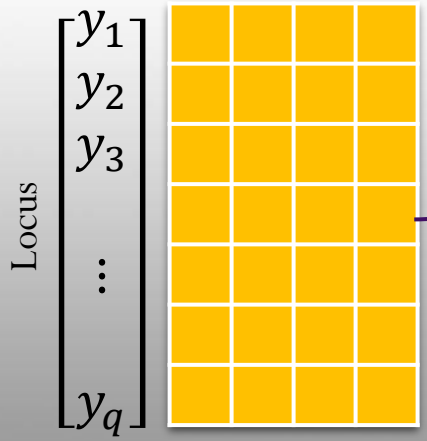


Training Data

X: Gene Expression

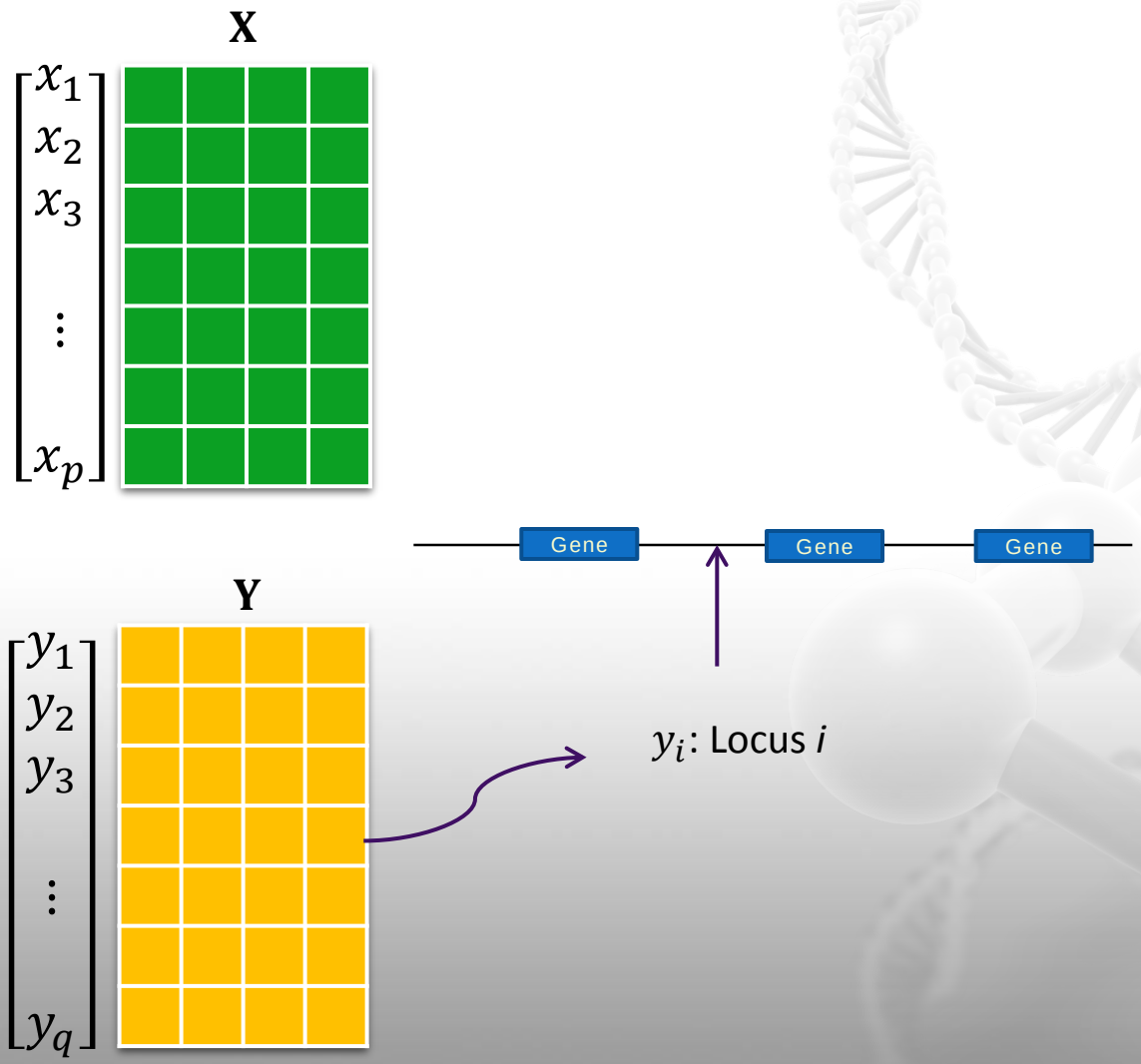


Y: DHS

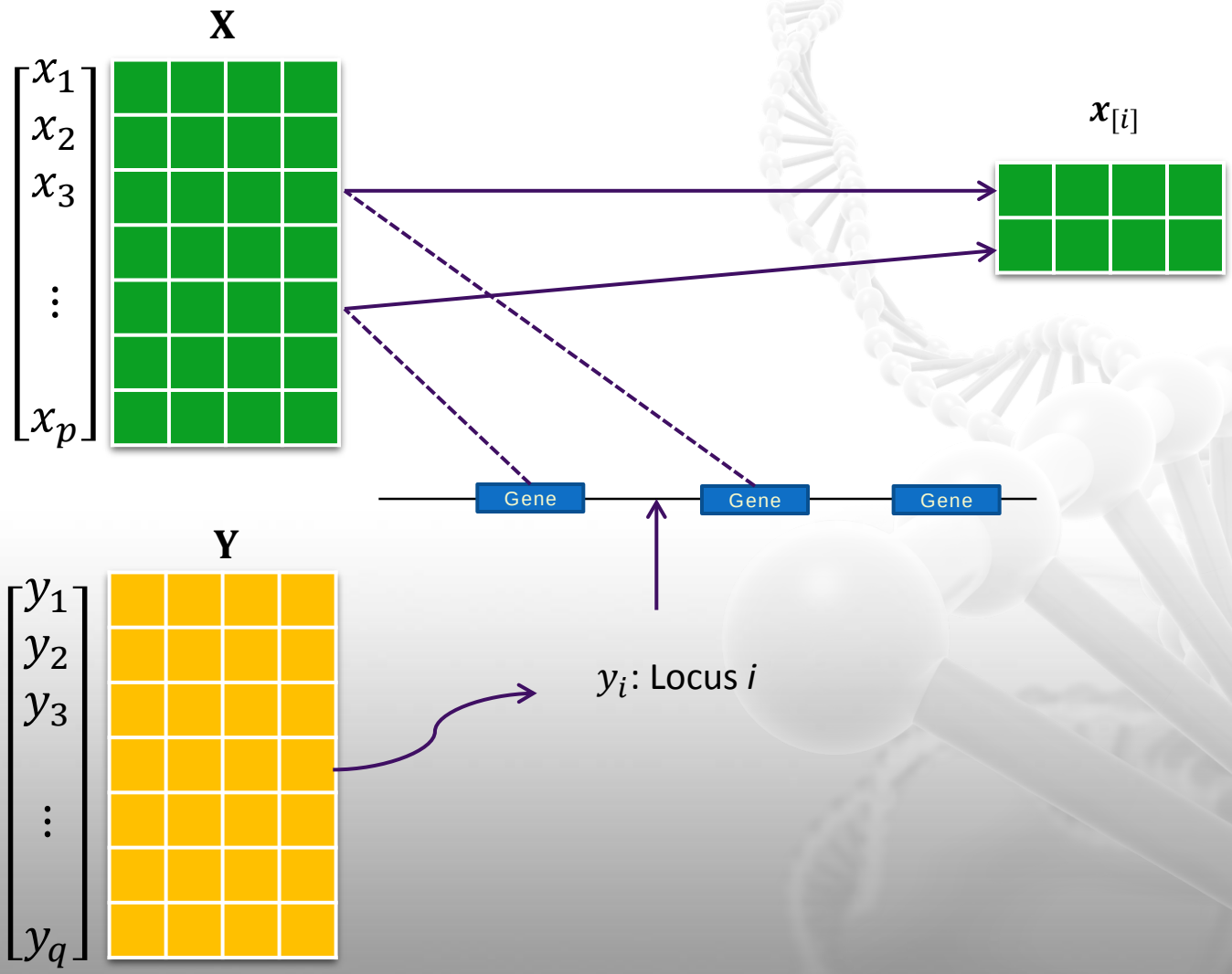


Locus *i*: $y_i = f_i(\mathbf{X}) + e$

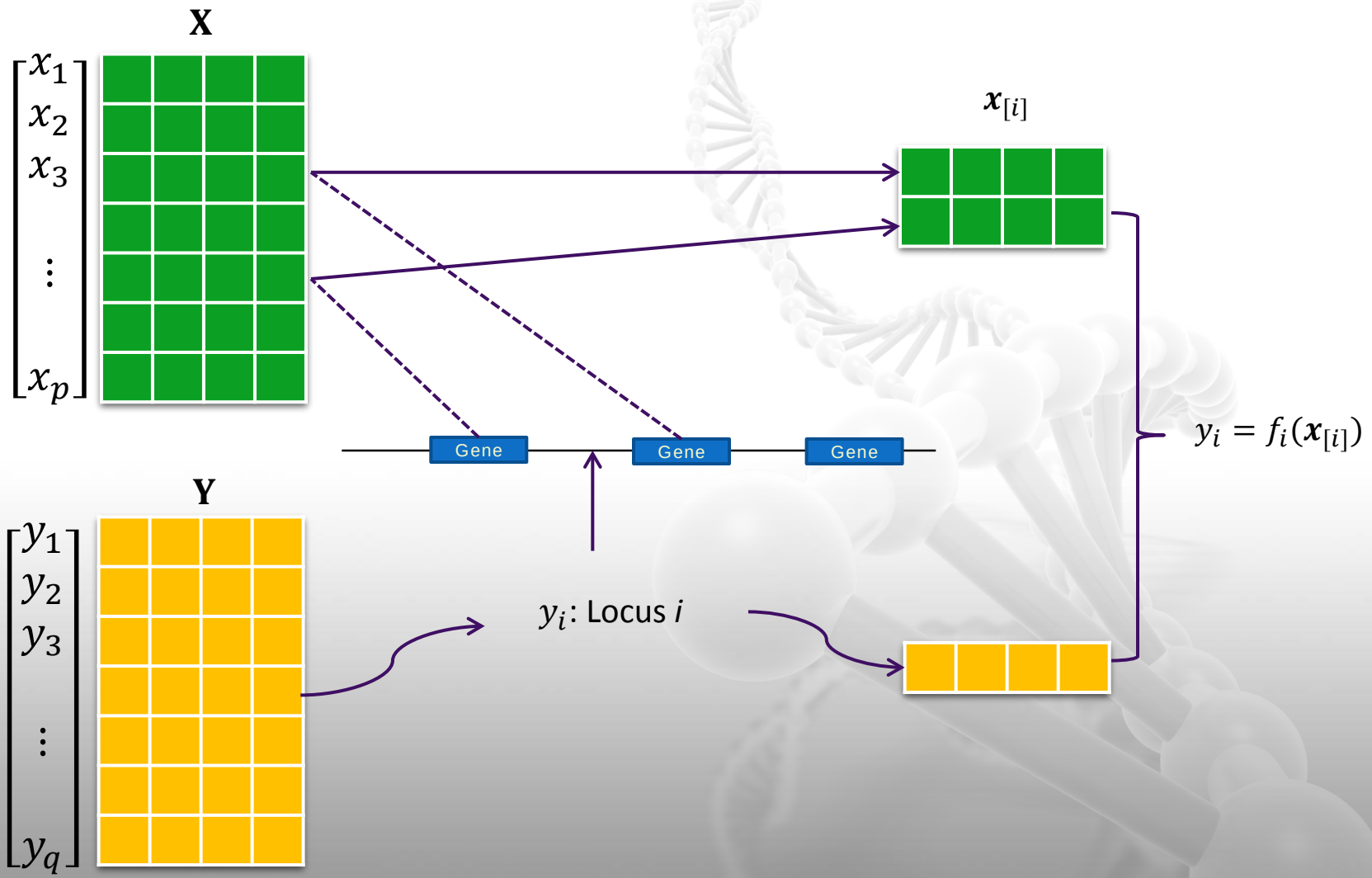
Neighboring Gene Approach



Neighboring Gene Approach

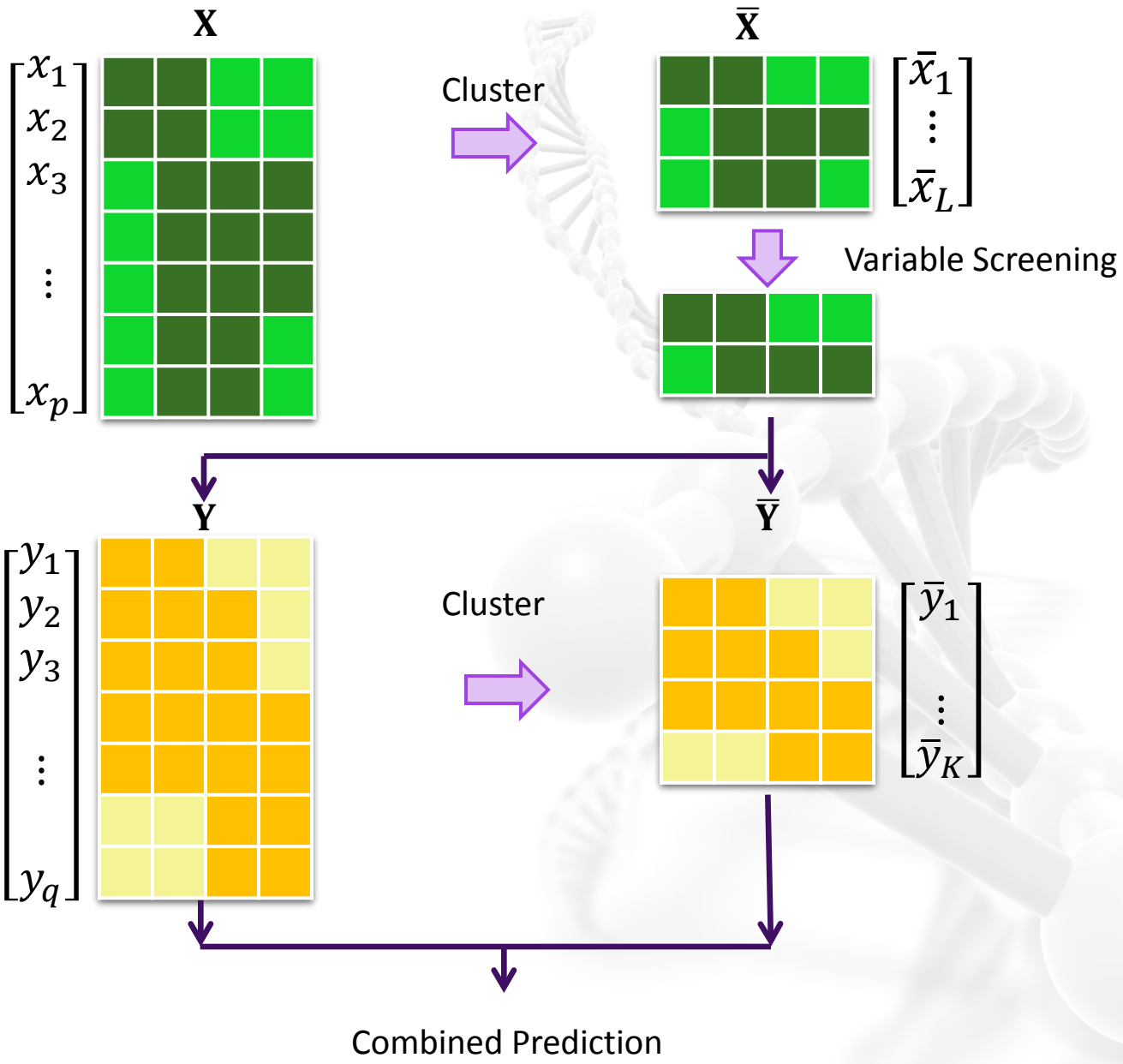


Neighboring Gene Approach



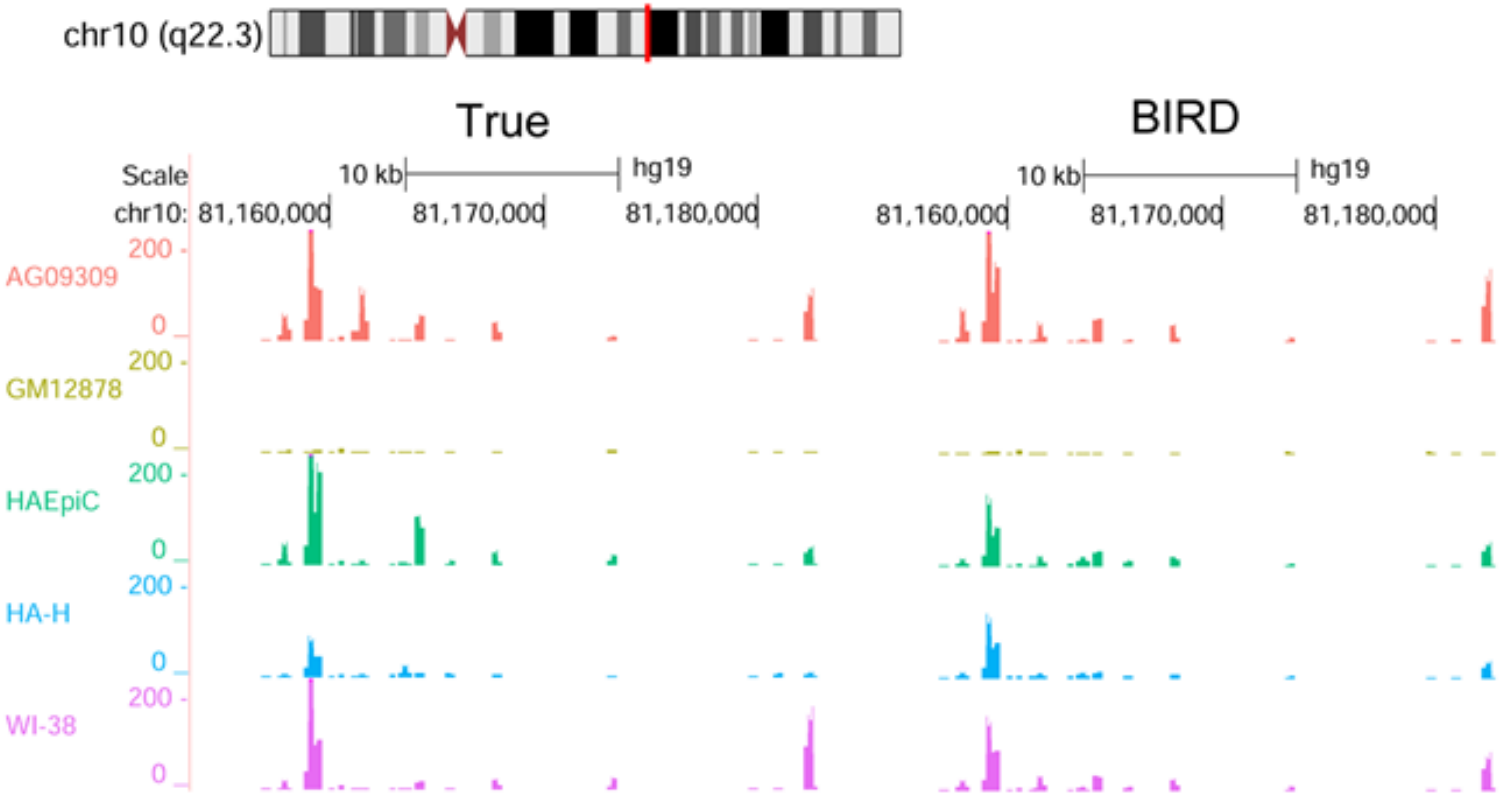
Problem: not all information is contained in the neighbors.

BIRD: Big Data Regression for Predicting DNase I Hypersensitivity



Evaluation Based on ENCODE Data

- 57 distinct human cell lines with DNase-seq and exon array
- 40 cell types as training dataset
- 17 cell types as test dataset

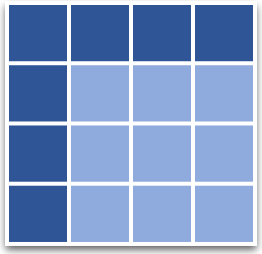


DHS Prediction Performance

Truth (Y)

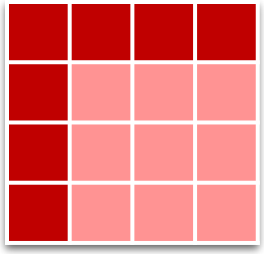
Cell type

Locus

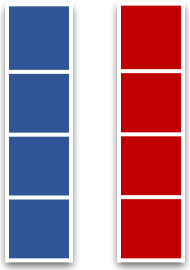


vs

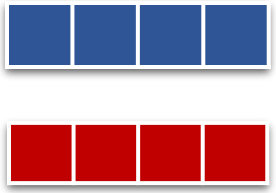
Prediction ($\hat{Y}$)



(1) Cross-Locus Correlation

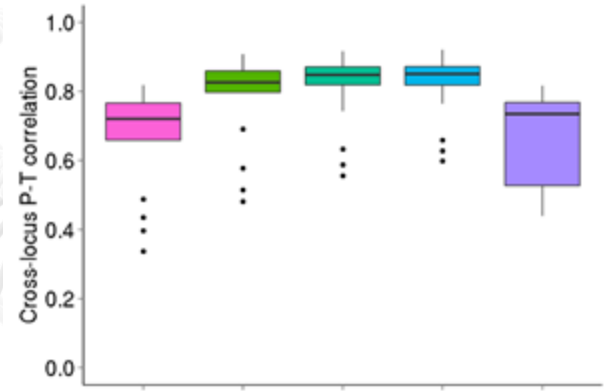


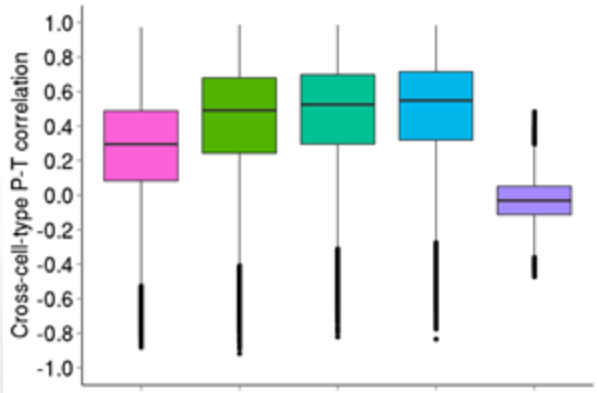
(2) Cross-Cell-Type Correlation

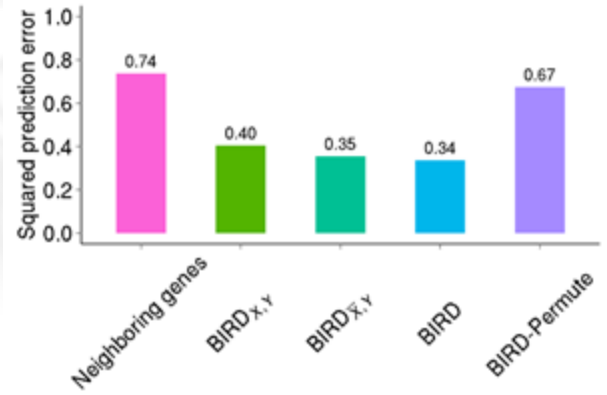


(3) Squared Pred. Err.

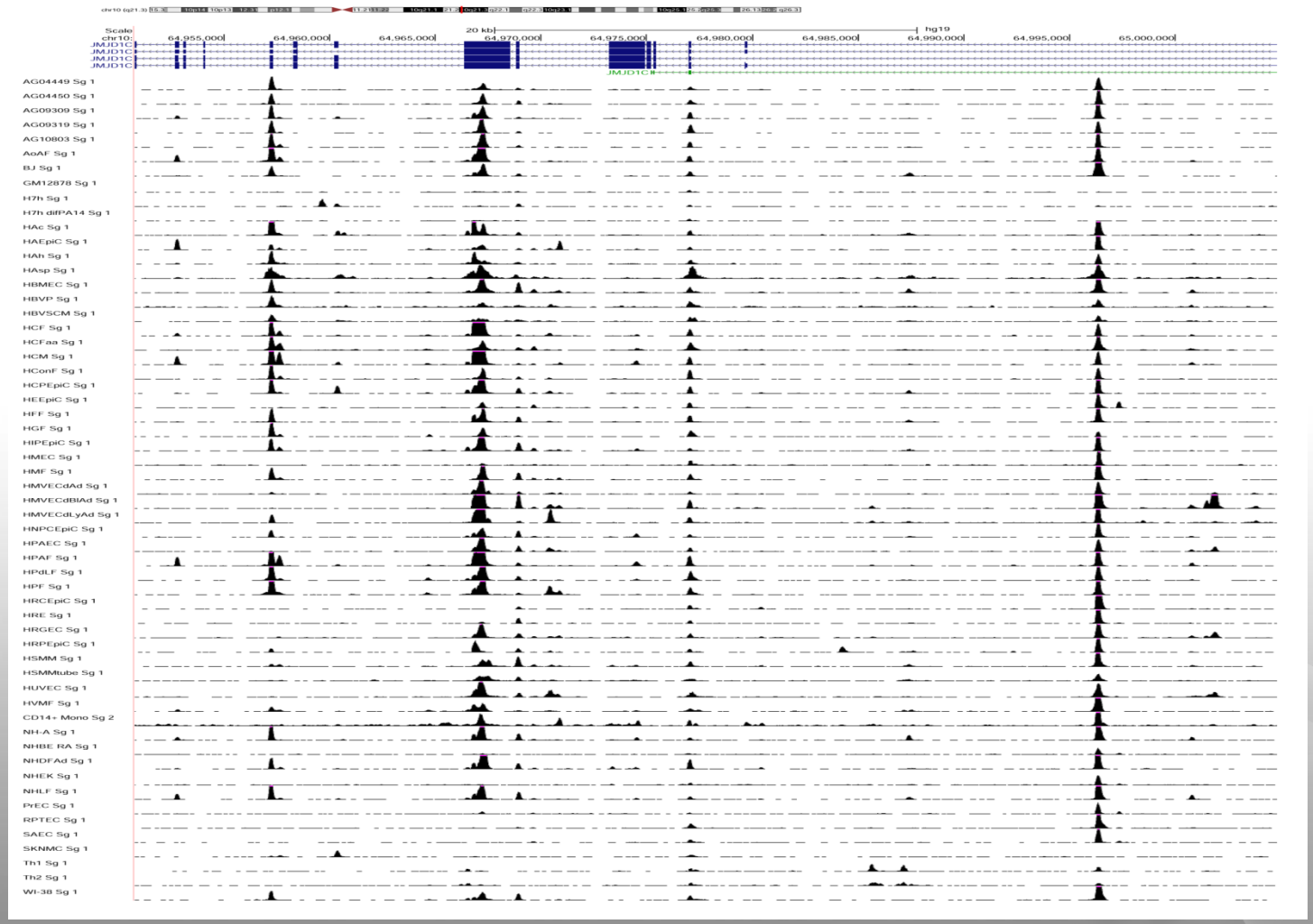
$$\tau = \frac{\sum_l \sum_m (y_{lm} - \hat{y}_{lm})^2}{\sum_l \sum_m (y_{lm} - \bar{y})^2}$$



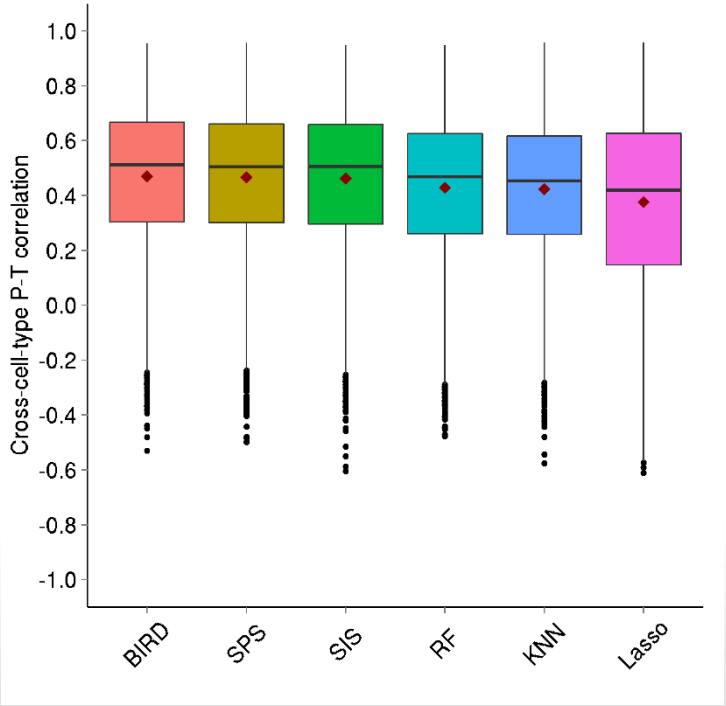


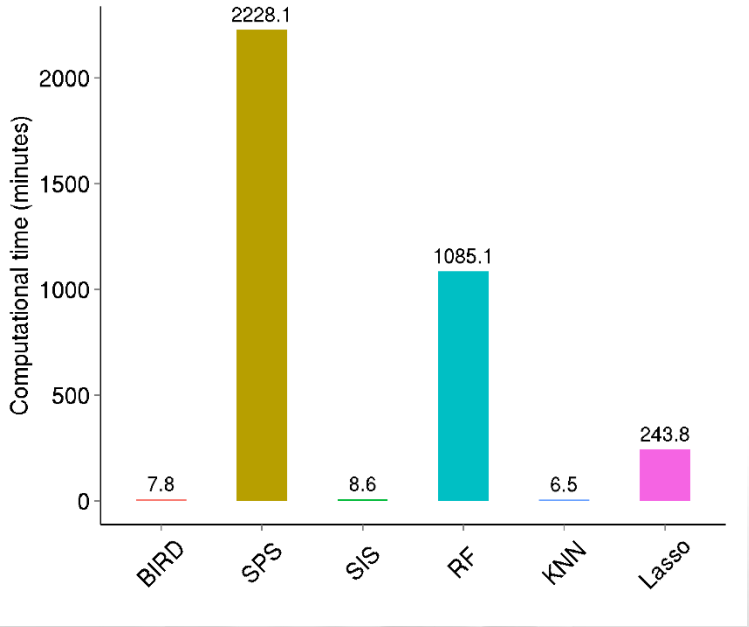


Locus Effects



BIRD vs. alternative methods

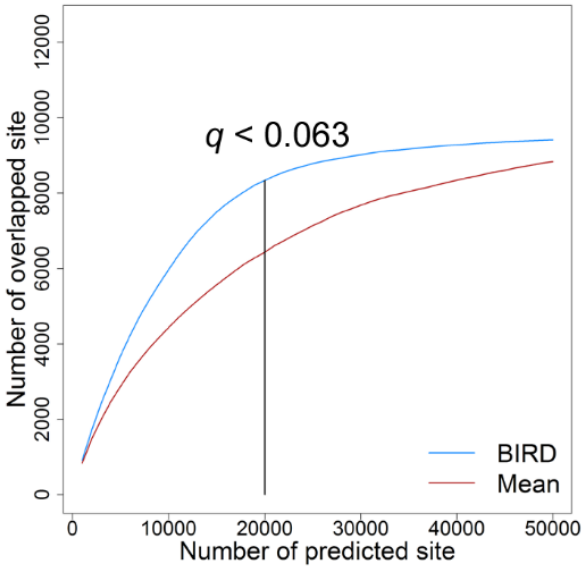


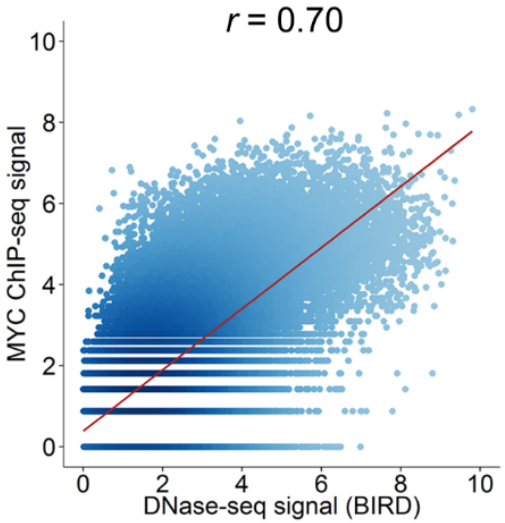


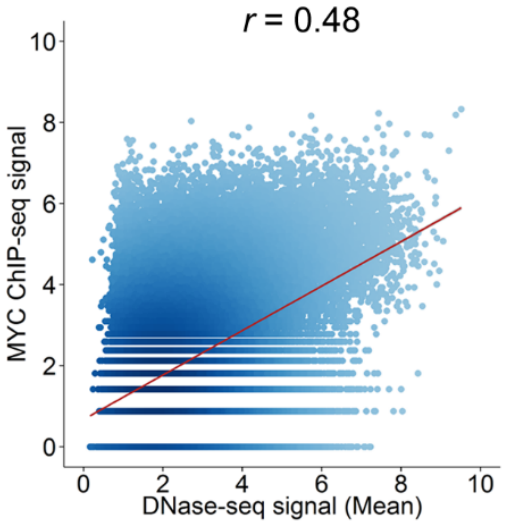
Method	BIRD	SPS	SIS	RF	KNN	Lasso
Mean r_c	0.4703	0.4667	0.4625	0.4289	0.4241	0.3757
Runtime (minute)	7.8	2228.1	8.6	1085.1	6.5	243.8

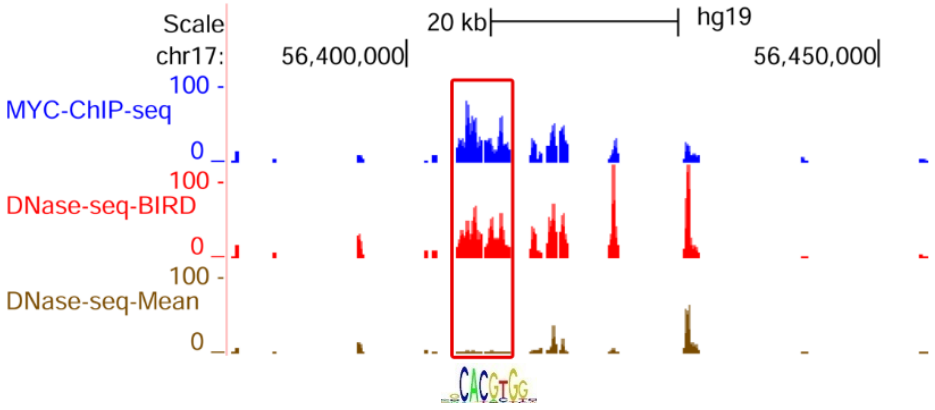
Transcription Factor Binding Site Prediction

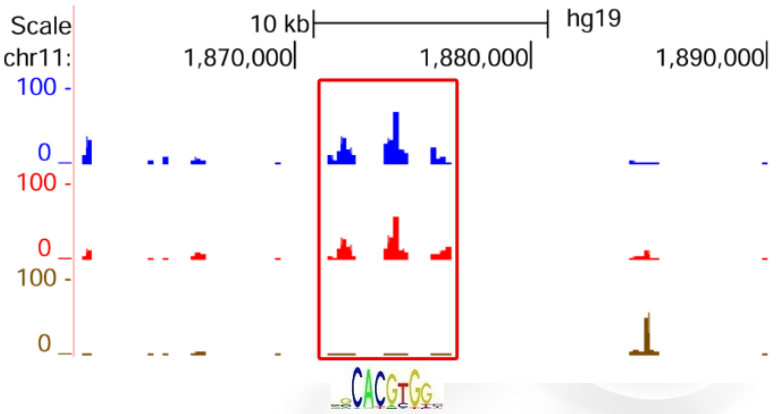
MYC binding in P493-6 B-cell lymphoma





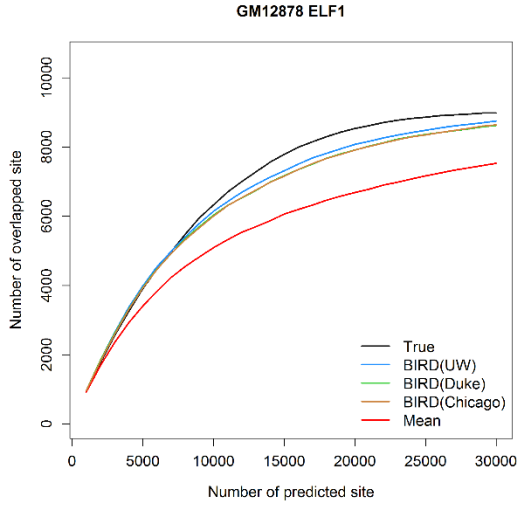


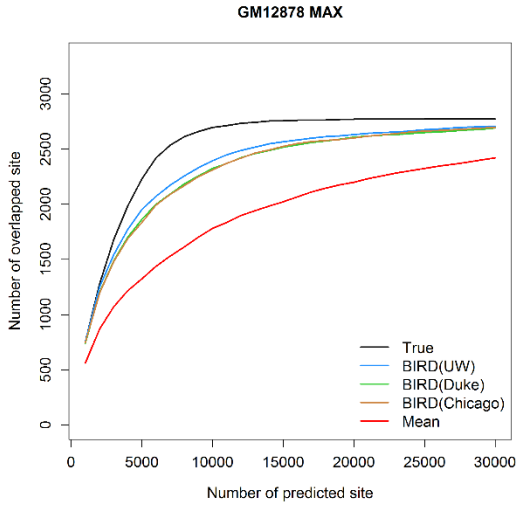


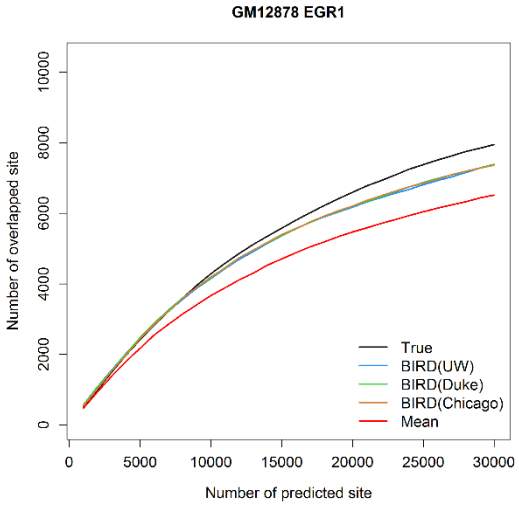


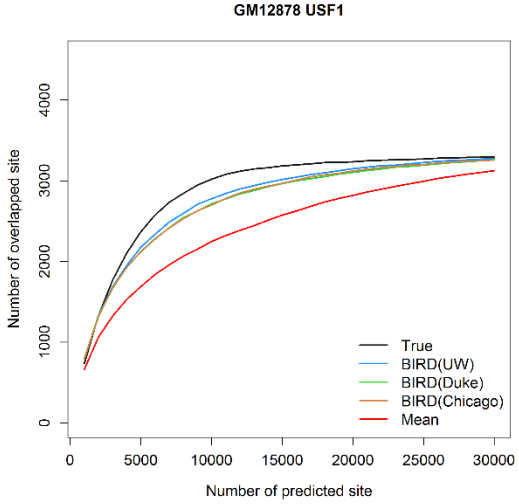
Transcription Factor Binding Site Prediction

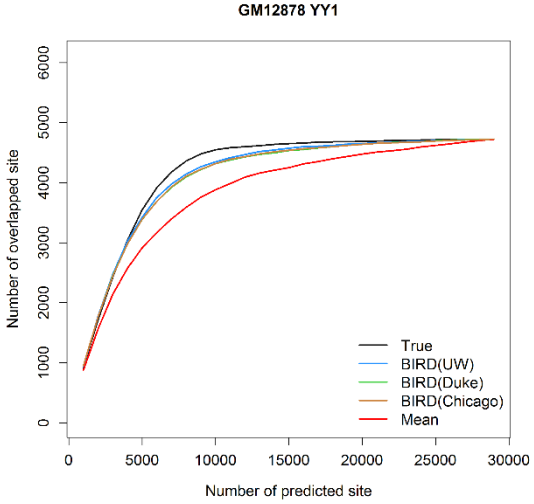
GM12878

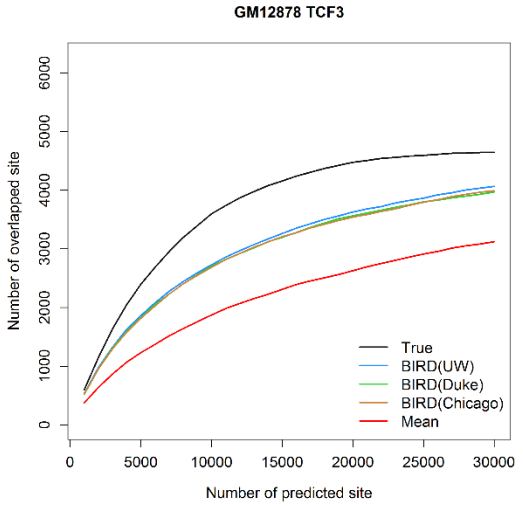






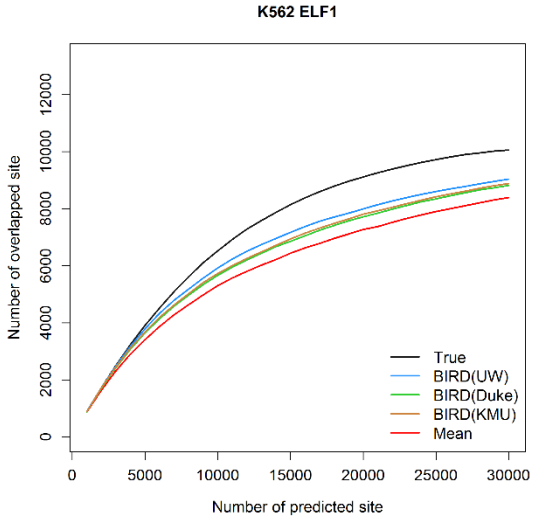


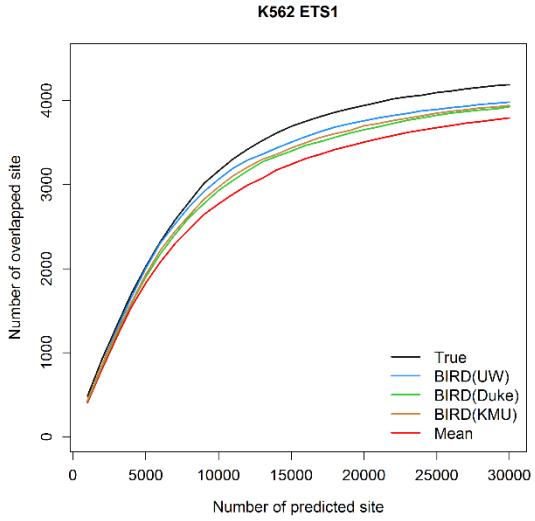


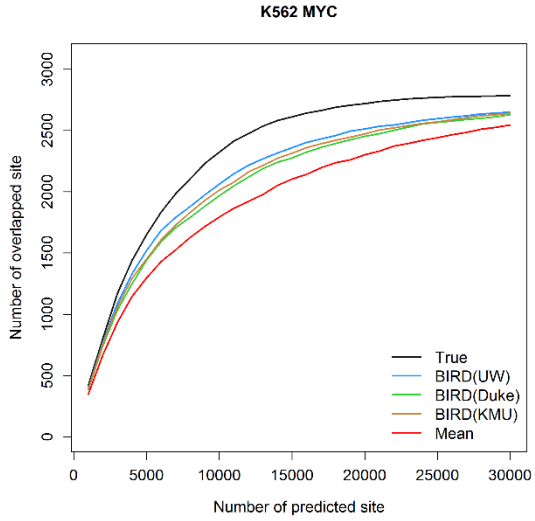


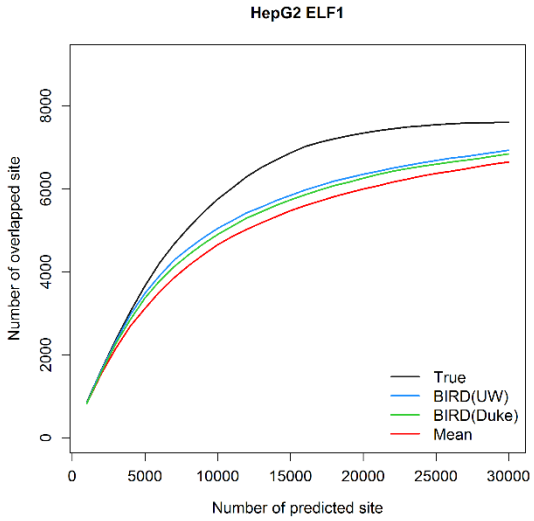
Transcription Factor Binding Site Prediction

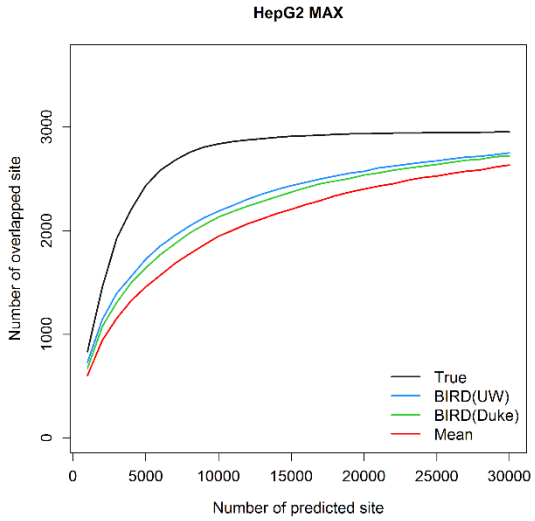
K562 and HepG2

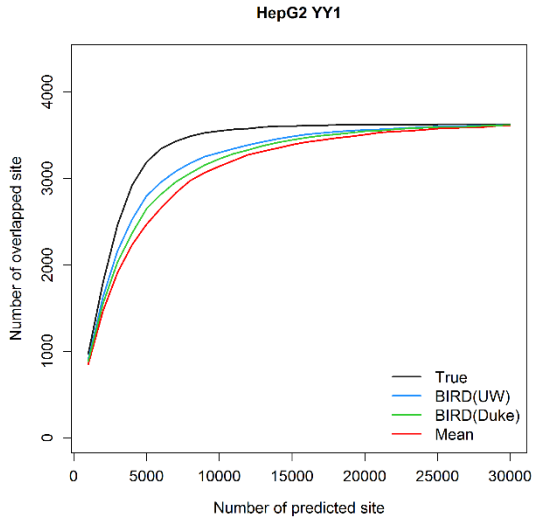












Global Prediction of DHS Using GEO

- **Apply BIRD to 2000 exon array samples in GEO**
- **Web database resource**

Upload tab delimited BED file (chr start_base_par end_base_pair):

Choose File | No file chosen

File was not uploaded. Check if it is formatted correctly

Or use textfield

Example:

chr1 10000 20000

chr2 20000 50000

… … …

Use tab to separate chromosome, start base pair and end base pair

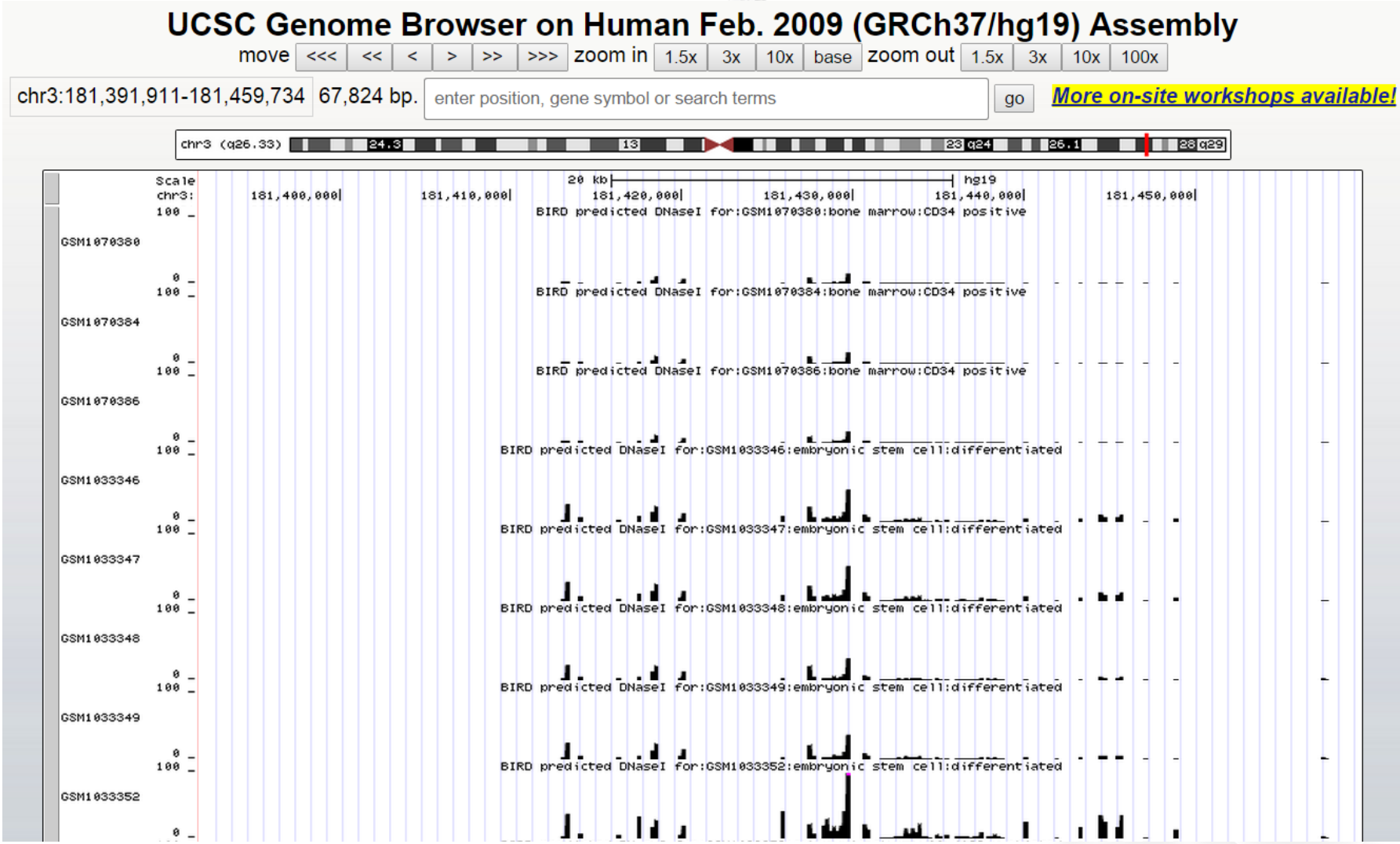
Search | Download DNase-Seq | Create Heat Map | Differential Analysis | Download Annotation D

Visualization of Predicted DNase-Seq data in UCSC Browser

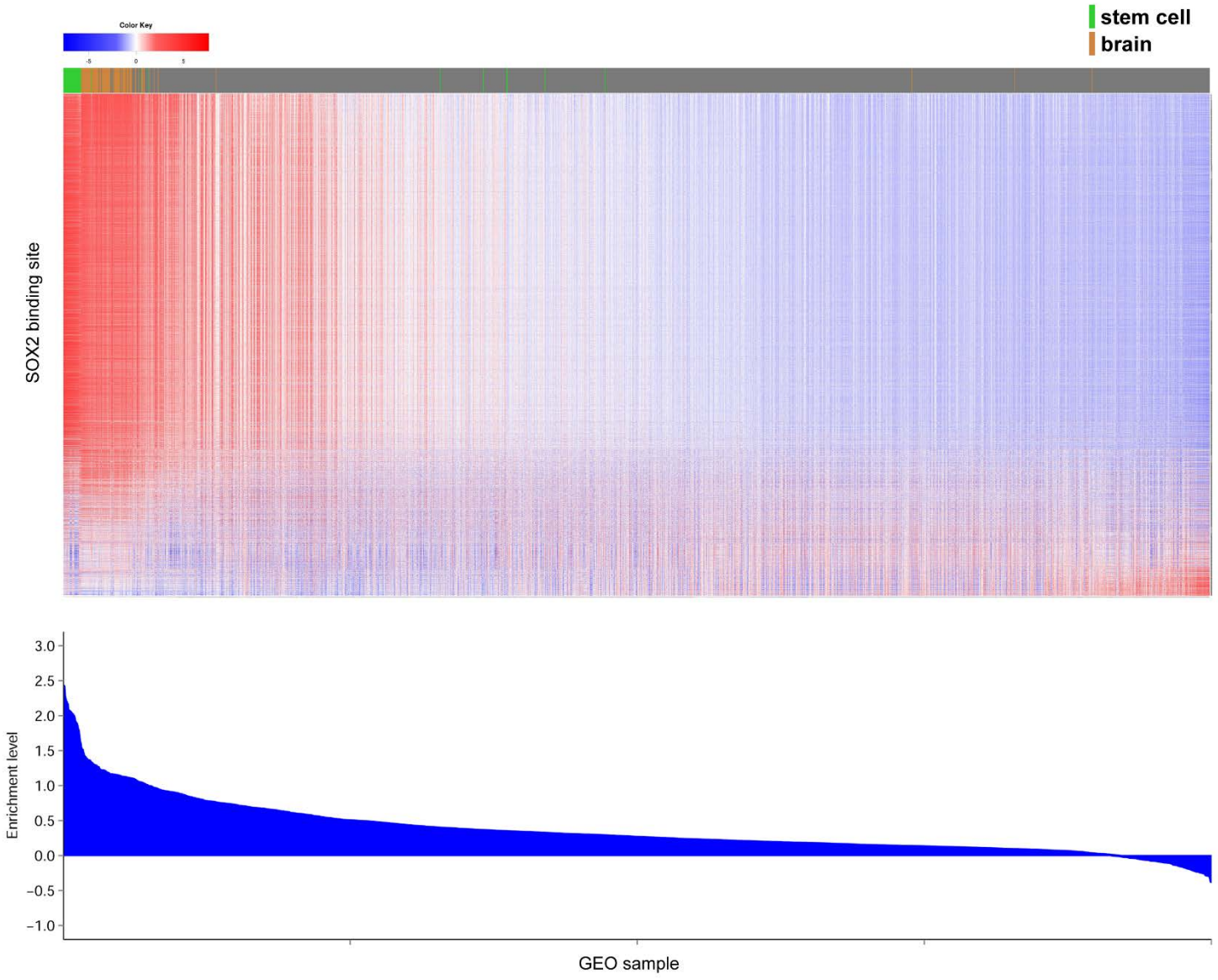
GSE:	GSM:	Cell Type:	Cell Status:	Sex:	Other:	Chromosome:
all ×	all ×	stem cell ×	all ×	all ×	all ×	all ×
GSE19090	GSM1033346	embryonic stem cell	differentiated	NA	cell line: H7-hESC; diffProtA_5d	
GSE19090	GSM1033347	embryonic stem cell	differentiated	NA	cell line: H7-hESC; diffProtA_5d	
GSE19090	GSM1033348	embryonic stem cell	differentiated	NA	cell line: H7-hESC; diffProtA_9d	
GSE19090	GSM1033349	embryonic stem cell	differentiated	NA	cell line: H7-hESC; diffProtA_9d	
GSE19090	GSM1033350	embryonic stem cell	differentiated	NA	cell line: H7-hESC; diffProtA_14d	
GSE19090	GSM1033351	embryonic stem cell	differentiated	NA	cell line: H7-hESC; diffProtA_14d	

Global Prediction of DHS Using GEO

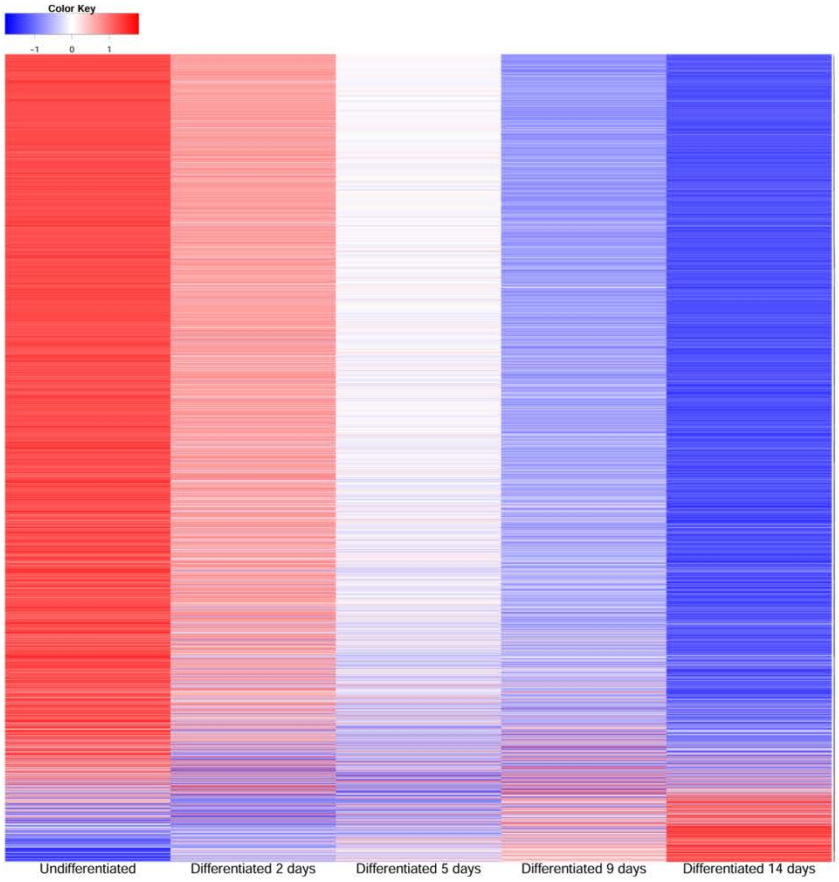
Visualization in UCSC genome browser

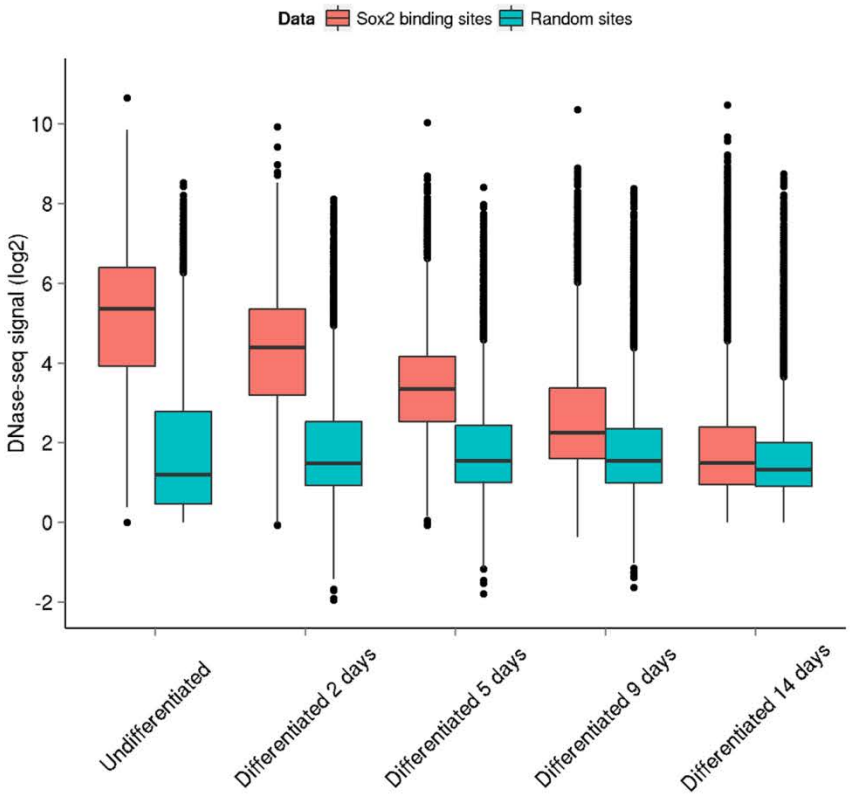


Example: SOX2 Binding Dynamics



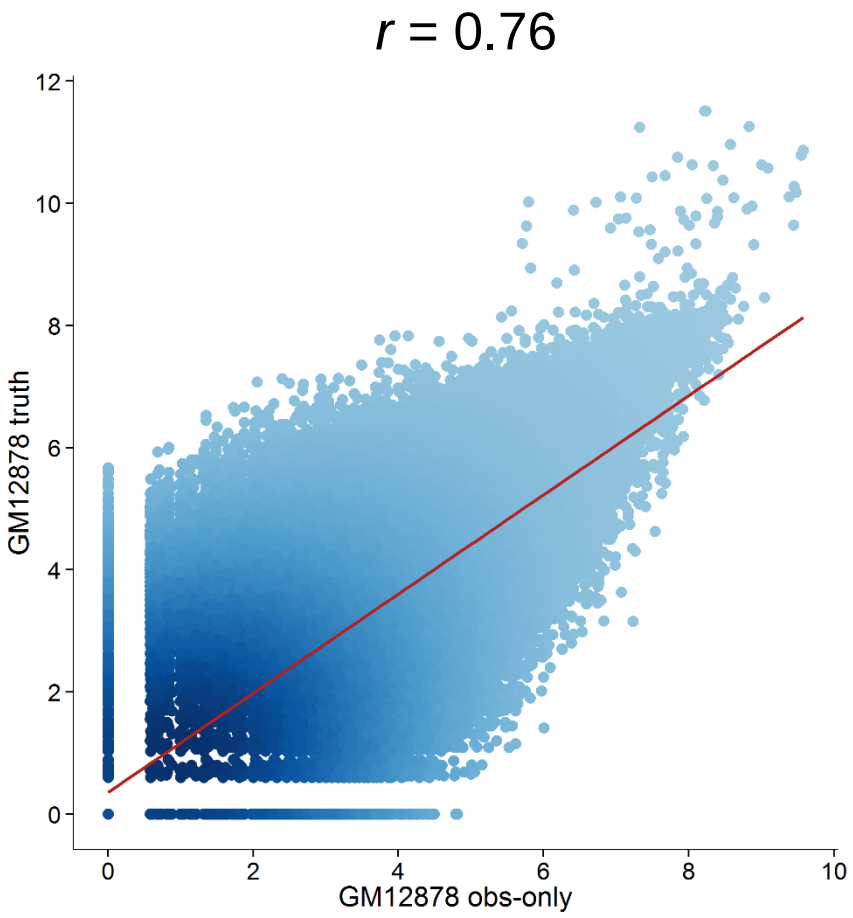
Dynamic SOX2 activity during stem cell differentiation

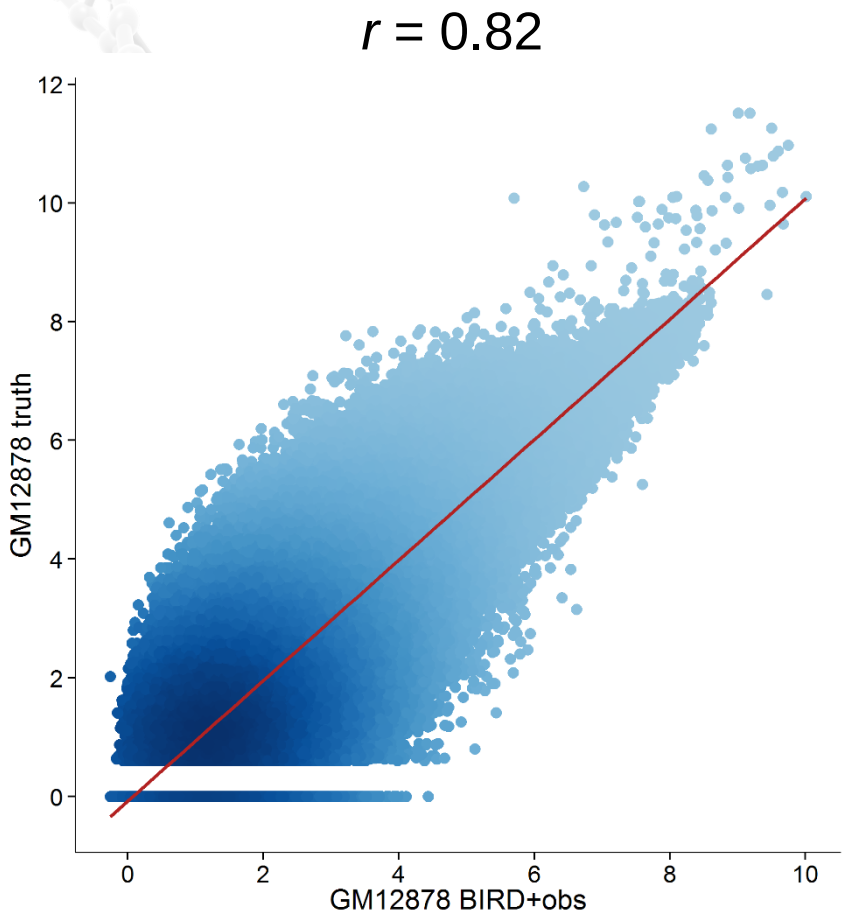




Improve Data Analysis Using Predicted DHS

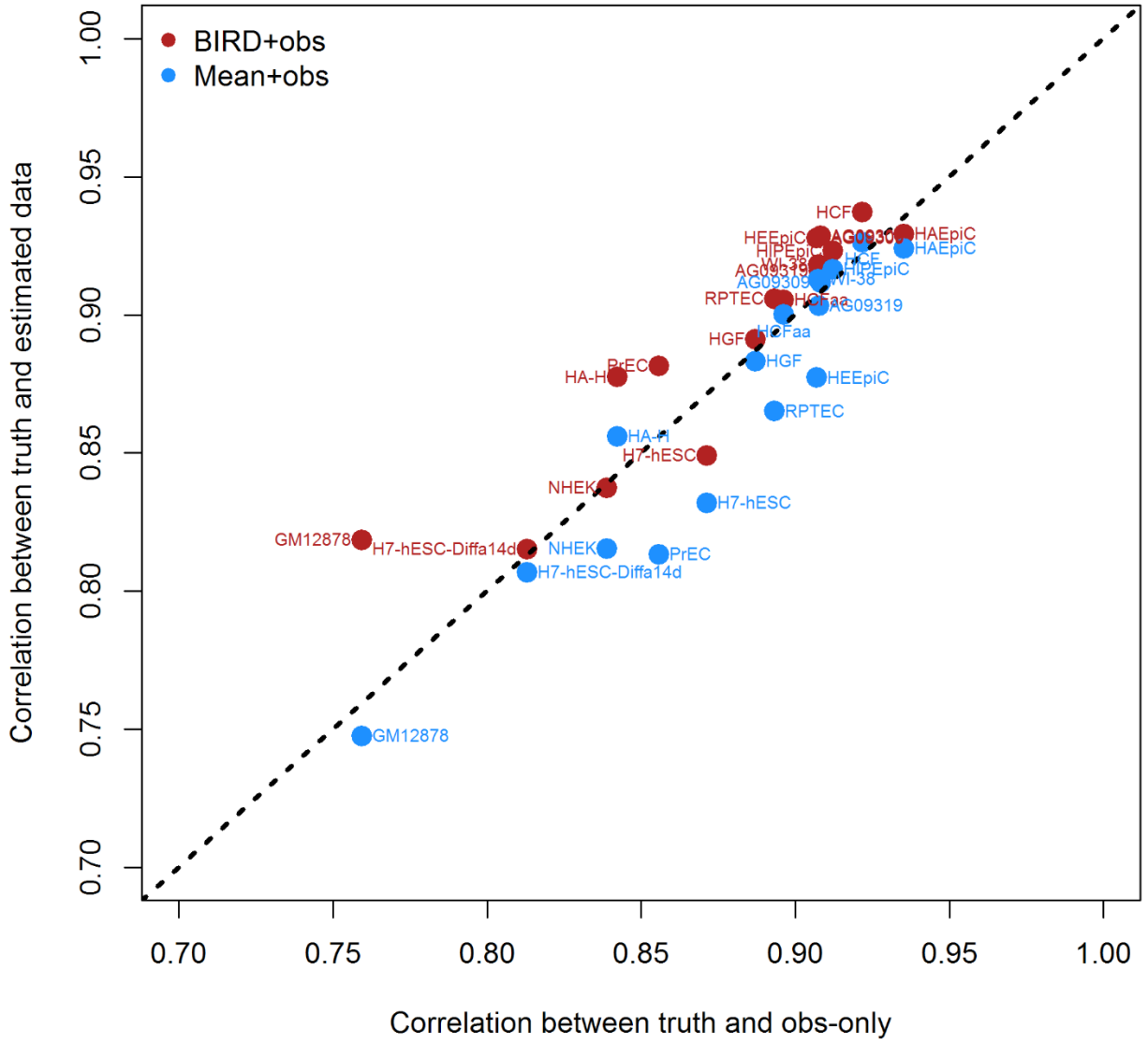
GM12878 DNase-seq





Improve Data Analysis Using Predicted DHS

16 test cells

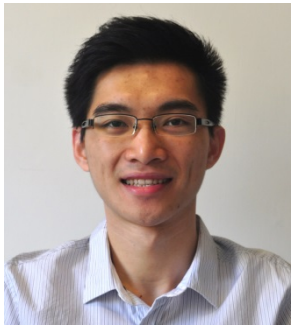


Summary

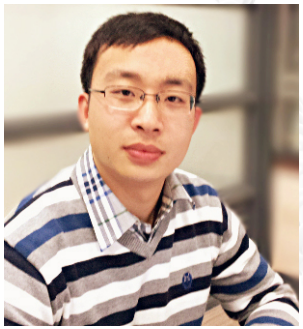
- Public data is a powerful tool to make discoveries
- BIRD: big data regression and prediction
- Regulatory element activities may be predicted using gene expression
- Prediction provides a new way to integrate two different data types

Acknowledgments

Group Members


Weiqiang Zhou


Ben Sherwood

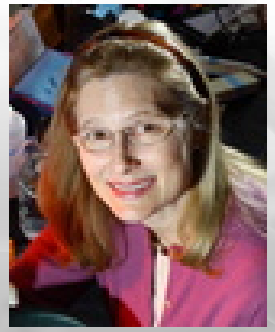

Zhicheng Ji


Fang Du


Jiawei Bai

Dawson Lab


Ted Dawson


Valina Dawson

Funding

IDIES Seed Fund
NIH R01HG006841, R01HG006282
Maryland Stem Cell Research Fund 2012-MSCRFE-0135-00