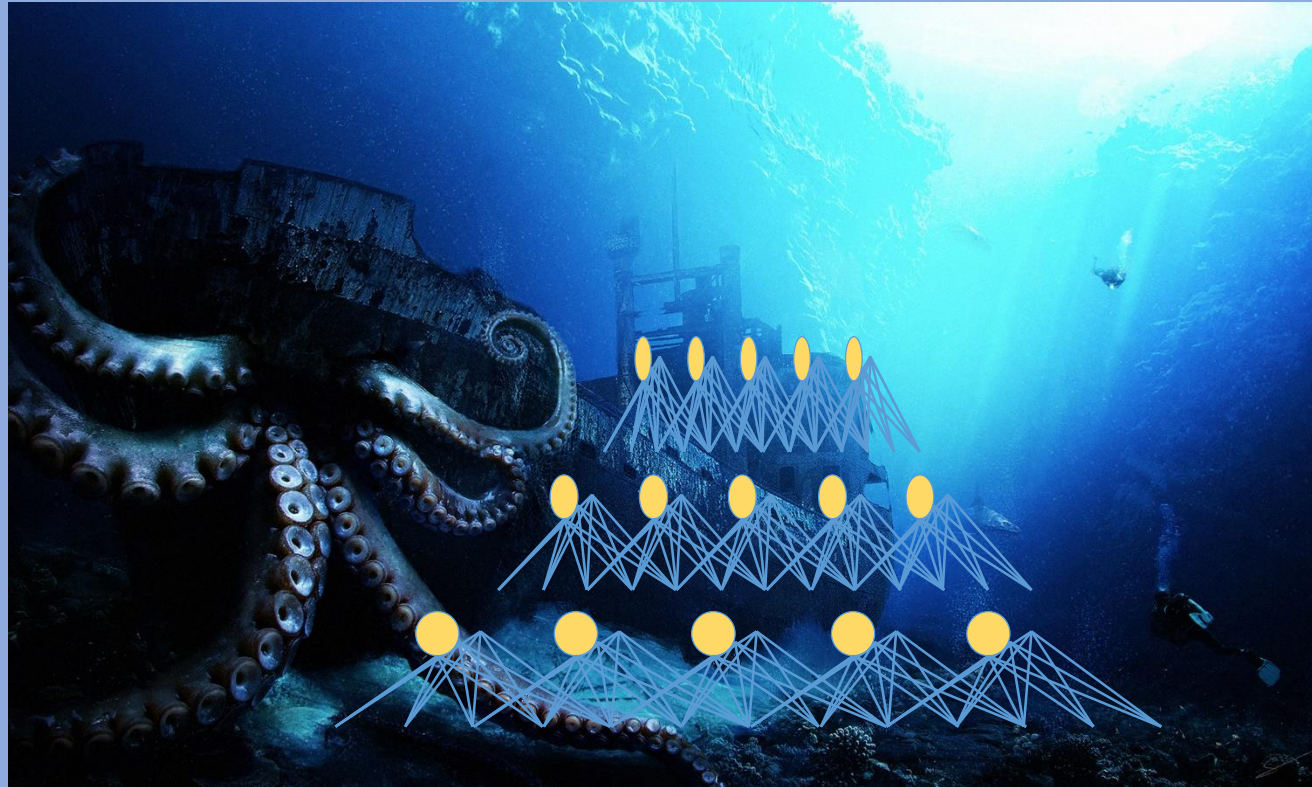


DeepSEA – Zhou & Troyanskaya

predicting the effects of non coding variants on chromatin and regulation

CS231B journal club



Arbel Harpak & Ziyue Gao

DeepSEA – Zhou & Troyanskaya

predicting the effects of non coding variants on chromatin
and regulation

Single noncoding SNP



Regulatory effect

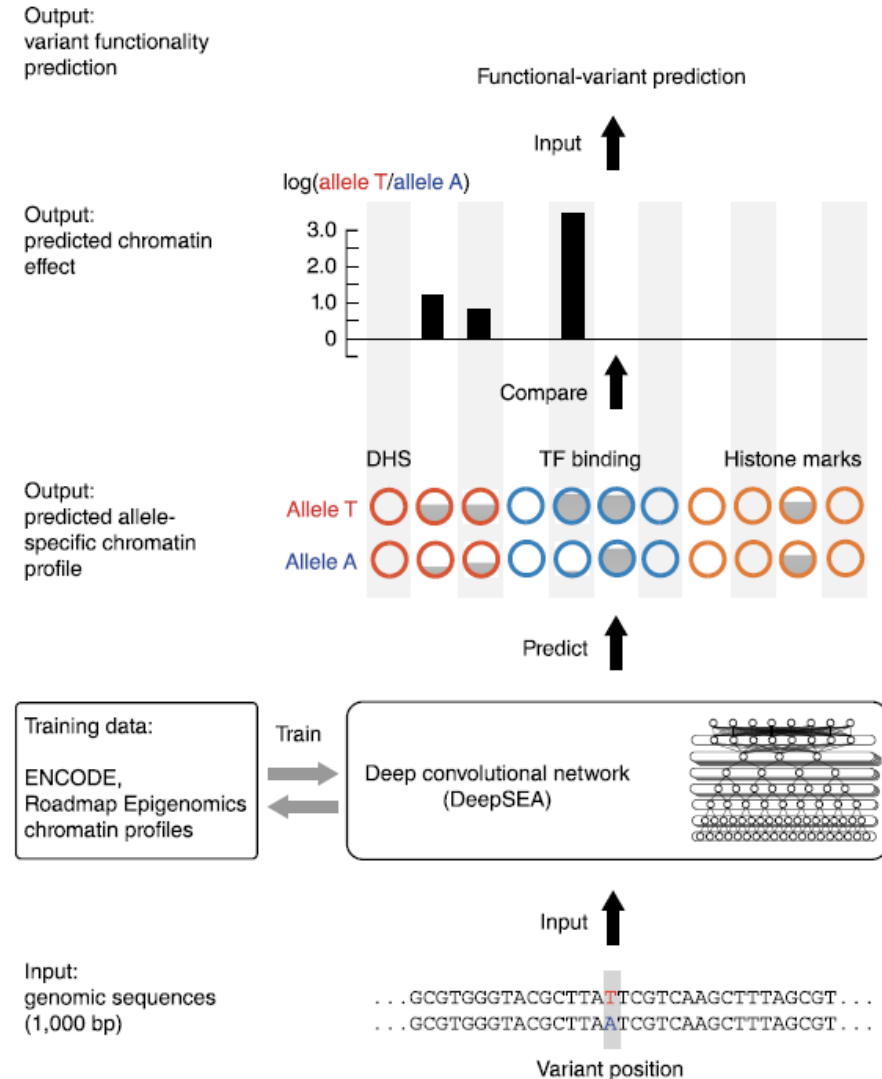


Function

Setup: multitask prediction of regulatory effects

First wave of genomics CNN papers,
Introducing:

- Integrating sequence from wide context
- Learn at multiple spatial scale with hierarchical architecture
- Joint learning of diverse chromatin factors sharing predictive features (690 TF profiles, 125 DHS, 104 histone mark)

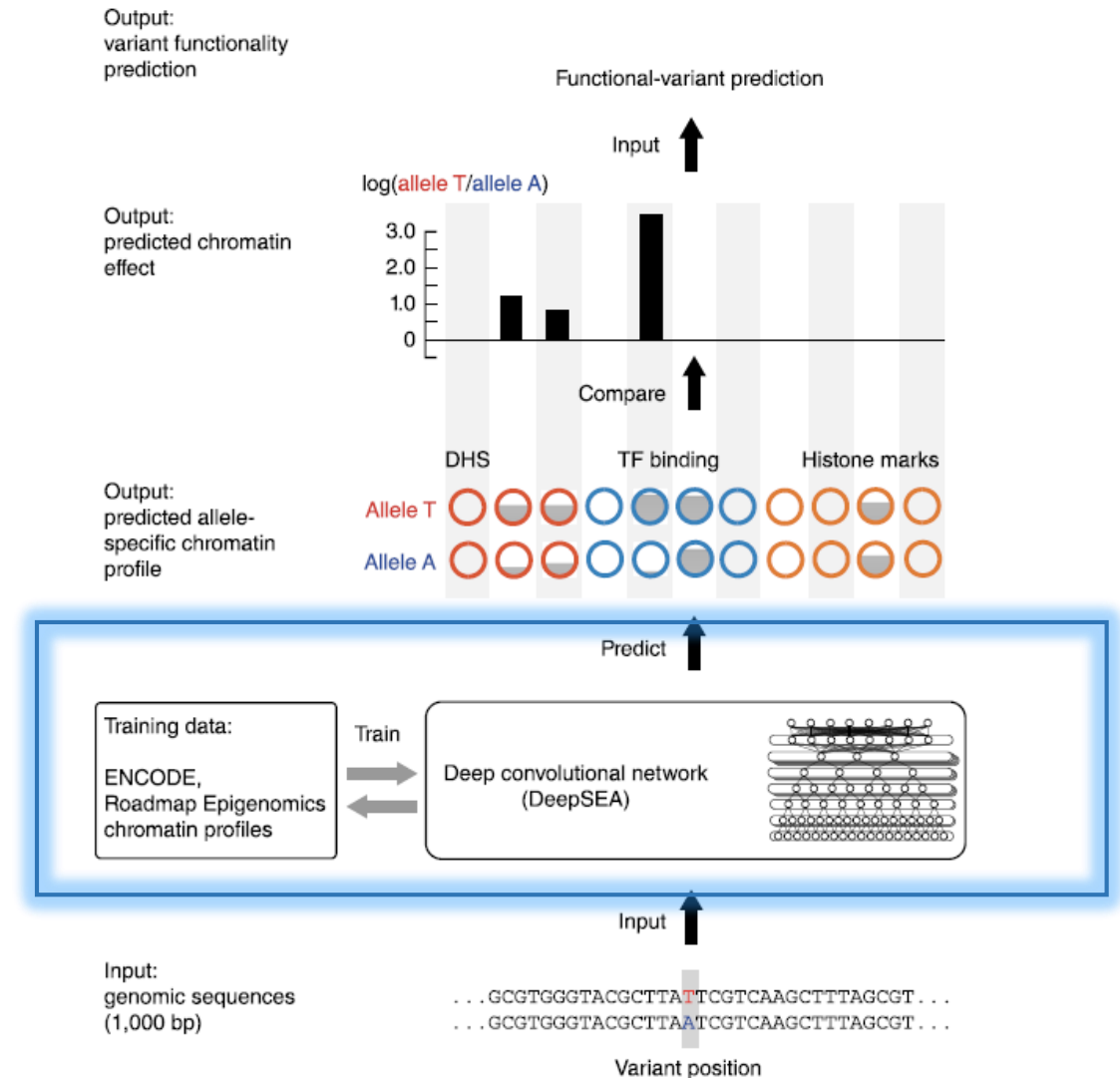


Part of first wave of CNN for genomics

Introducing:

- Integration of sequence from wide context
- Learning at multiple spatial scale with hierarchical architecture
- Joint learning of diverse chromatin factors sharing predictive features

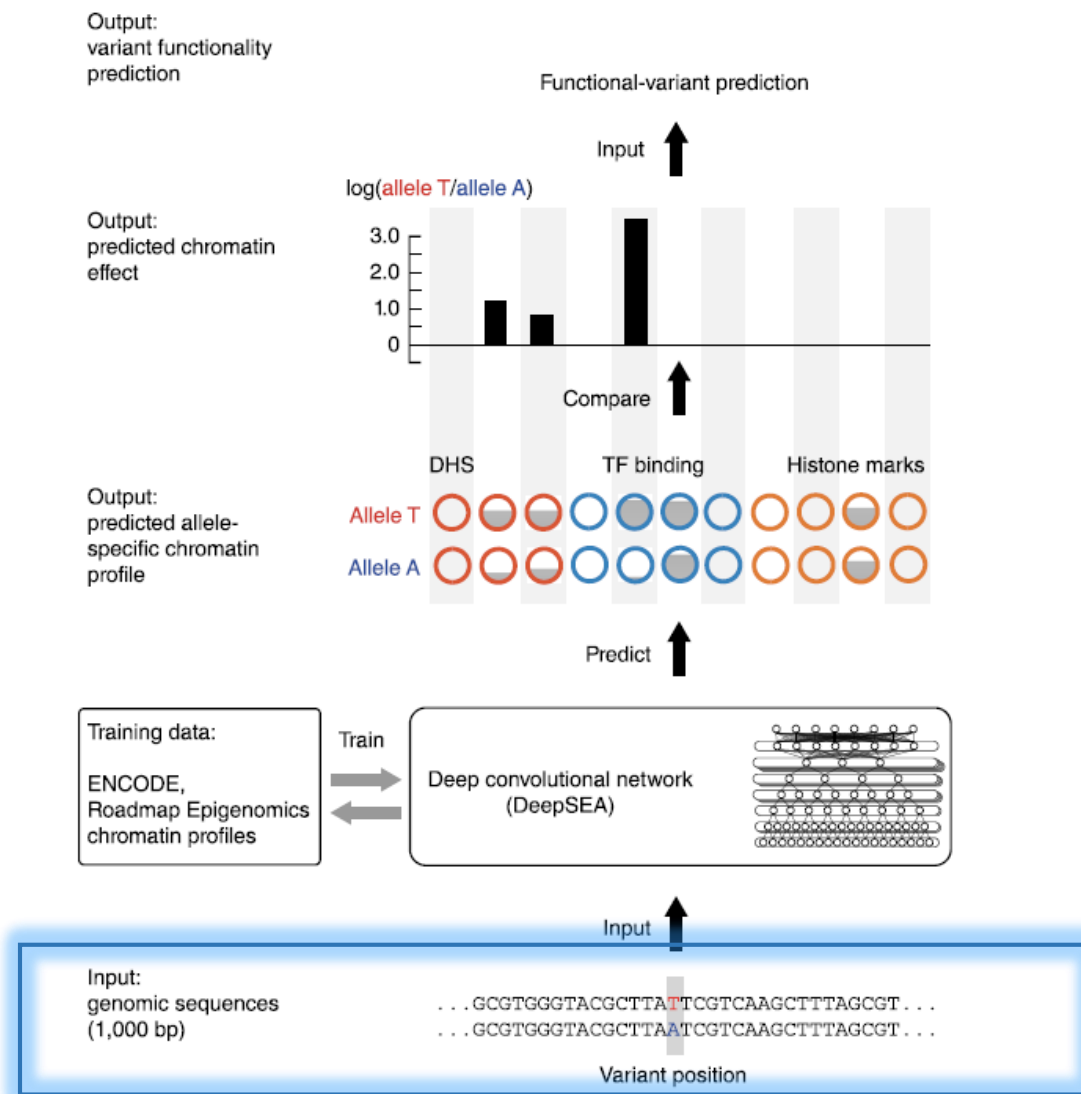
Is multitasking a good idea?



Sequence-only → factor peaks → Overall functional effect

Data:

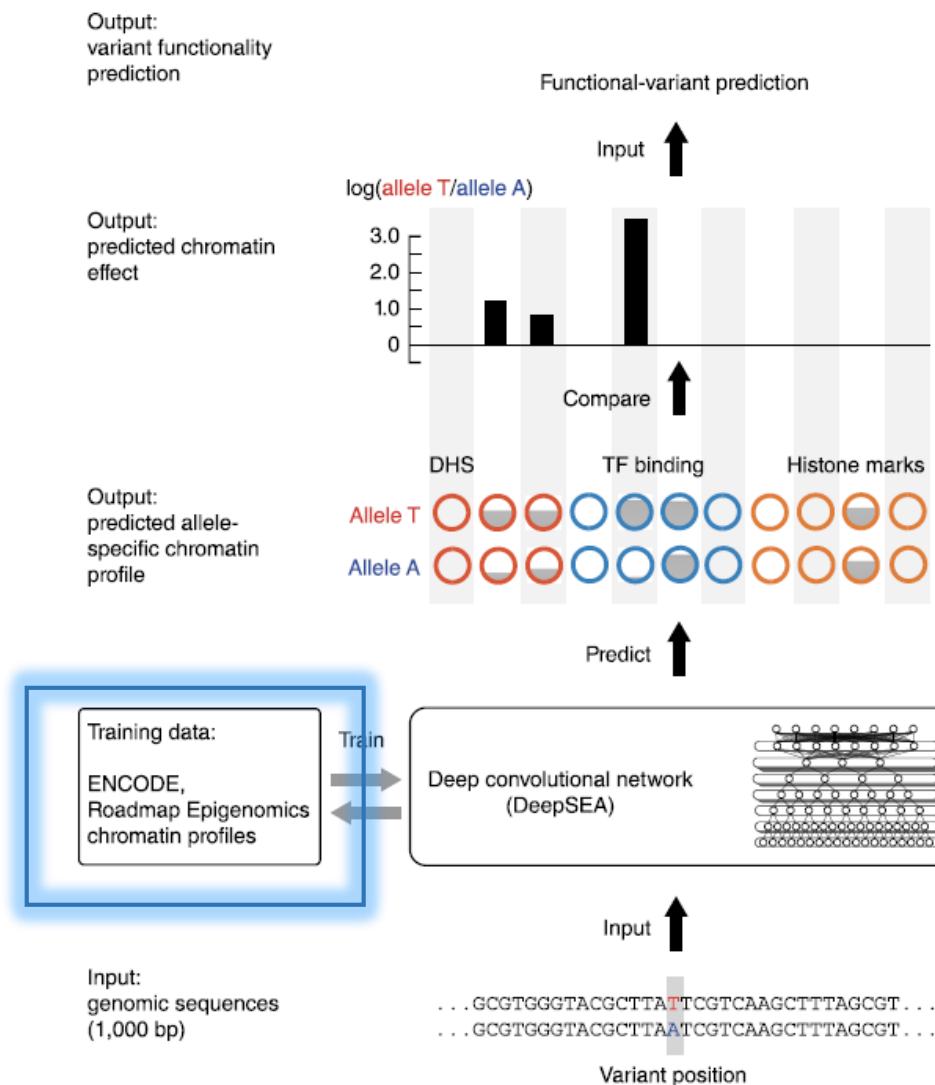
- Samples: stride of 1bp along the genome
- Input features: 1000bp one-hot, reference genome



Sequence-only → factor peaks → Overall functional effect

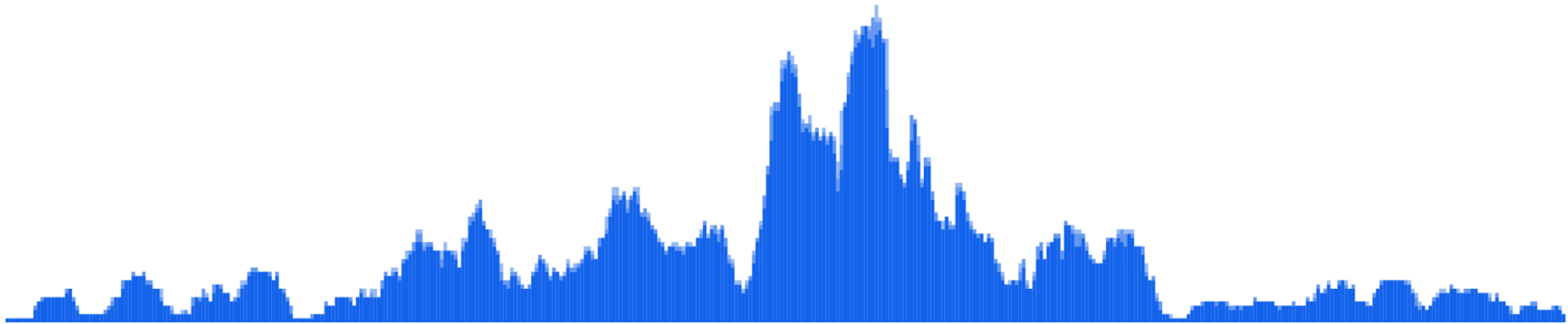
Data:

- Samples: stride of 1bp along the genome
- Input features: 1000bp one-hot, reference genome
- Response (output): 0/1 for each chromatin factor (based on previously called peaks)



Response: discretized peaks

Read density

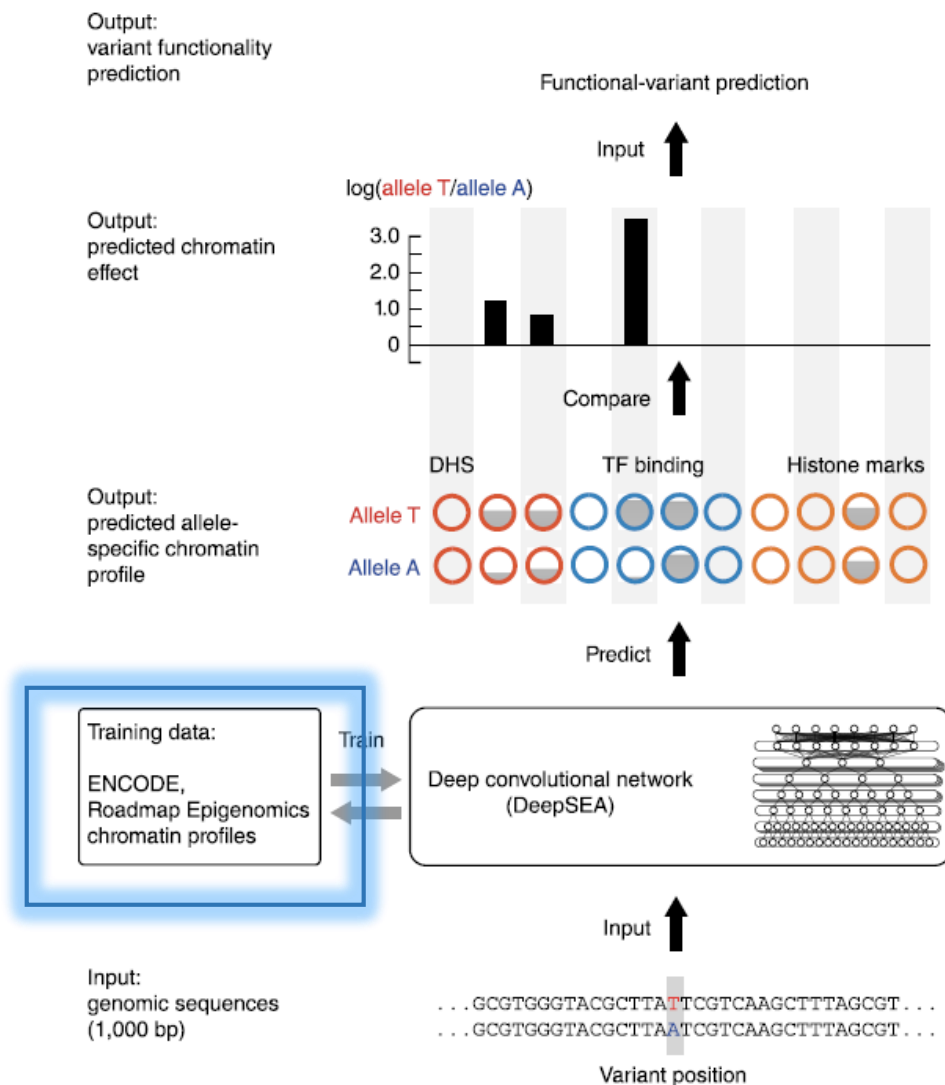


Position (bp)

Sequence-only → factor peaks → Overall functional effect

Data:

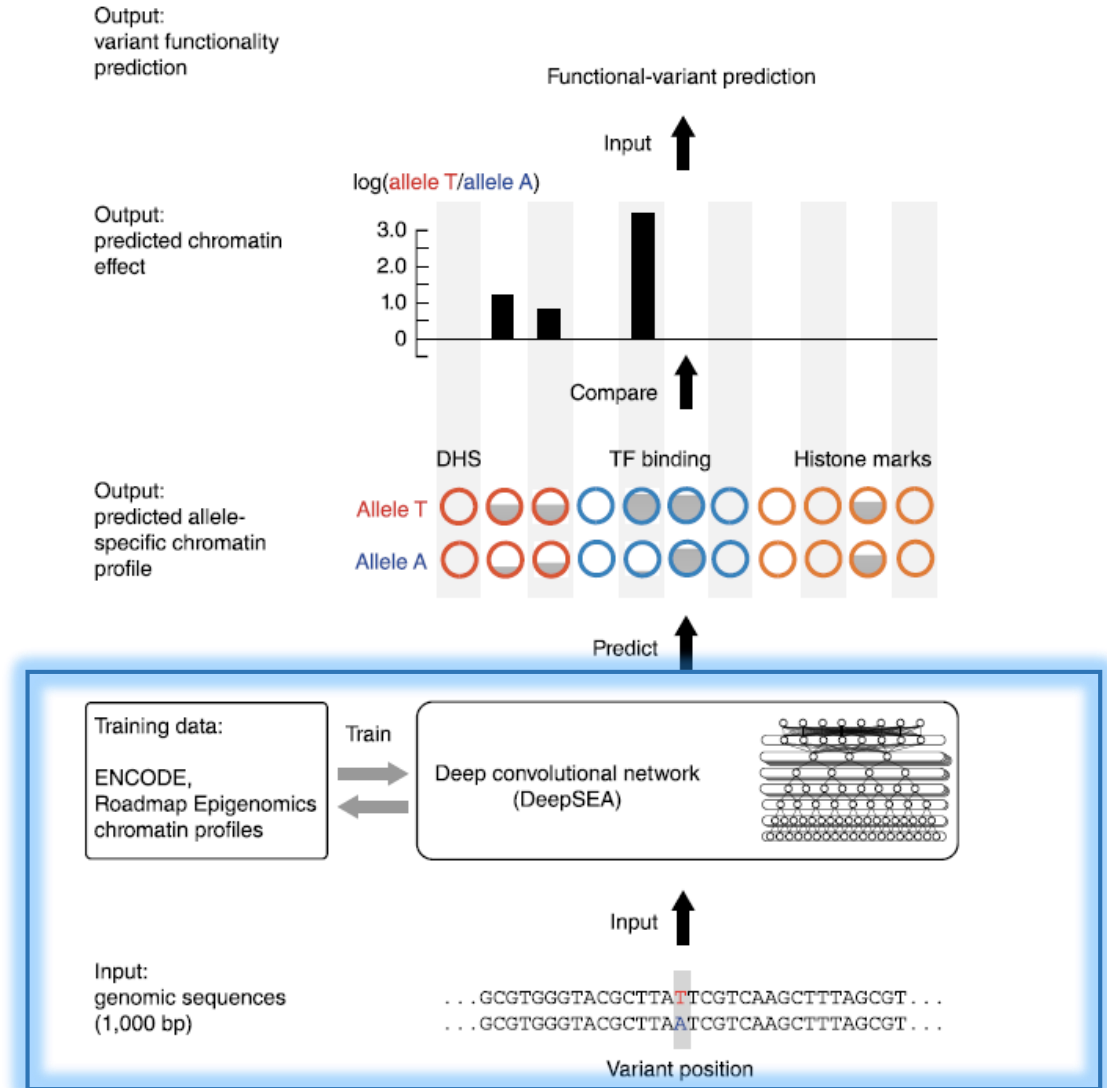
- Samples: stride of 1bp along the genome
- Input features: 1000bp one-hot, reference genome
- Response (output): 0/1 for each chromatin factor (based on previously called peaks)
- Train (only samples with >1TF), validate (only 4000 samples), test (2 chromosomes)



Architecture – your standard deep CNN

Architecture:

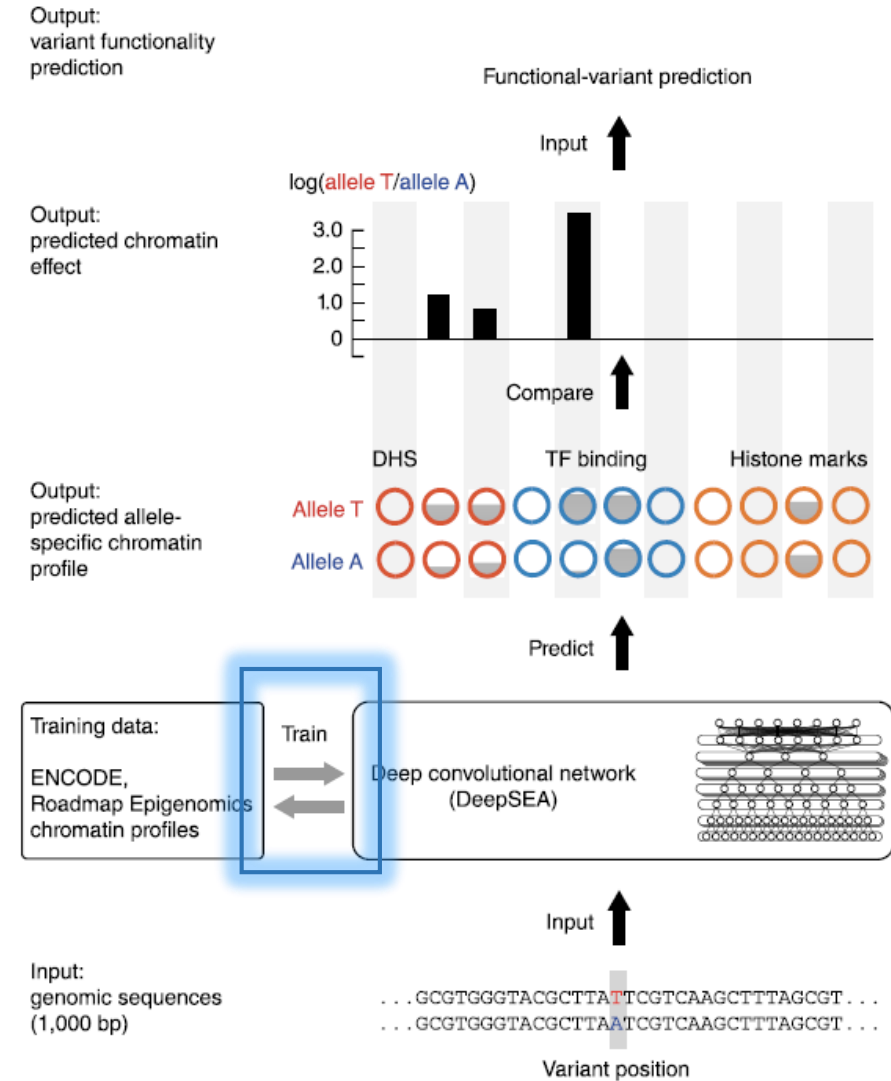
- 3 convolutional layers with ReLU activation + max pooling
- # Kernels is 240, 480, 960 respectively
- Followed by a fully-connected layer with ReLU(WX)
- Last layer (919 outputs) is logistic, represents probability of peak



Objective function: sum of Negative Log Likelihood

objective = NLL + Regularization

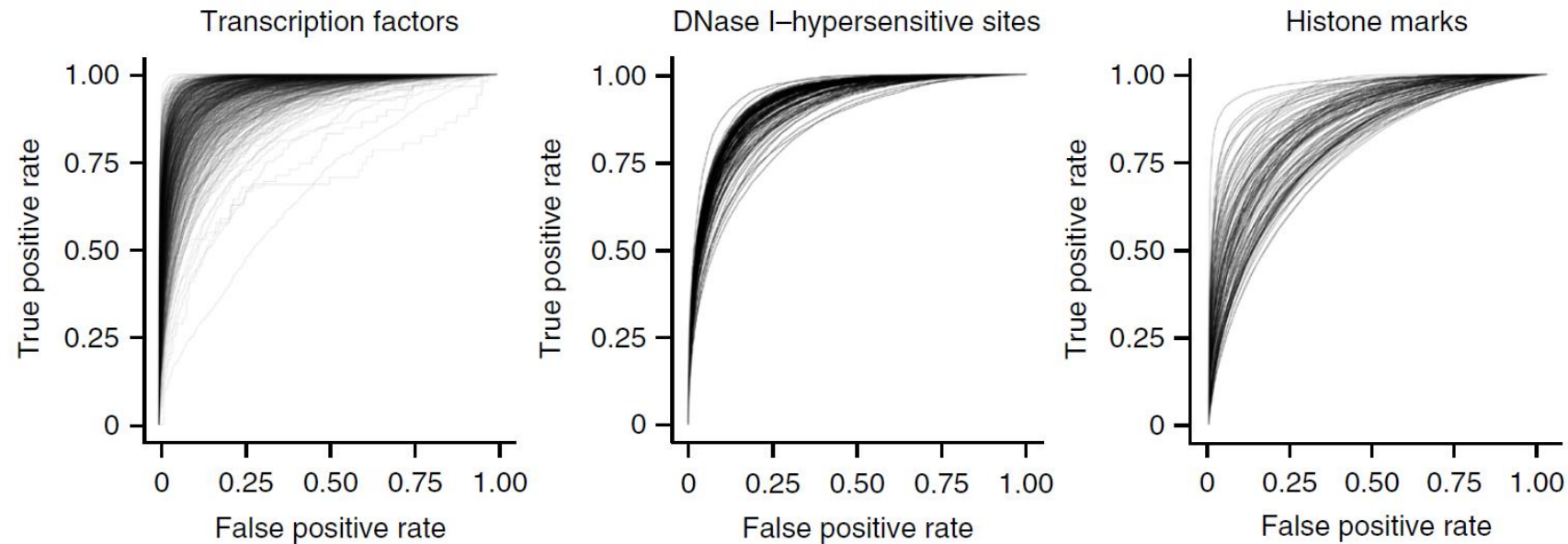
$$\text{NLL} = - \sum_s \sum_t \log(Y_t^s f_t(X^s) + (1 - Y_t^s)(1 - f_t(X^s)))$$



Objective function overweights transcription factors?

objective = NLL + Regularization

$$\text{NLL} = - \sum_s \sum_t \log(Y_t^s f_t(X^s) + (1 - Y_t^s)(1 - f_t(X^s)))$$



Regularization—I just can't get enough

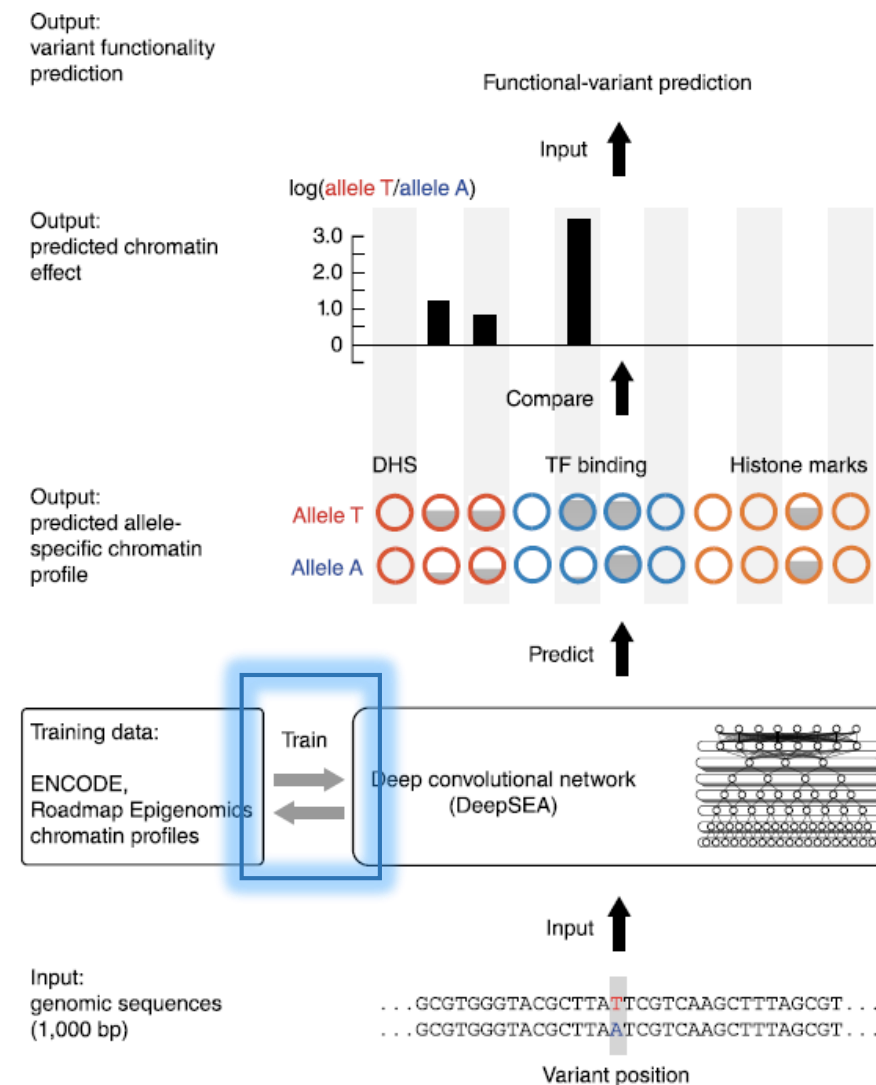
$$\text{objective} = \text{NLL} + \lambda_1 \|W\|_2^2 + \lambda_2 \|H^{-1}\|_1$$

Also:

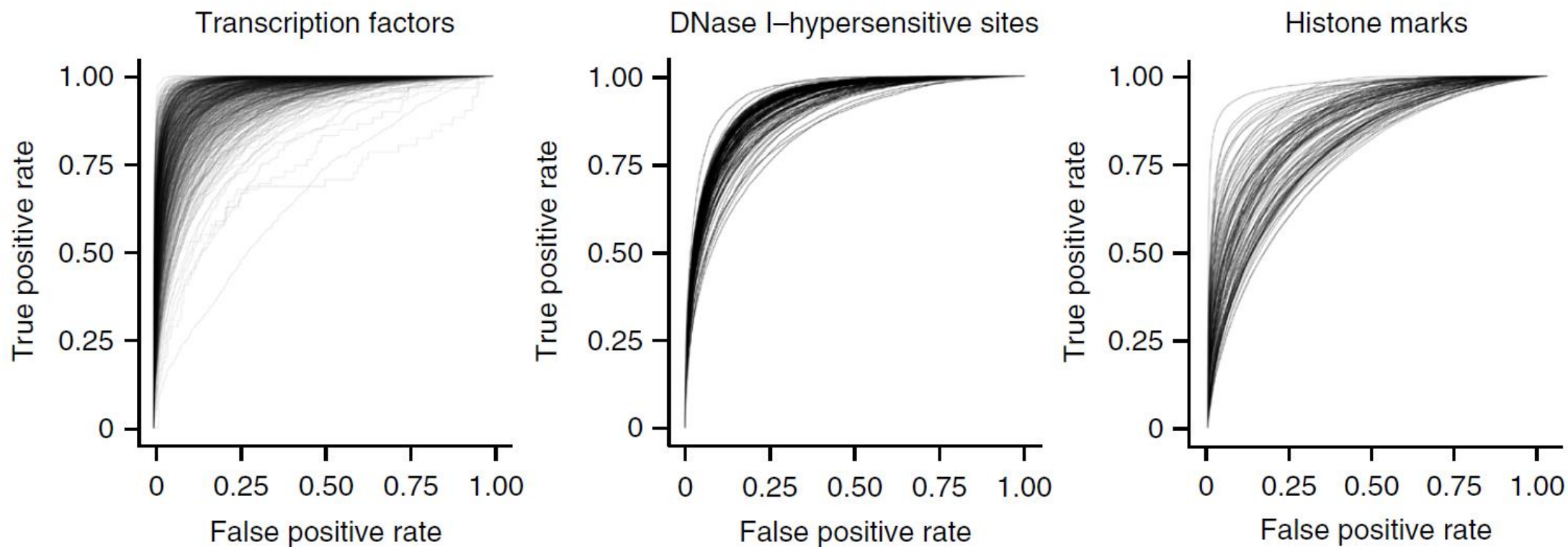
λ_3 - (shared) regularization on weight matrix for each neuron

“ λ_4 ” - dropout training

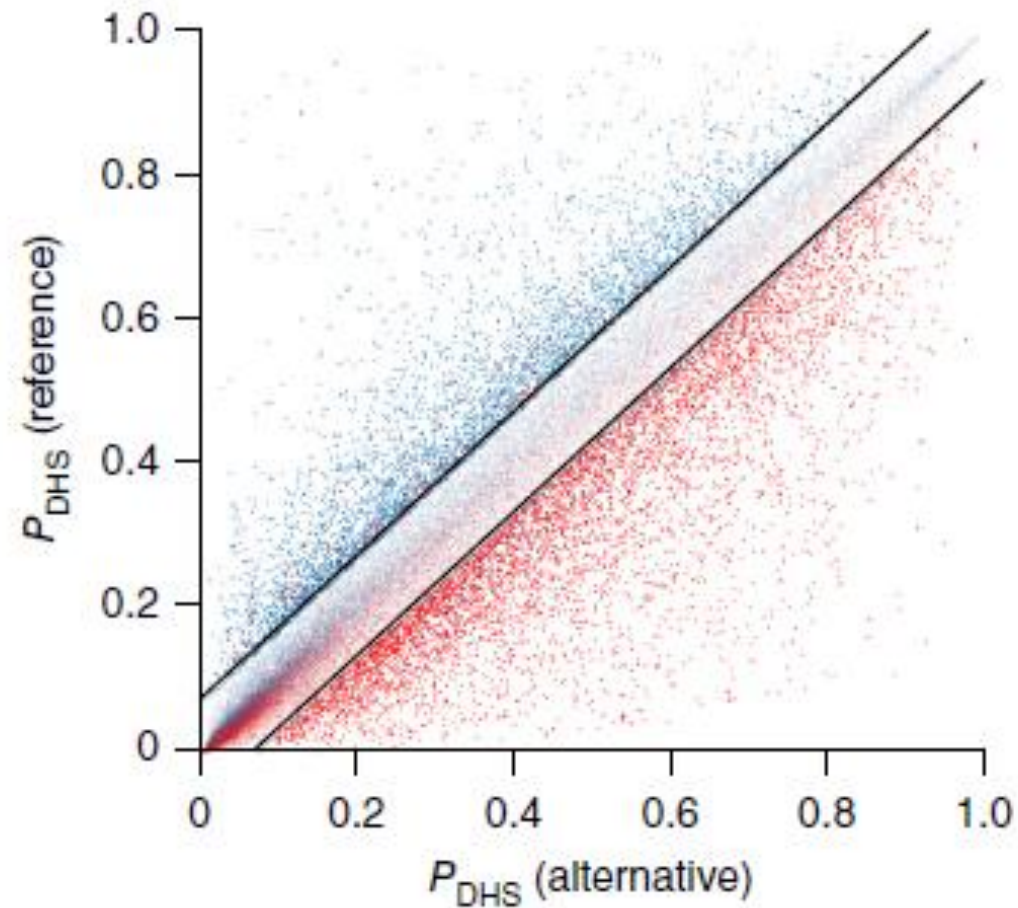
“ λ_5 ” - multi-task prediction



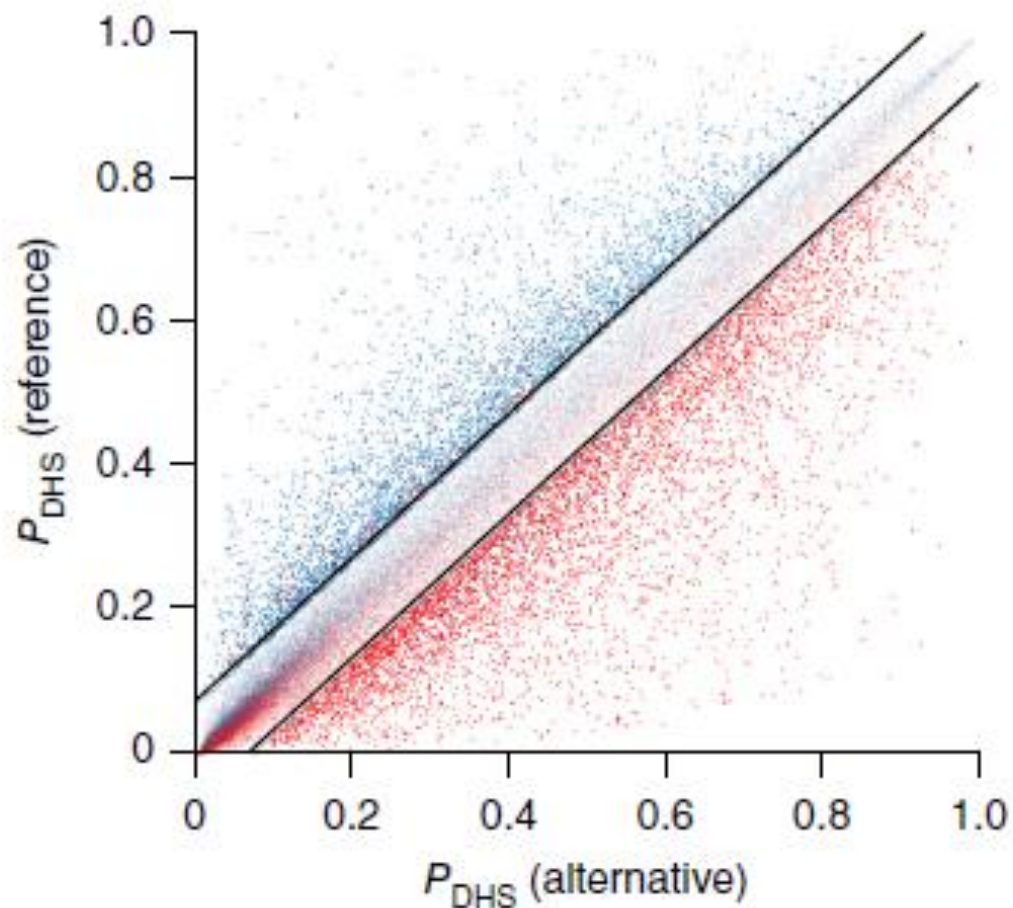
Test performance metrics: The infamous ROC AUC



Test performance of importance scoring: Allelic imbalance



Validation of importance scoring: Allelic imbalance



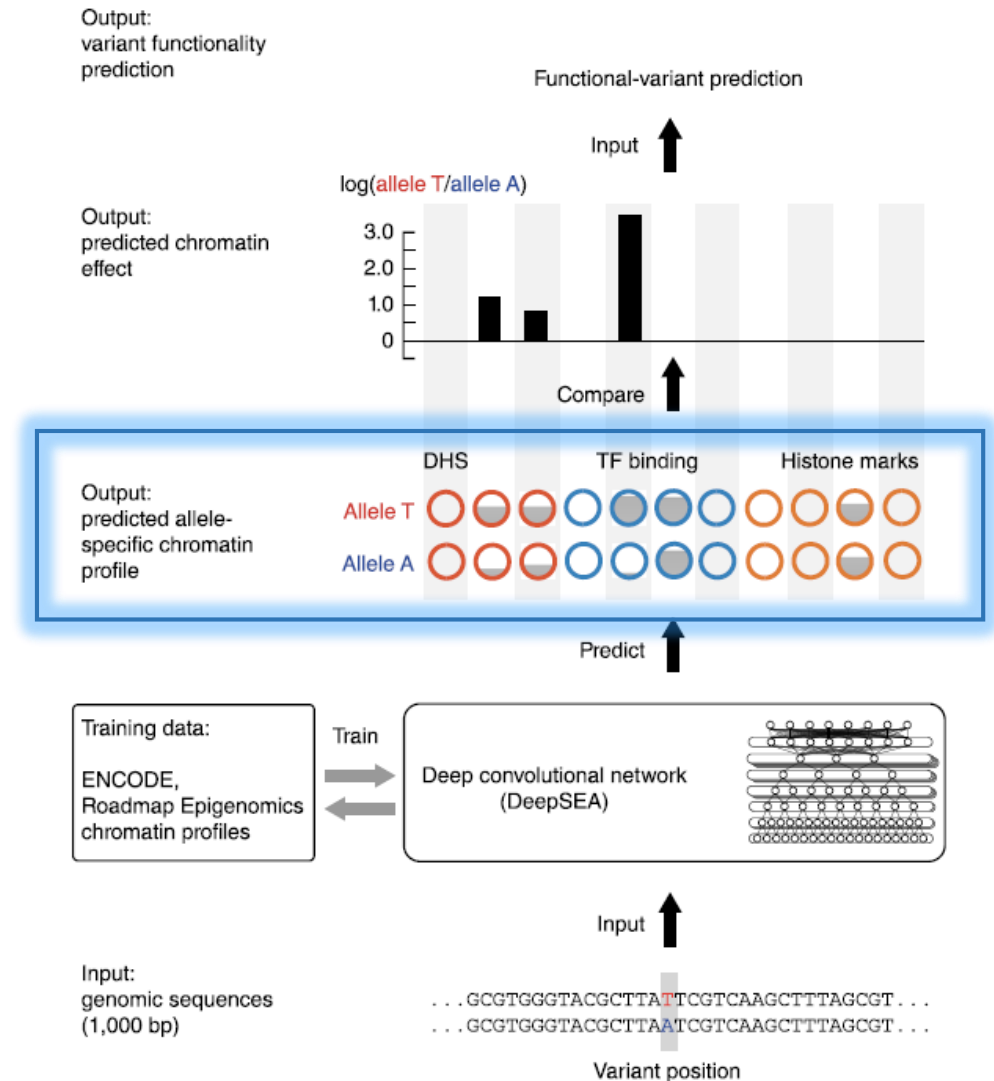
Axes = DeepSEA estimates
Color = Allelic imbalance

Importance scoring: in-silico mutagenesis

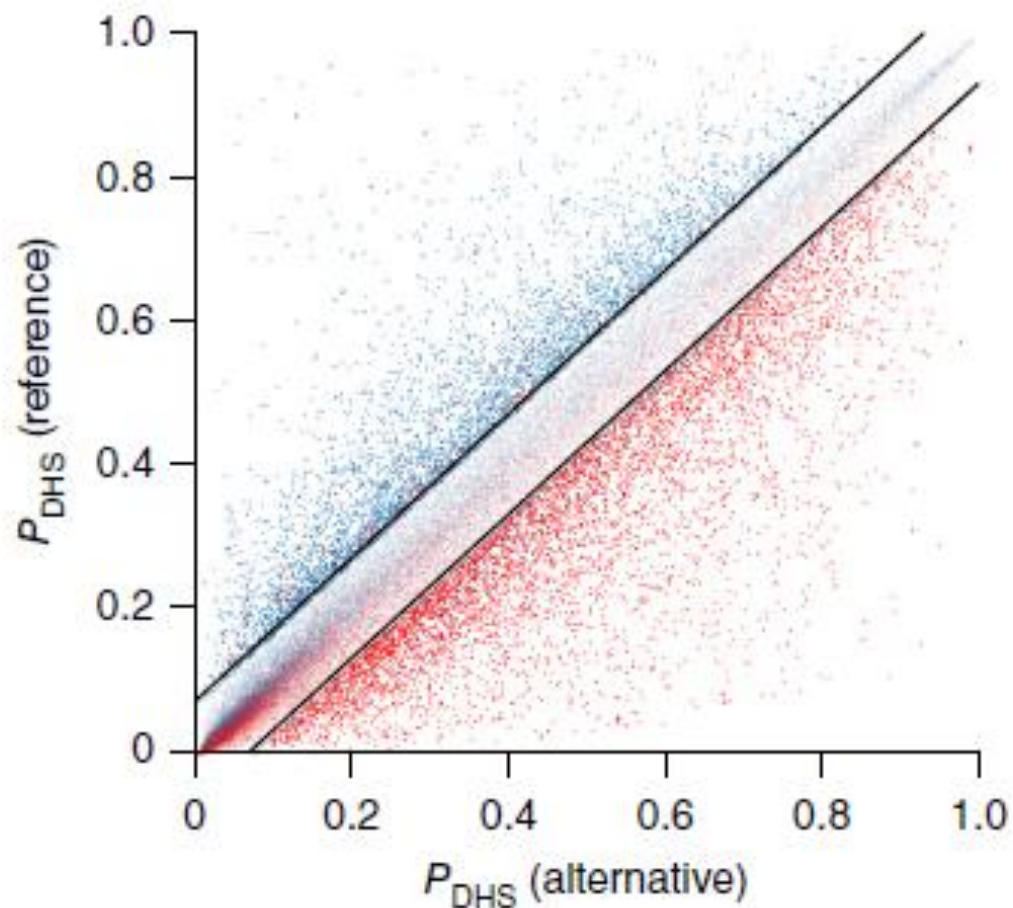
Probability of 1 (peak)
with reference allele

$$\log_2 \left(\frac{P_0}{1 - P_0} \right) - \log_2 \left(\frac{P_1}{1 - P_1} \right)$$

Probability of 1 (peak)
with alternative allele

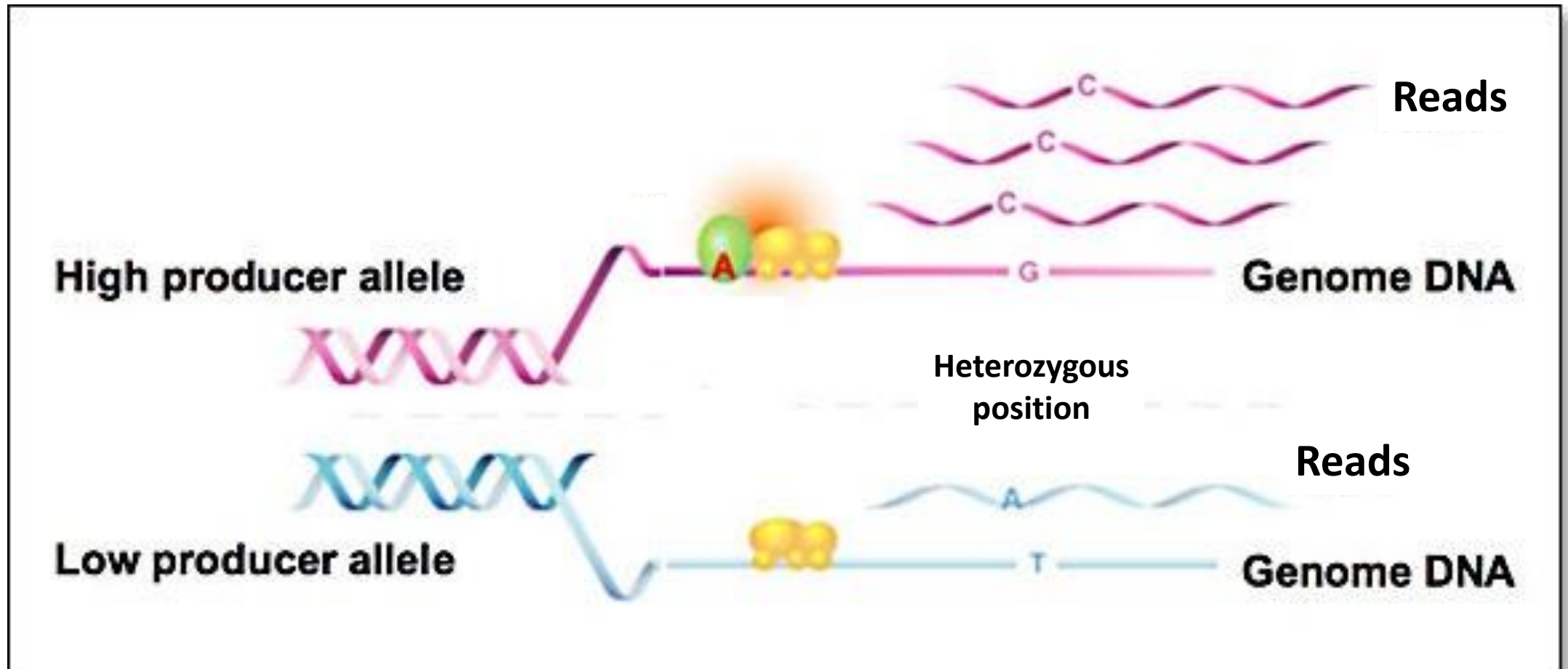


Validation of importance scoring: Allelic imbalance

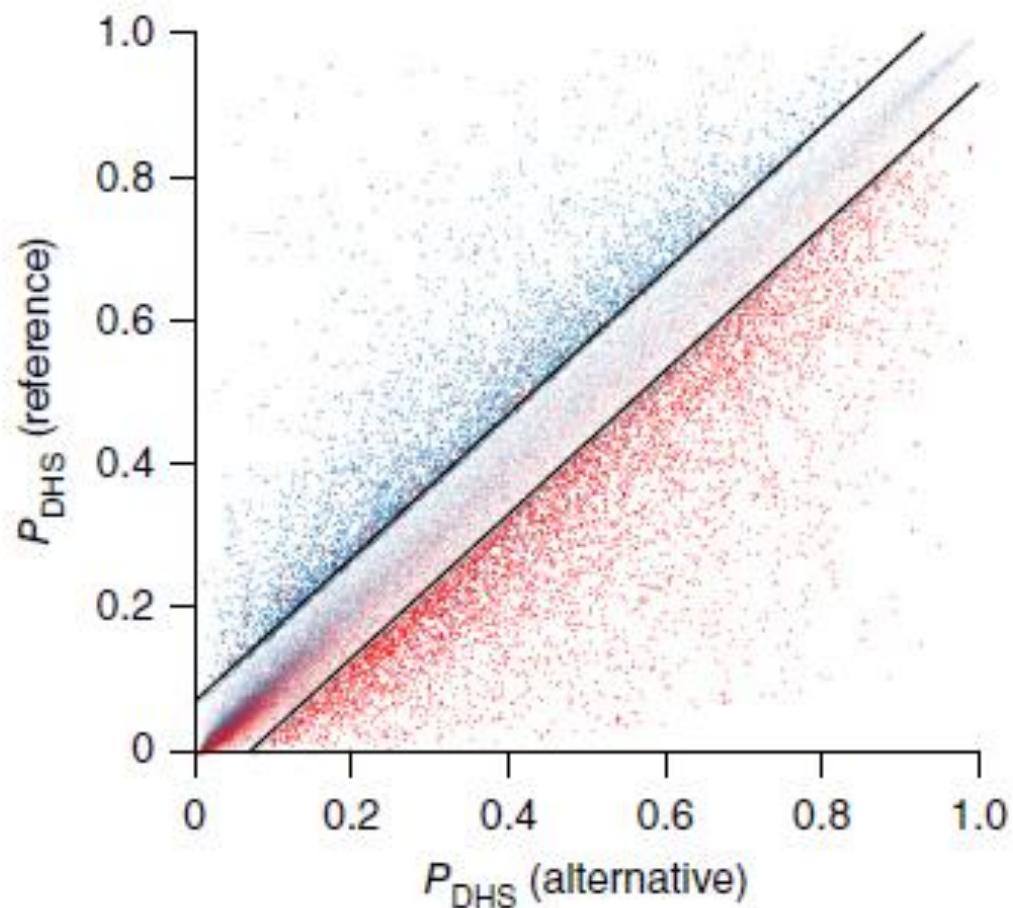


Axes = DeepSEA estimates
Color = Allelic imbalance

Validation of importance scoring: Allelic imbalance

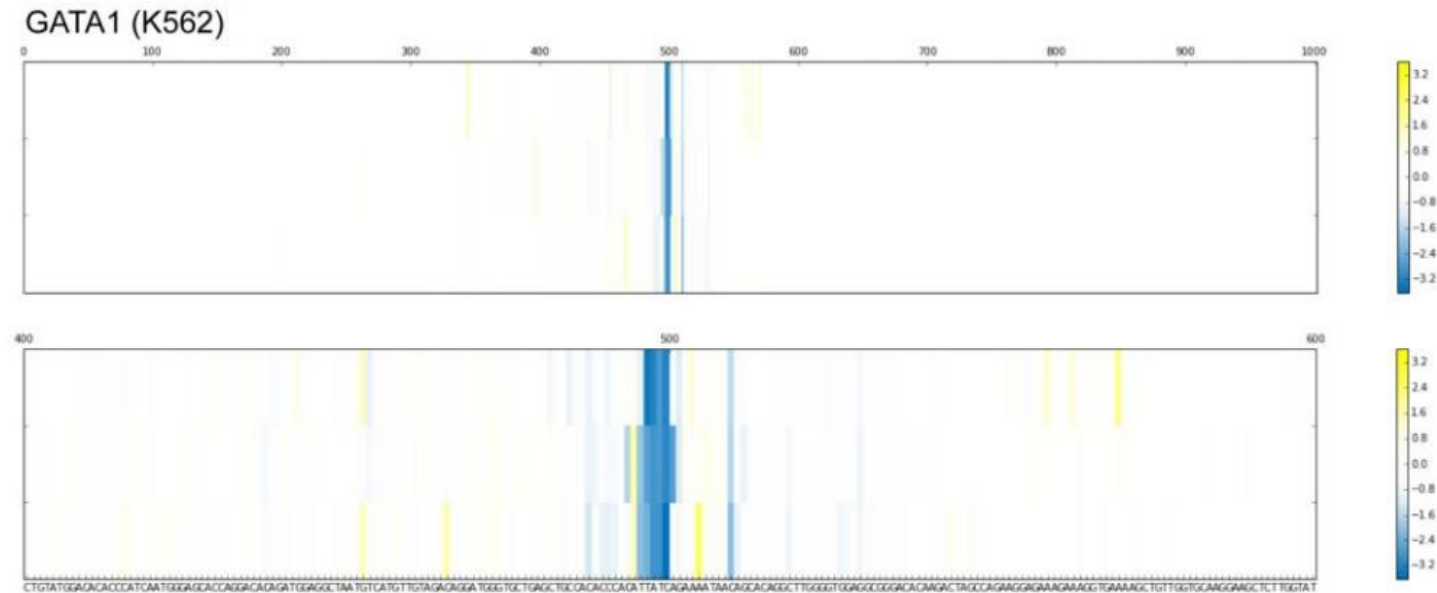


Validation of importance scoring: Allelic imbalance



Axes = DeepSEA estimates
Color = Allelic imbalance

Validation of importance scoring: positive controls

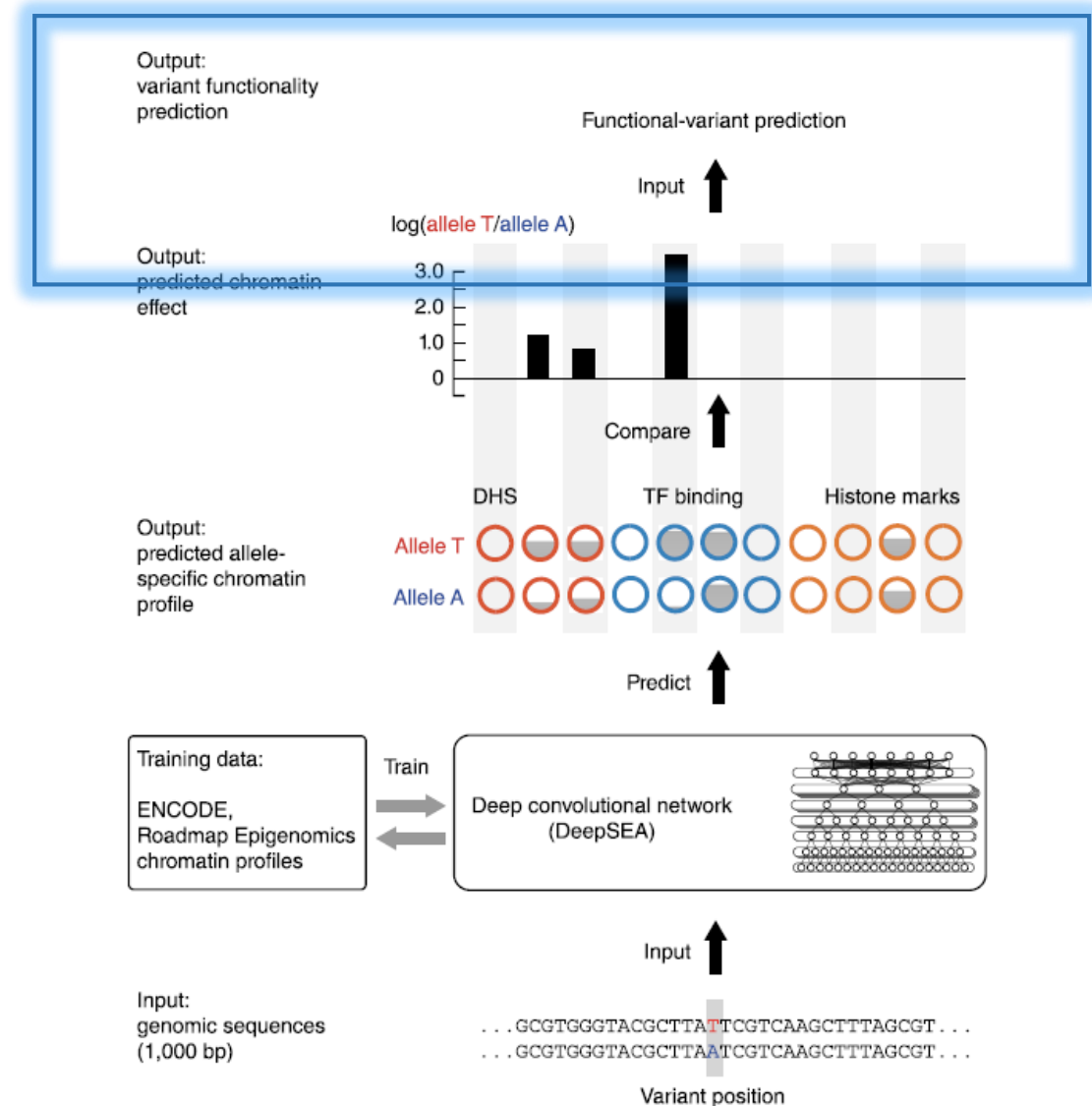


Blood disorder

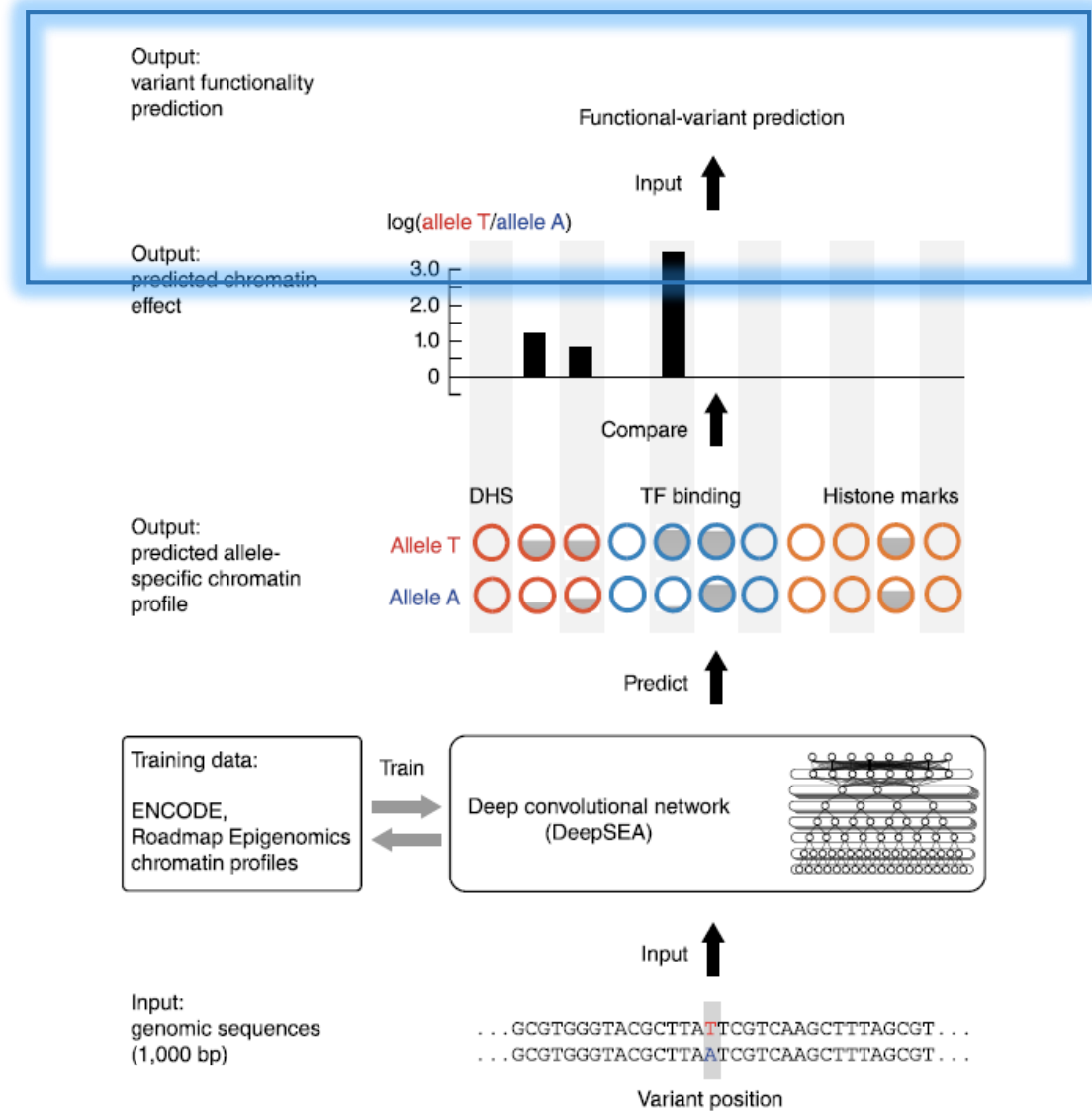
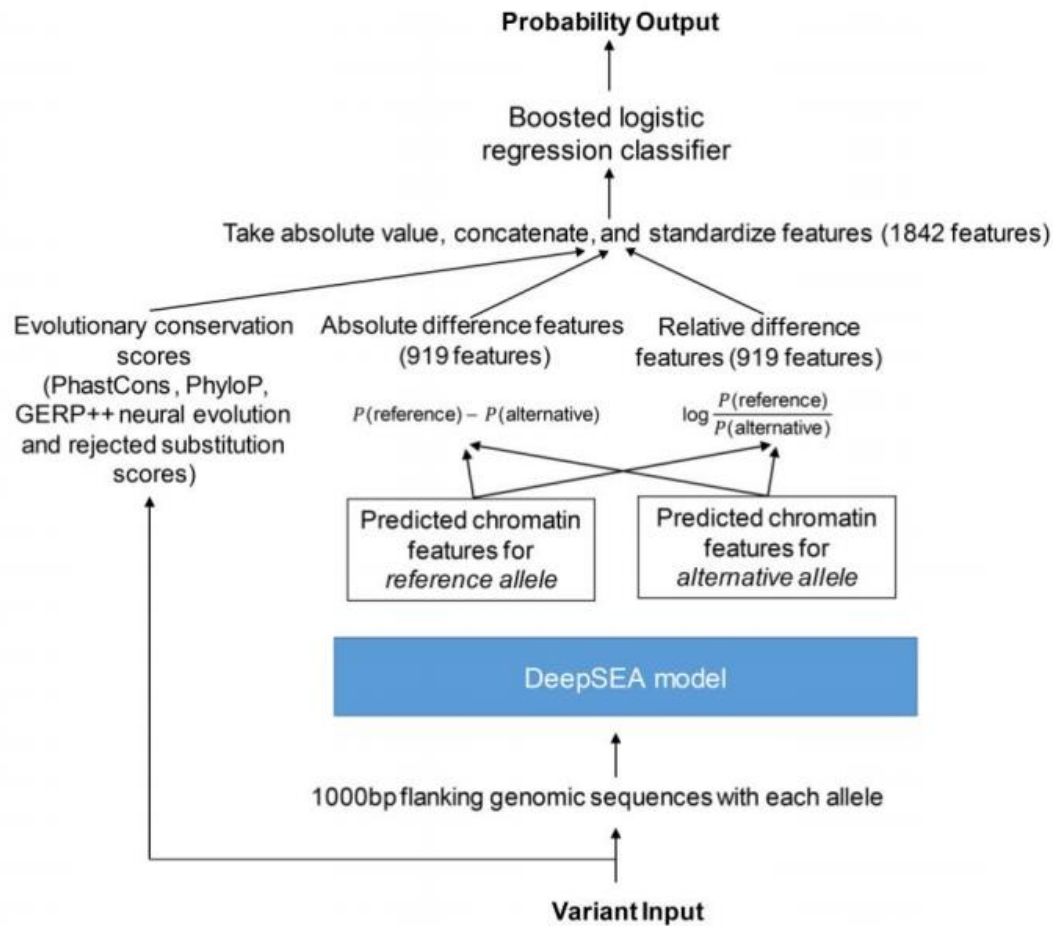
Prioritization / overall effect of variant on function

- Competing methods use a lot of high-throughput data as well, but virtually always include **evolutionary conservation**

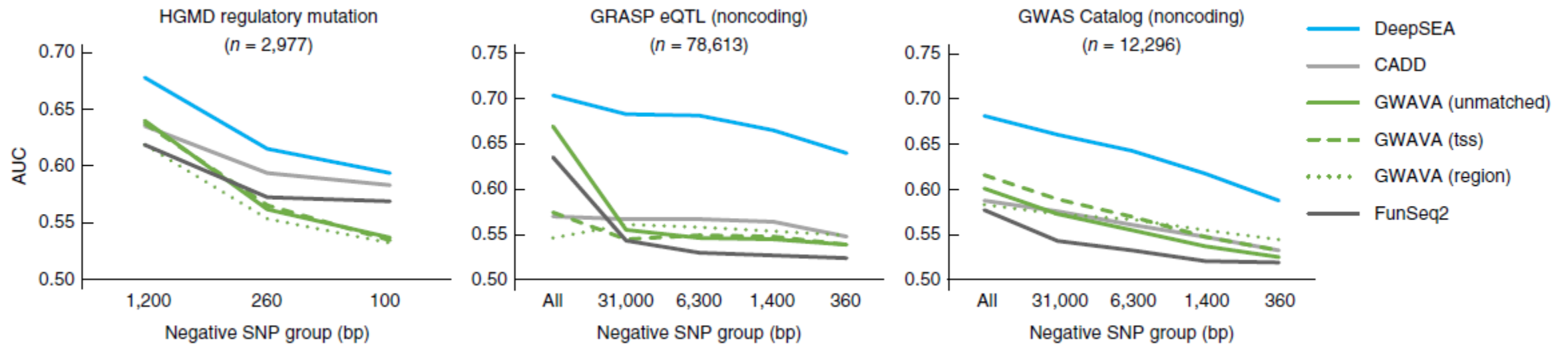
$$\text{Logit}(\text{Probability variant is functional}) \approx \beta_0 + \vec{\beta}_1 \cdot \overrightarrow{\text{DeepSEA}} + \vec{\beta}_2 \cdot \overrightarrow{\text{Evol. conservation}}$$



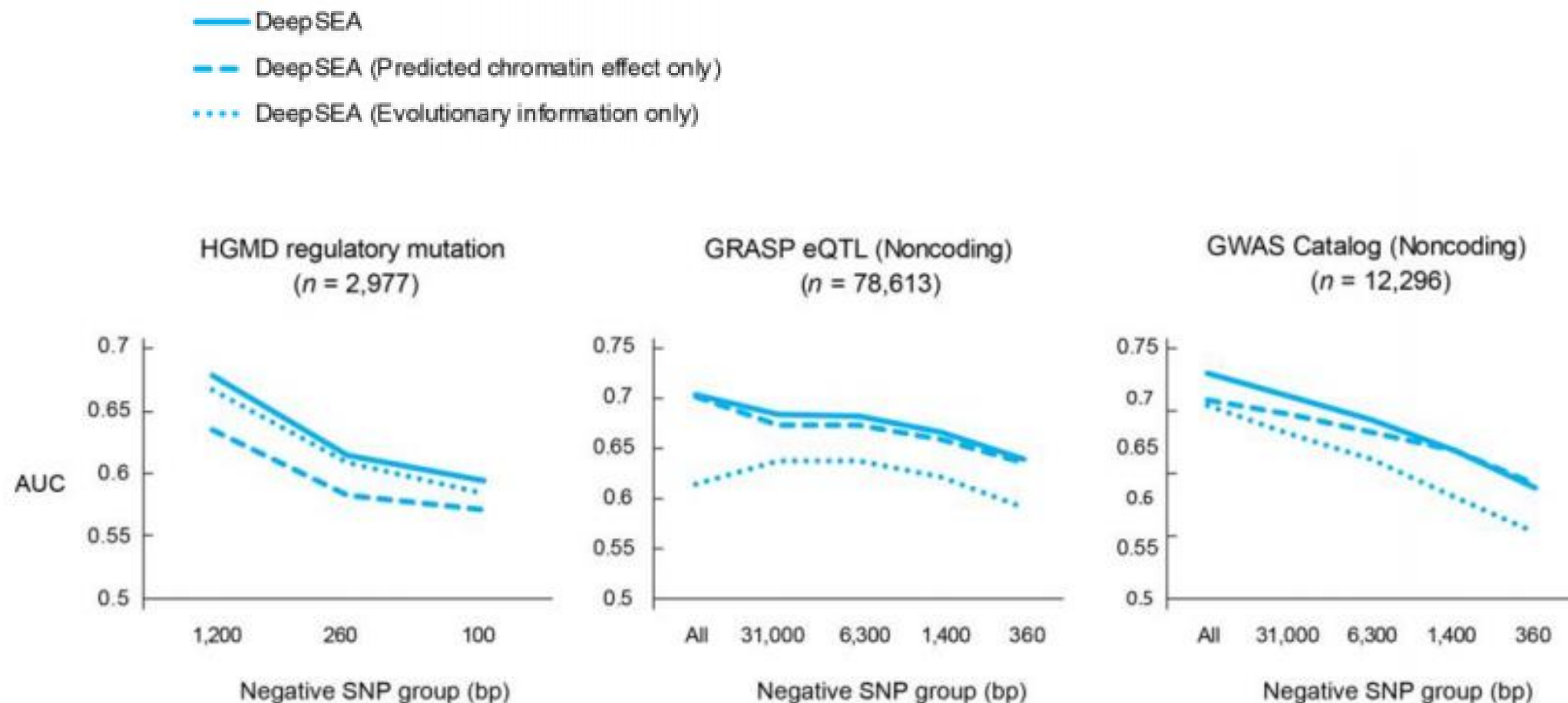
Prioritization / overall effect of variant on function



Performance of prioritization method



Prioritization / overall effect of variant on function



DeepSEA - Summary

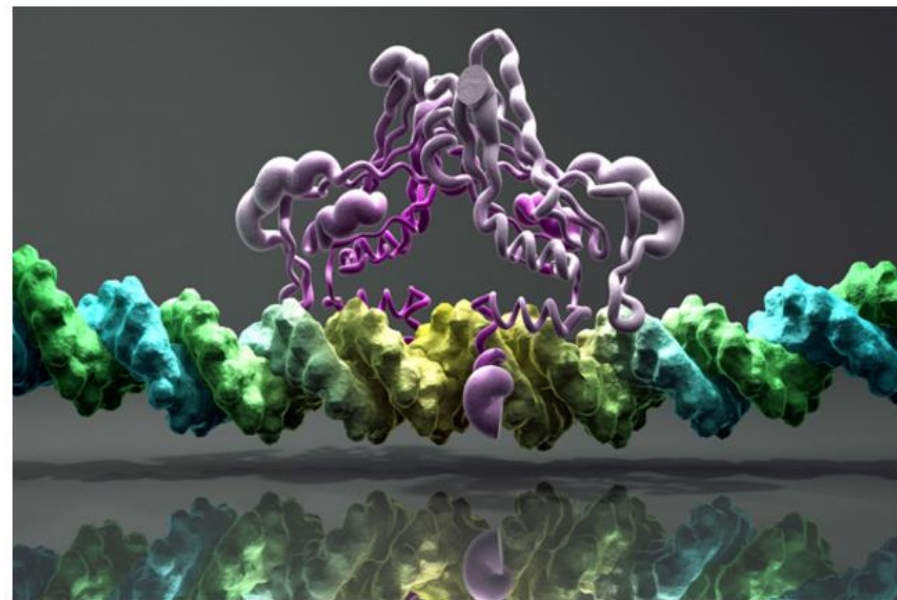
- (1) First wave of genomics CNN; predict functional effect from sequence
- (2) Performance:
 - Surprisingly good importance scoring
 - Per task—could prob. be improved
- (3) Some questionable choices e.g. objective function, learning rate, test performance metric, training and validation set choices

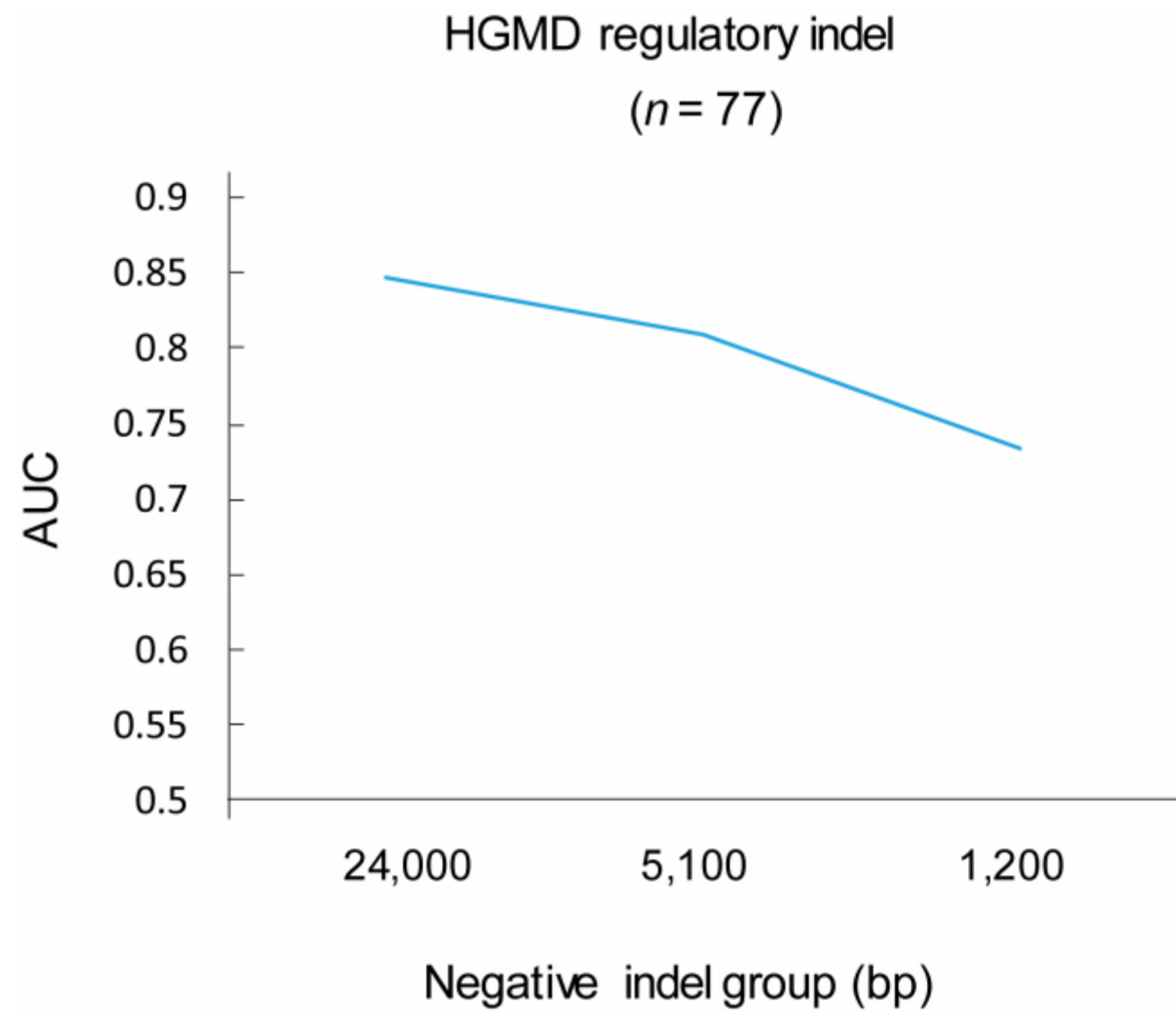
but...

Flexible **CNN** + Heavy **regularization**
compensate for all crimes
(e.g. hyperparameters don't seem to matter much)

Software forecasts effects of mysterious mutations

BY KATE YANDELL / 26 AUGUST 2015





Model Architecture:

1. Convolution layer (320 kernels. Window size: 8. Step size: 1.)
2. Pooling layer (Window size: 4. Step size: 4.)
3. Convolution layer (480 kernels. Window size: 8. Step size: 1.)
4. Pooling layer (Window size: 4. Step size: 4.)
5. Convolution layer (960 kernels. Window size: 8. Step size: 1.)
6. Fully connected layer (925 neurons)
7. Sigmoid output layer

Regularization Parameters:

Dropout proportion (proportion of outputs randomly set to 0):

Layer 2: 20%

Layer 4: 20%

Layer 5: 50%

All other layers: 0%

L2 regularization (λ_1): 5e-07

L1 sparsity (λ_2): 1e-08

Max kernel norm (λ_3): 0.9