Graph Convolutional Networks for Epigenetic State Prediction Using Both Sequence and 3D Genome Data

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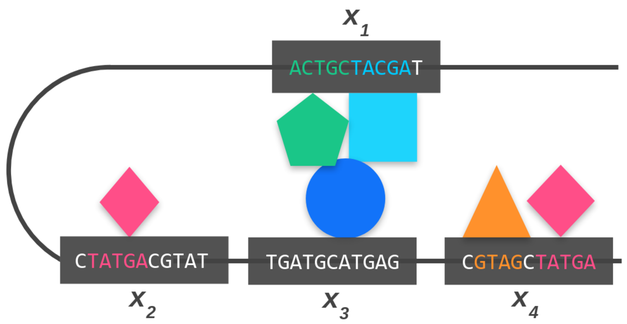
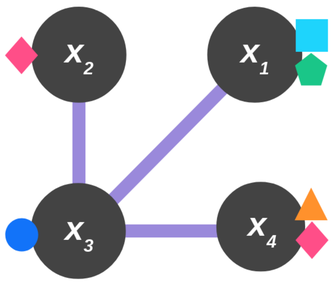
Epigenetic State Prediction

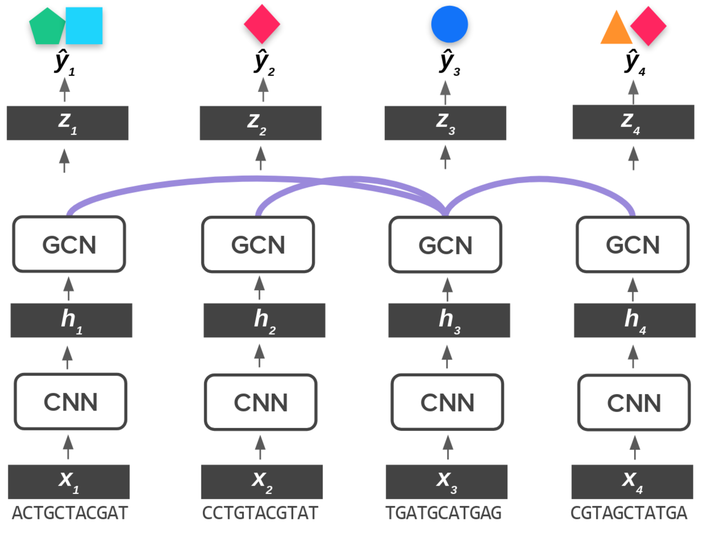


Epigenetic state of DNA window $\mathbf{x}_i$: active chromatin elements at that location (TF binding, histone modifications, and accessibility).

Modeling the 3D Genome Using Hi-C Data



ChromeGCN: Combining Sequence and 3D Genome Data for Epigenetic State Prediction



Method: ChromeGCN

Goal: given DNA window $\mathbf{x}_i$ predict the probability of a set of epigenetic labels $\hat{\mathbf{y}}_i = f(\mathbf{x}_i)$, where $\hat{\mathbf{y}}_i \in \mathbb{R}^L$.

1. Local Sequence Representations Using a CNN

f_{CNN} encodes each local sequence window $\mathbf{x}_i$ into $\mathbf{h}_i \in \mathbb{R}^d$ using a shared convolutional network:

$$\mathbf{h}_i = f_{CNN}(\mathbf{x}_i)$$

2. Long-Range 3D Relationships Using a GCN

f_{GCN} encodes 3D genome relationships between windows $\mathbf{h}_i$ using a graph convolutional network. Relationships are defined by Hi-C edges in the form of adjacency matrix $\mathbf{A}$:

$$\mathbf{z}_i = f_{GCN}(\mathbf{h}_i, \mathbf{A})$$

Each $\mathbf{h}_i^t$ is revised using a function of its neighbors $\mathcal{N}(i)$:

$$\mathbf{z}_i = \sigma\left(\frac{1}{|\mathcal{N}(i)|}\sum_{j\in\mathcal{N}(i)} \mathbf{h}_j^t \mathbf{W}^t\right)$$

3. Predicting Label Probabilities for Each Window

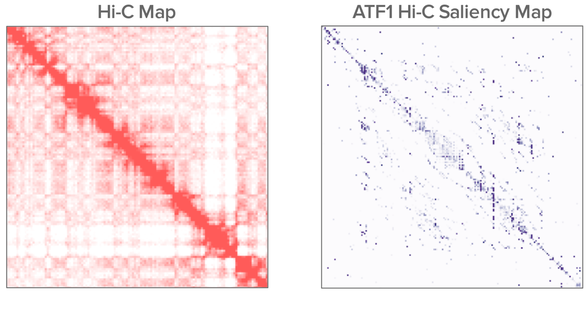
f_{Pred} uses linear classifier layer to classify each $\mathbf{z}_i$ into its output space (a set of epigenetic labels):

$$\hat{\mathbf{y}}_i = f_{Pred}(\mathbf{z}_i)$$

Finding Important Hi-C Edges via Saliency Maps

We propose Hi-C Saliency Maps, a method to identify the important 3D relationships for ChromeGCN's predictions:

$$S_{Hi\text{-}C}^{\ell} = \sum_{i=1}^{N} \mathbf{A} \circ \left|\frac{\partial \hat{\mathbf{y}}_i^{\ell}}{\partial \mathbf{A}}\right|$$

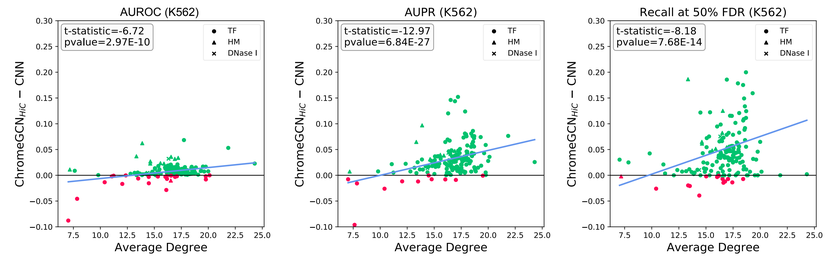


Prediction Performance

	GM12878			K562		
	Mean AUROC	Mean AUPR	Mean Recall at 50% FDR	Mean AUROC	Mean AUPR	Mean Recall at 50% FDR
CNN [1]	0.895	0.350	0.293	0.894	0.325	0.265
DanQ [2]	0.886	0.348	0.290	0.900	0.343	0.290
ChromeRNN	0.906	0.384	0.342	0.910	0.365	0.327
ChromeGCN$_{const}$	0.904	0.377	0.331	0.904	0.358	0.321
ChromeGCN$_{Hi\text{-}C}$	0.904	0.385	0.341	0.903	0.358	0.319
ChromeGCN$_{const+Hi\text{-}C}$	**0.909**	**0.395**	**0.356**	**0.912**	**0.372**	**0.338**

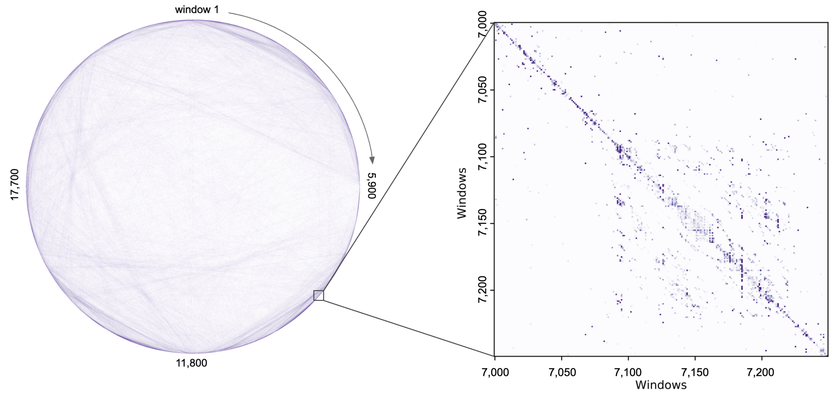
We find that across two cell types, using known long range 3D genome data from Hi-C maps improves prediction accuracy.

Analysis of Using Hi-C Data



Each point represents one epigenetic state label. As the average label degree increases, the improvement of ChromeGCN$_{Hi\text{-}C}$ over the CNN increases.

Hi-C Saliency Map



Saliency Map for all 500k edges in $\mathbf{A}_{Hi\text{-}C}$ for YY1 transcription factor in GM12878 Chromosome 8 (total of 23,600 windows). The darker the line, the more important that edge was for predicting the correct epigenetic state.

References

[1] J. Zhou et al, "Deep learning sequence-based ab initio prediction of variant effects on expression and disease risk," *Nature genetics*, vol. 50, no. 8, p. 1171, 2018.

[2] D. Quang and X. Xie, "Danq: a hybrid convolutional and recurrent deep neural network for quantifying the function of dna sequences," *Nucleic acids research*, 2016.