



Making Deep Learning Understandable for Analyzing Sequential Data about Gene Regulation

Dr. Yanjun Qi

2017/11/26

Roadmap

- ✧ Background of Machine Learning
- ✧ Background of Sequential Data about Gene Regulation
- ✧ AttentiveChrome for understanding gene regulation by selective attention on chromatin

Roadmap

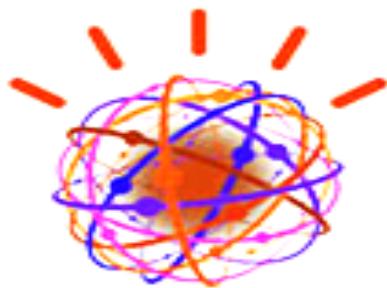
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Machine Learning is Changing the World

**How may I help you,
human?**



Apple Siri / Amazon Echo



IBM WATSON



Control learning

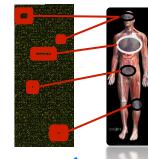


Object recognition

Many more !

Challenge of data explosion

Molecular signatures of tumor / blood sample



Signs & Symptoms



Information Explosion

▲ Volume
▲ Variety
▲ Velocity

Ability to Analyze

Analysis Gap

Patient Medical History & Demographics



Public Health Data



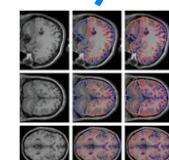
Genetic Data



Mobile medical sensor data



Medical Images



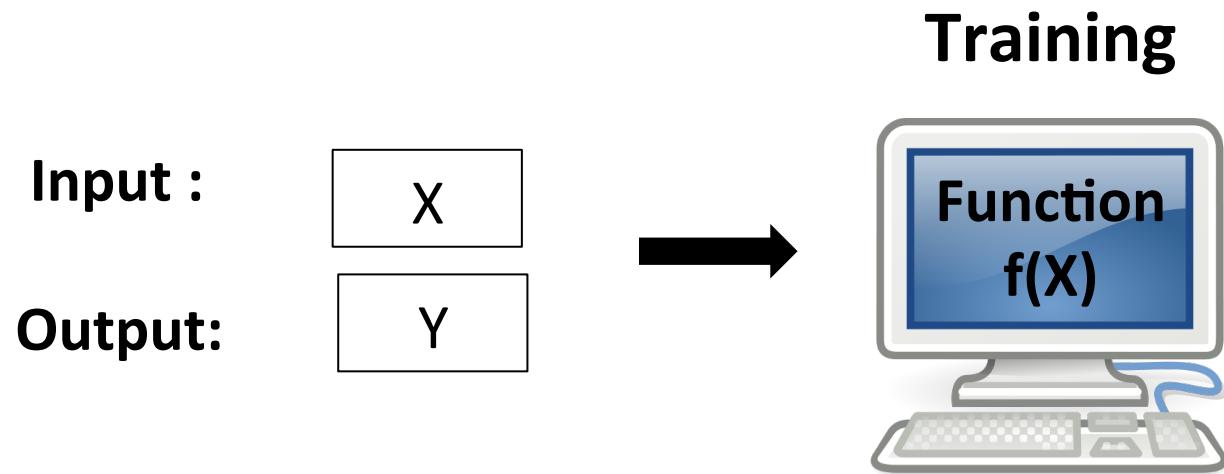
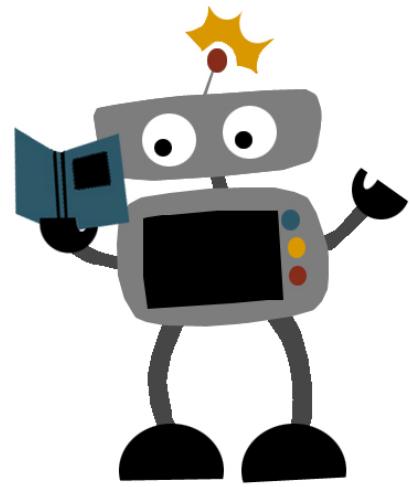
Traditional Approaches



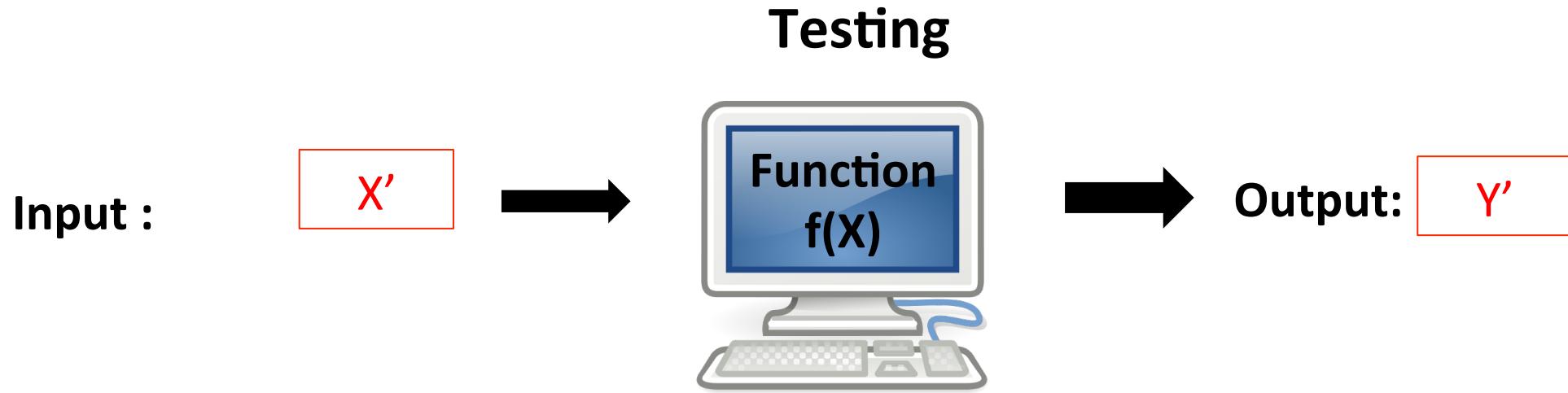
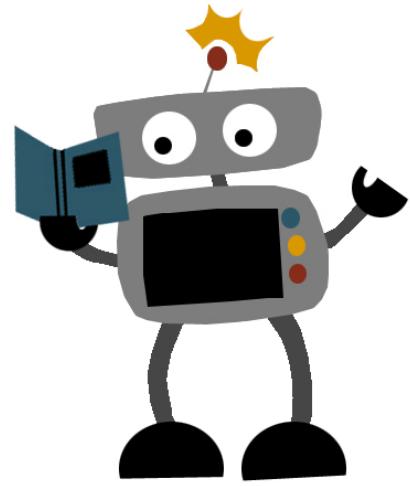
Data-Driven Approaches

Machine Learning

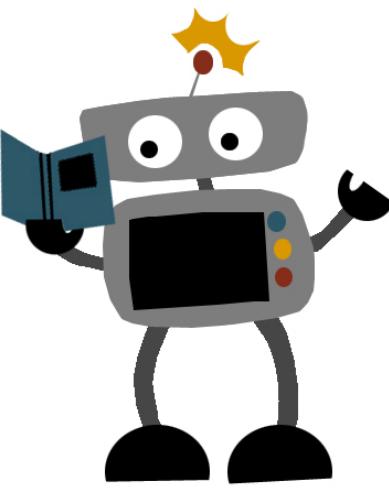
What is Machine Learning?



What is Machine Learning?

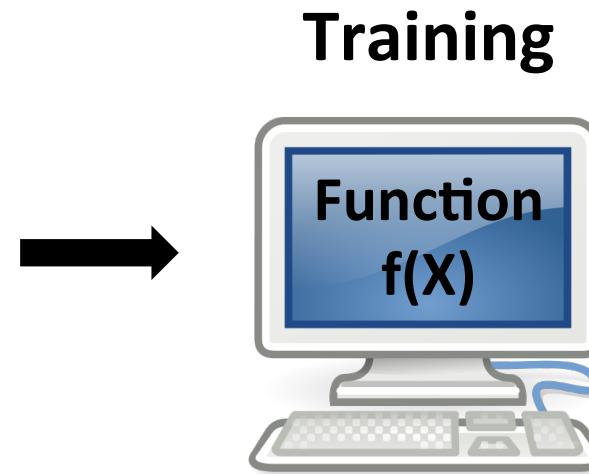


[Example:] What is Machine Learning?



Output: CAR

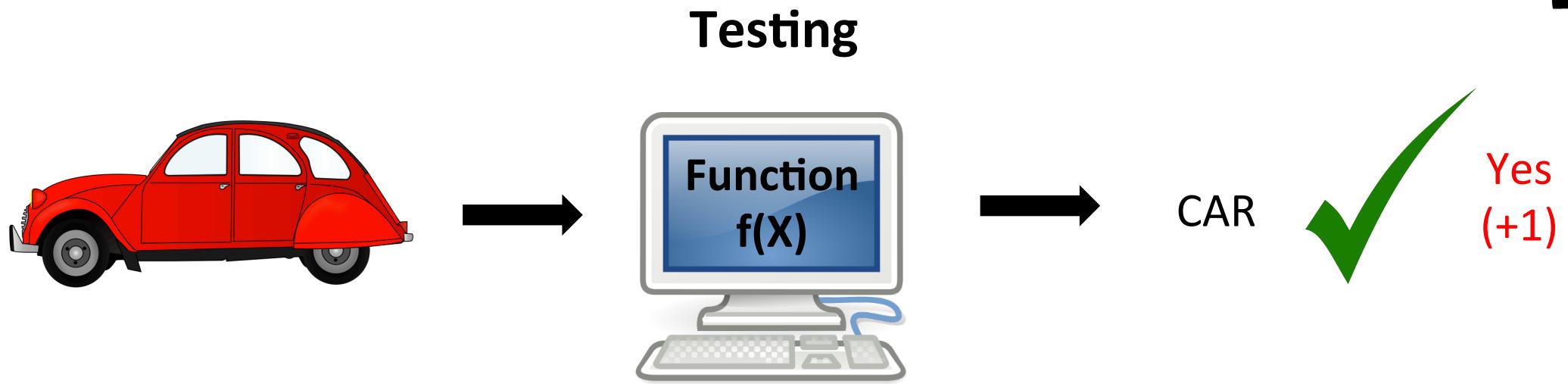
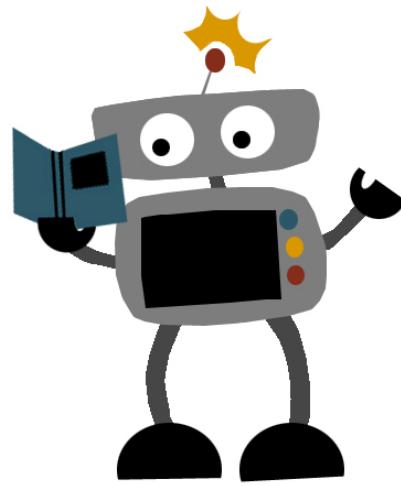
Inputs:



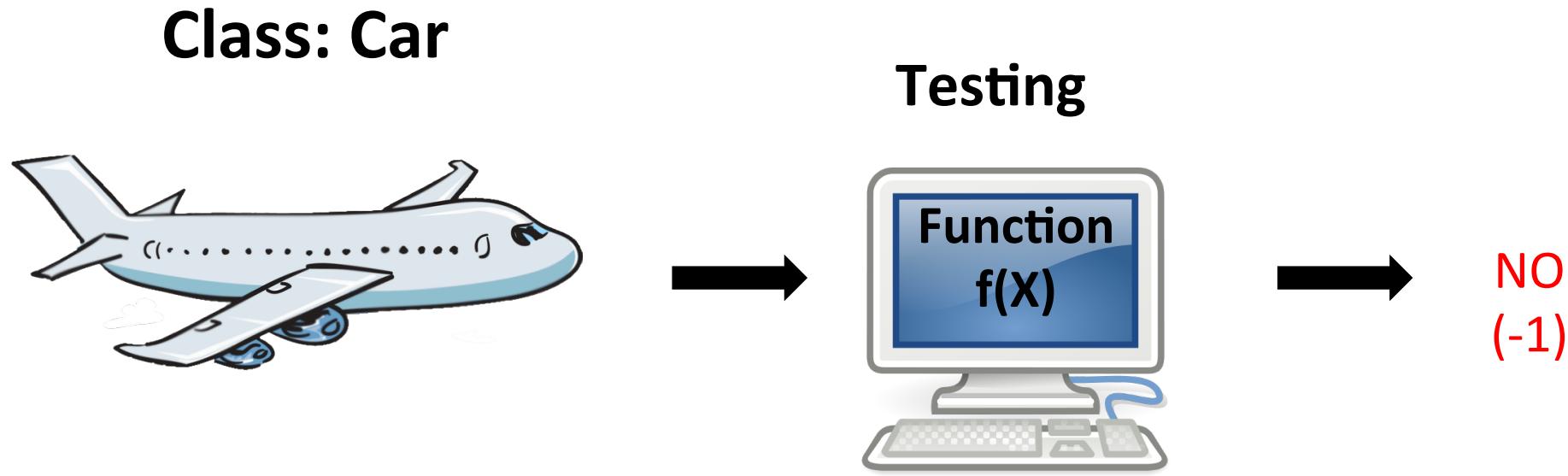
Training

Function
 $f(X)$

[Example:] What is Machine Learning?

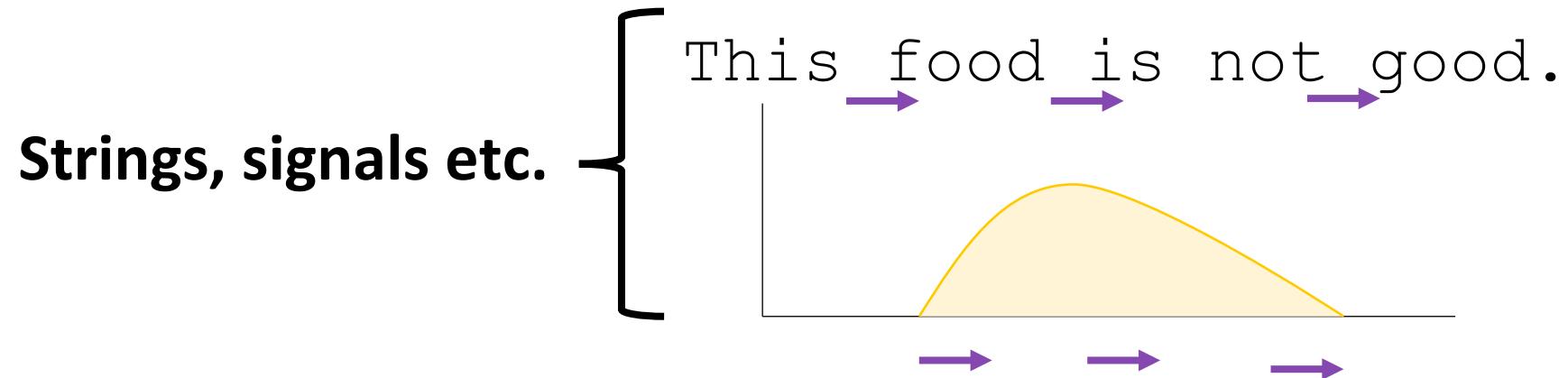
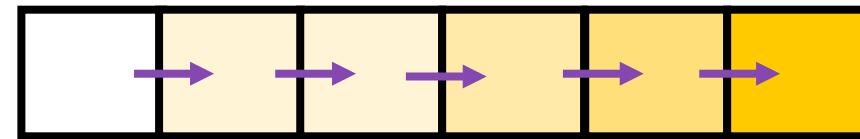


[Example:] Classification task in Machine Learning

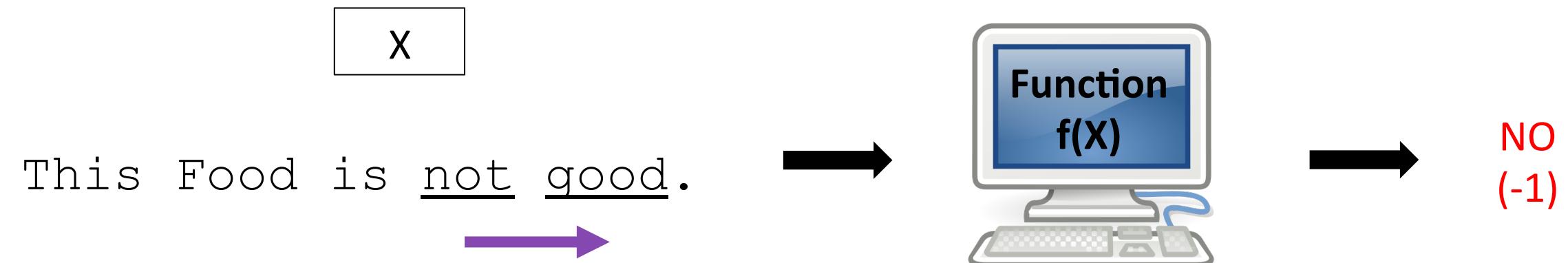


Sequential Data

**Sequential
Data:**

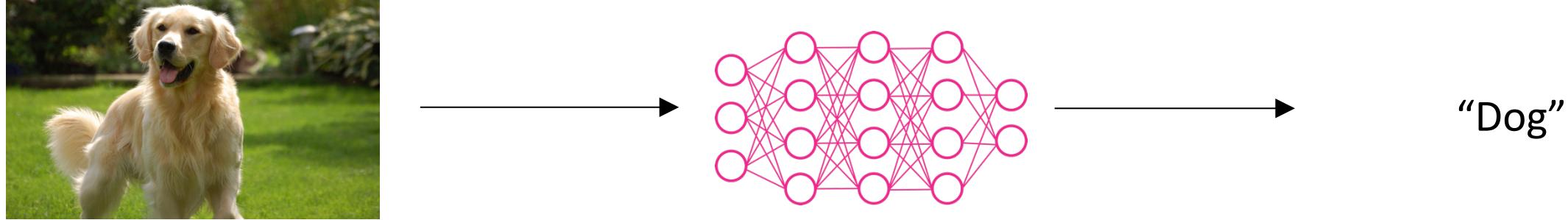


[Example:] Classification of Sequential Data



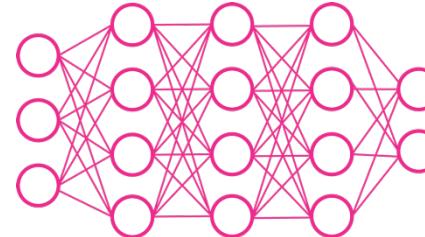
State-of-the-art Machine Learning

- Deep Neural Networks (DNN)



State-of-the-art Machine Learning

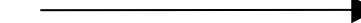
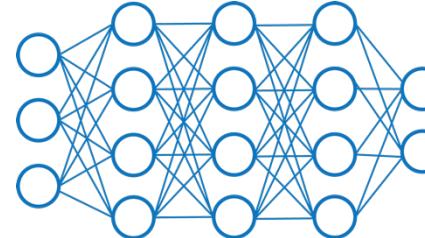
- Deep Neural Networks (DNN)



"Dog"

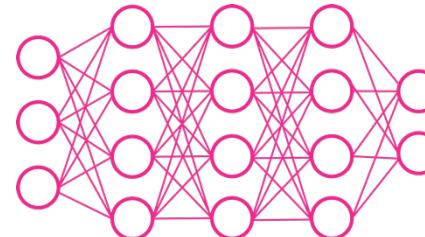
Can get overly sentimental at times, but Gus Van Sant's sensitive direction... and his excellent use of the city make it a hugely entertaining and effective film.

[Full Review...](#) | May 25, 2006

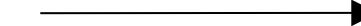
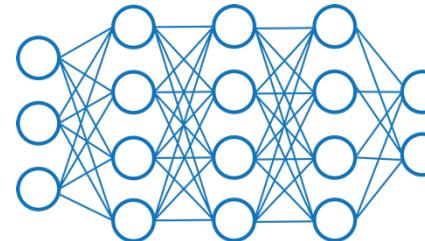
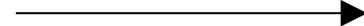
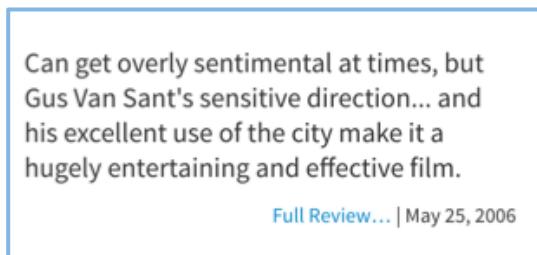
A blue rectangular callout box with a white background and a thin blue border. It contains a snippet of a movie review from a website.

State-of-the-art Machine Learning

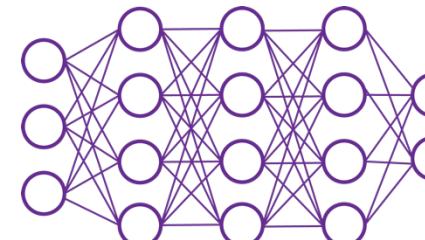
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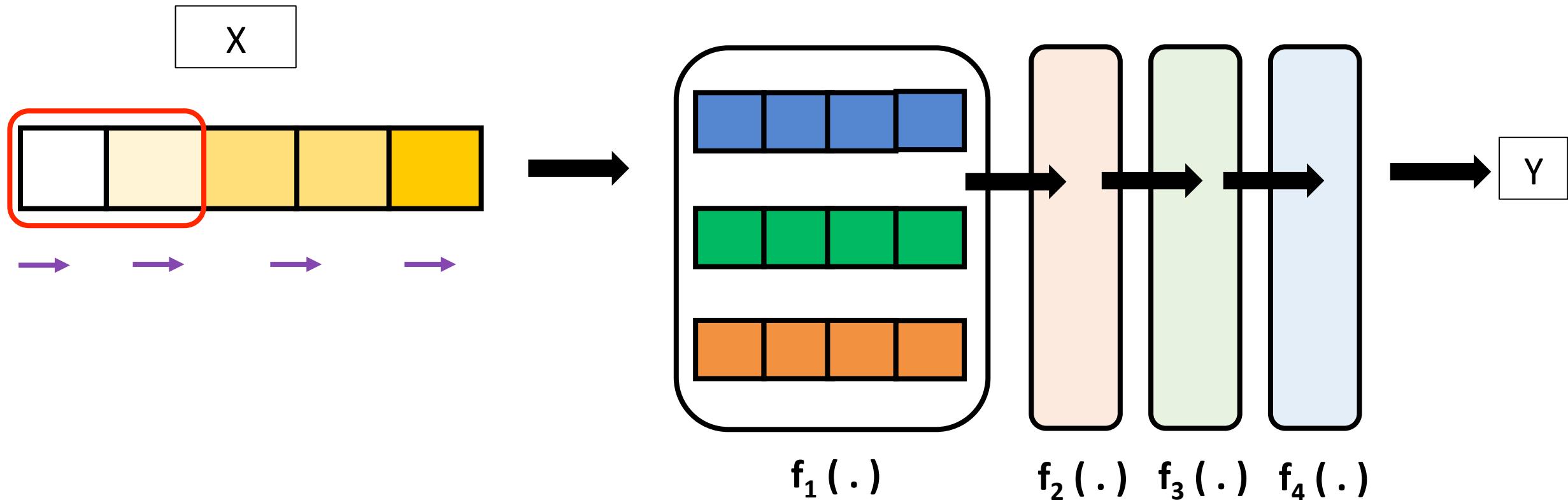


ATGCGATCAAGTCTG

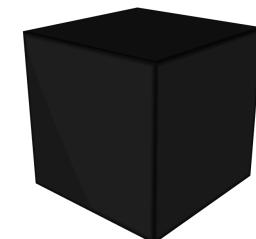


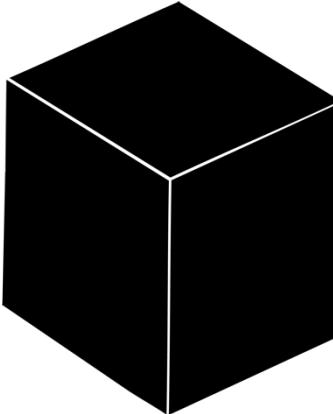
“Protein Binding Site”

Deep Neural Networks (DNN)

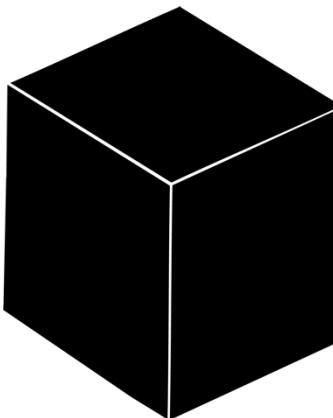


$$Y = f_4(f_3(f_2(f_1(X))))$$

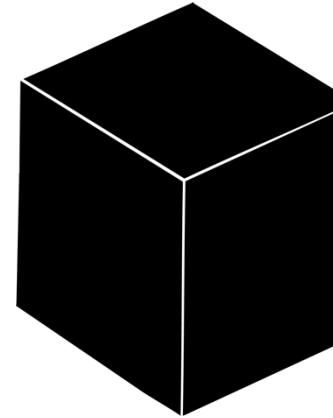




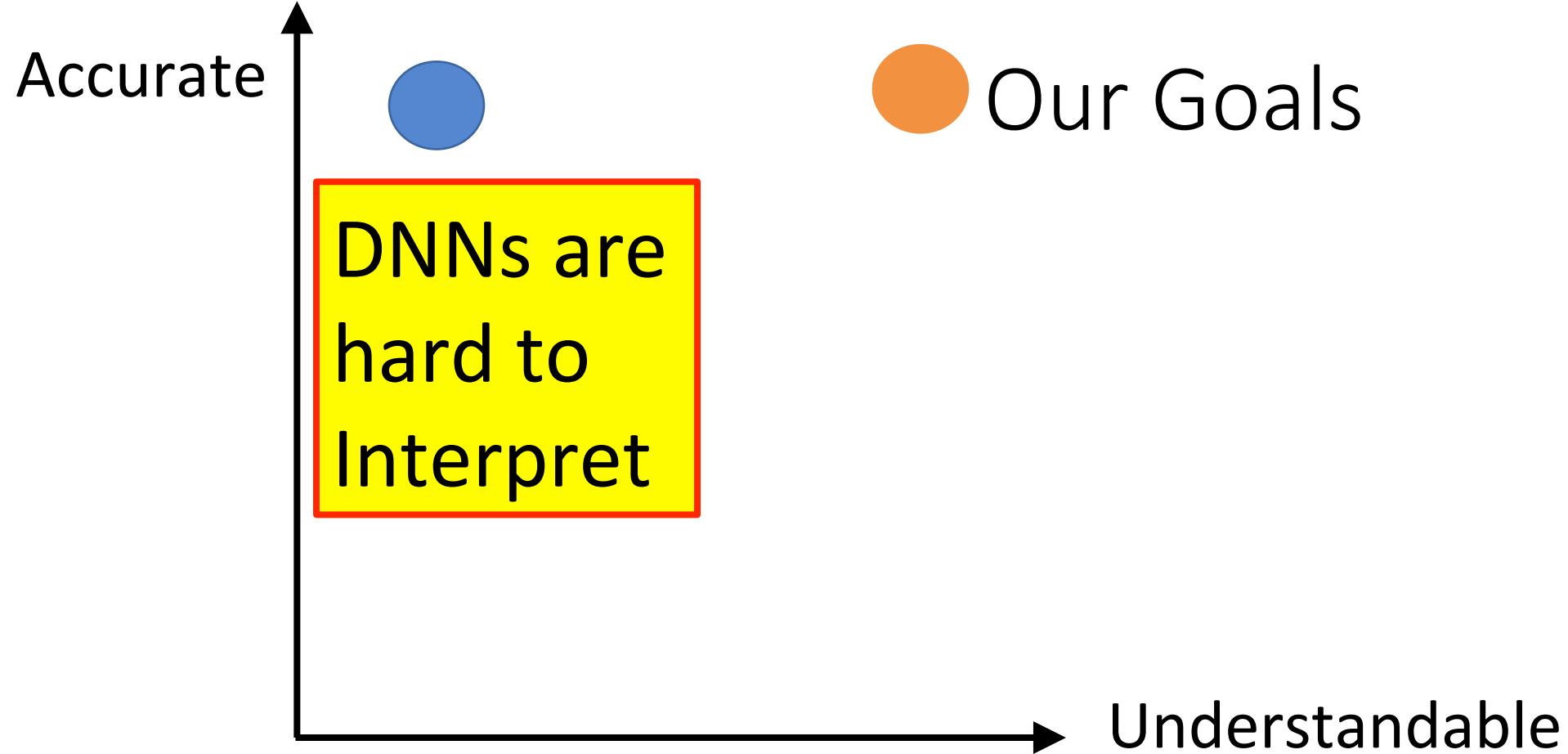
“Dog”



ATGC**GATCAAGTCTG**



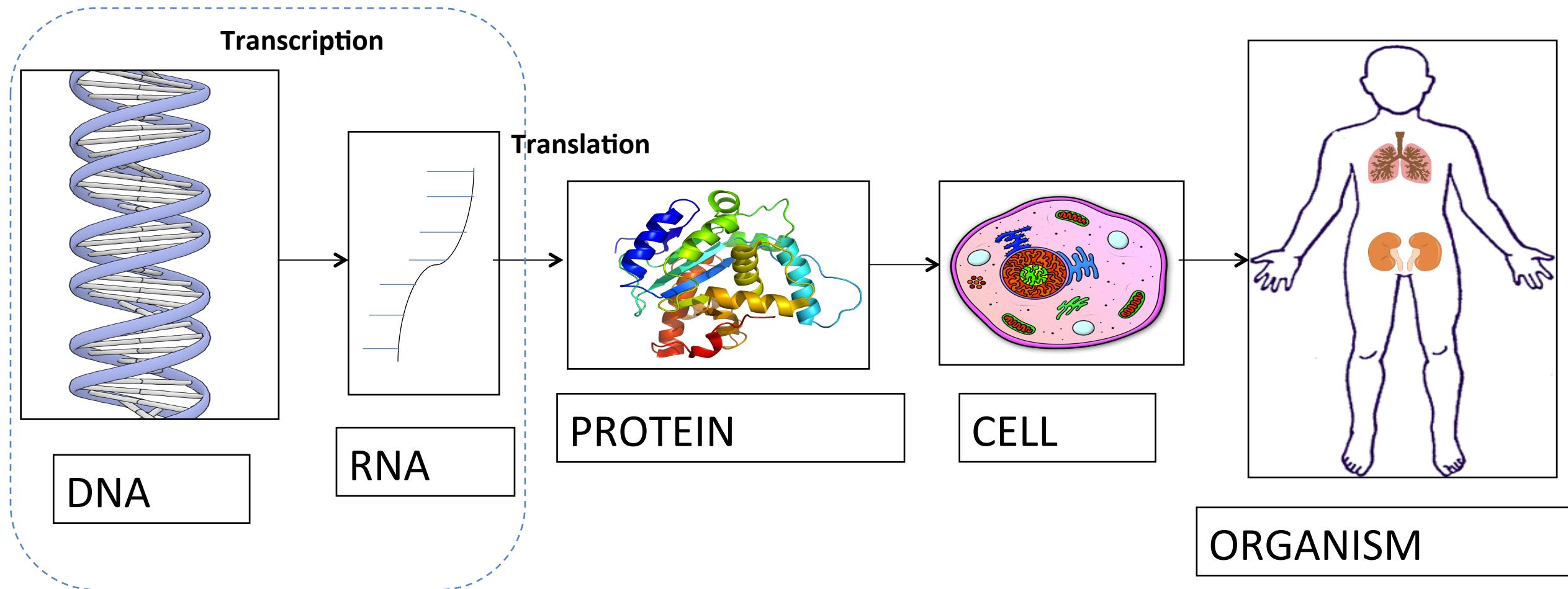
“Protein Binding Site”



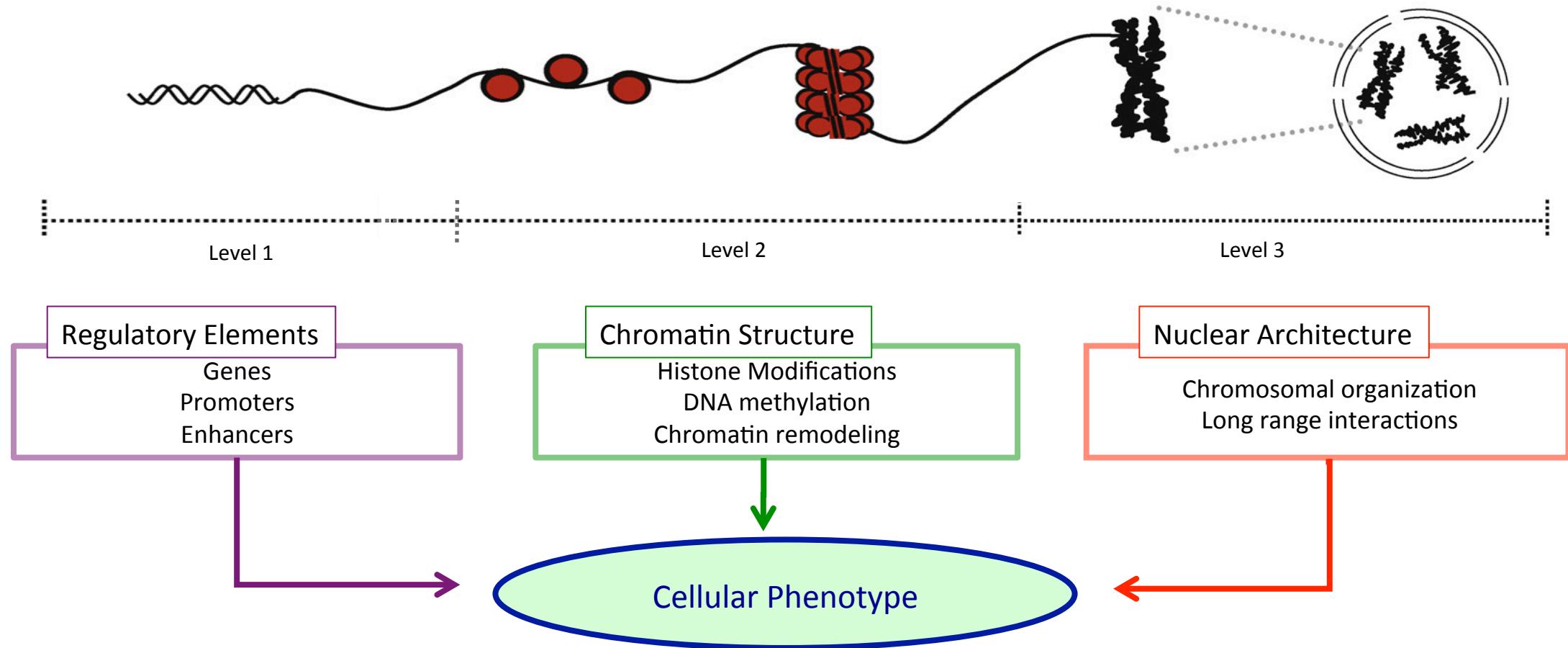
Roadmap

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- ✧ AttentiveChrome for understanding gene regulation by selective attention on chromatin

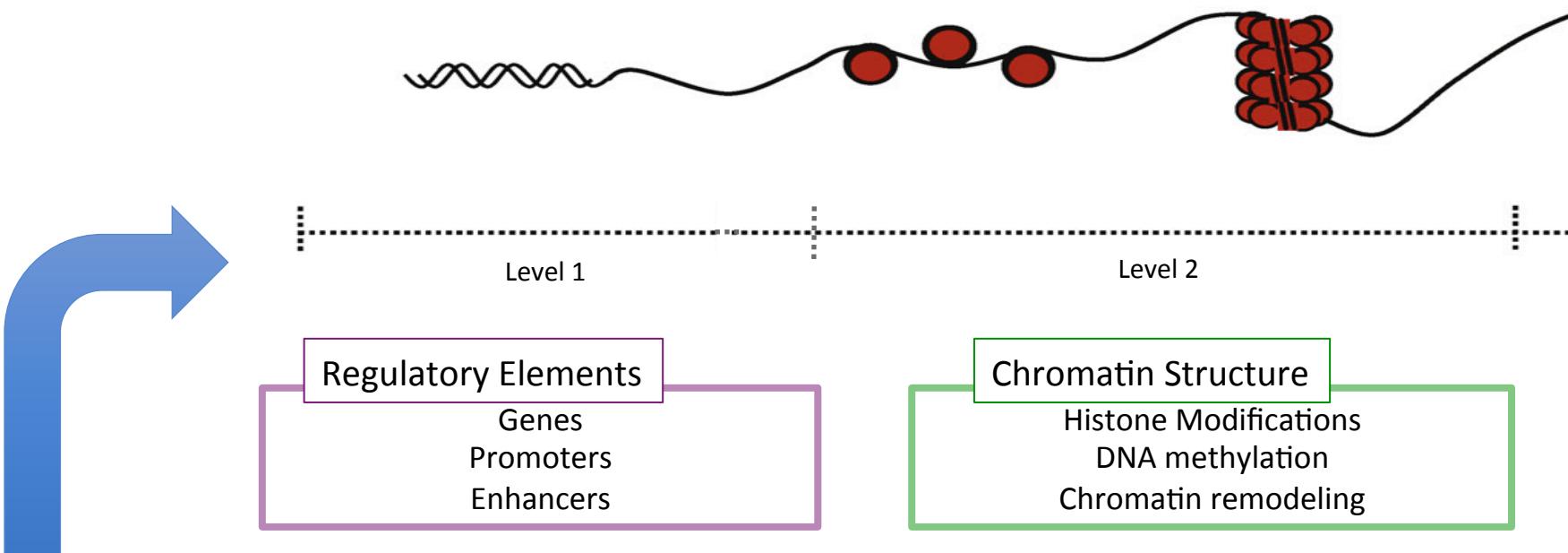
Biology in a Slide



Genome Organization and Gene Regulation



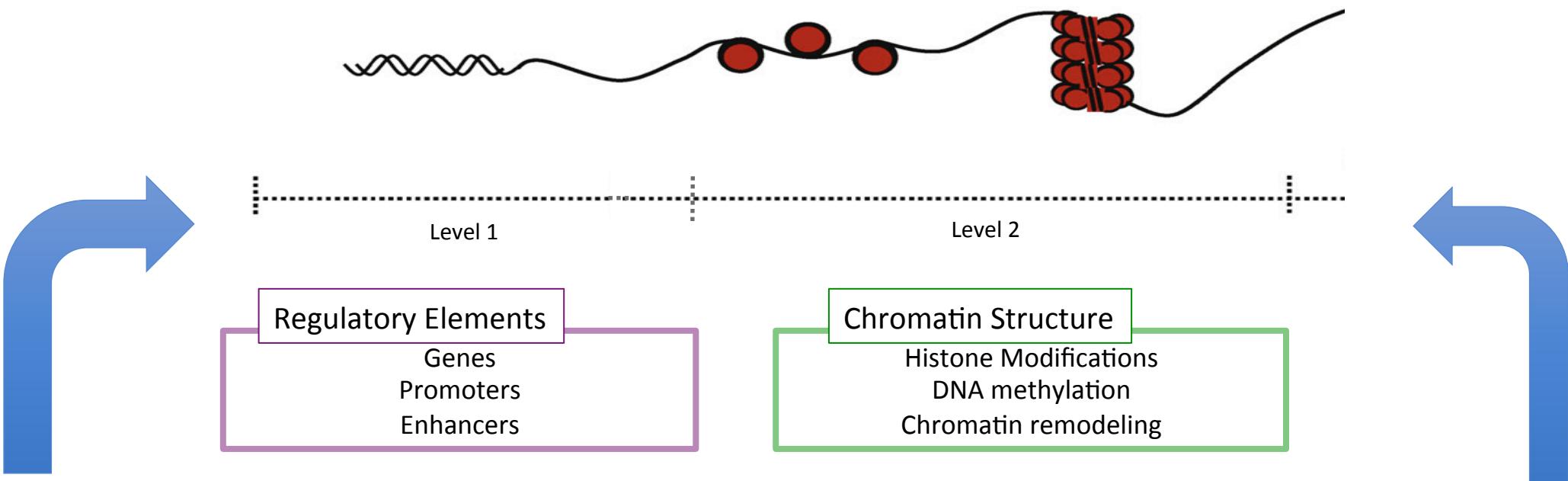
(adapted from Babu et al., 2008)



ENCODE Project (2003-Present)

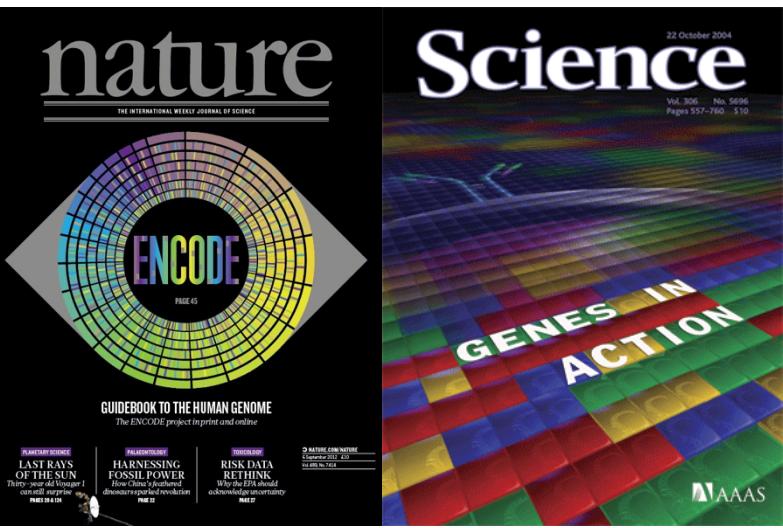
Describe the functional elements encoded in human DNA





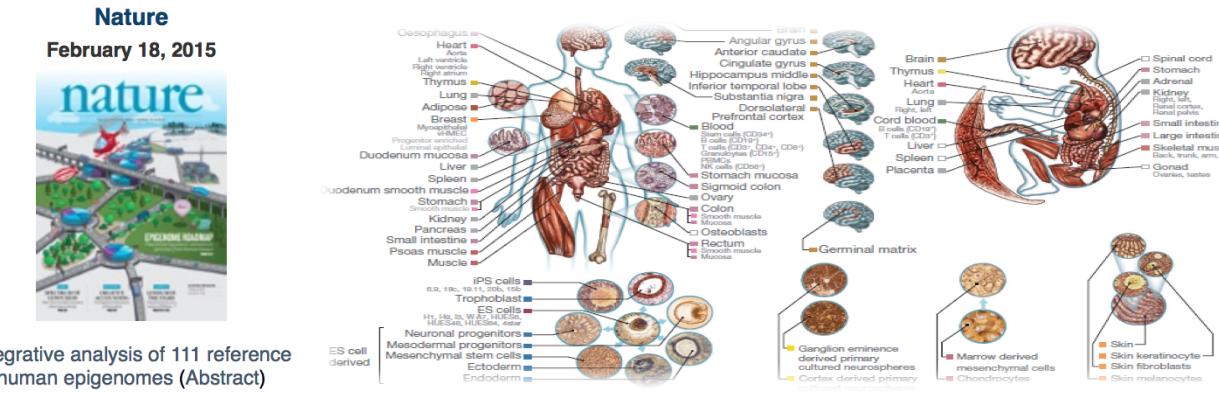
ENCODE Project (2003-)

Describe the functional elements encoded in human DNA



Roadmap Epigenetics Project (REMC, 2008-)

To produce a public resource of epigenomic maps for stem cells and primary ex vivo tissues selected to represent the normal counterparts of tissues and organ systems frequently involved in human disease.

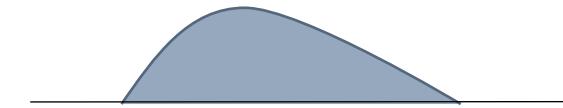


Current Available Large-Scale Data about Gene Transcription

DNA
Segments
on
Genomes

ATGCGATCAAGTCTG

TF Binding
Signals



Histone
Modification
Signals



Gene
Expression



Two Important Data-Driven Computational Tasks

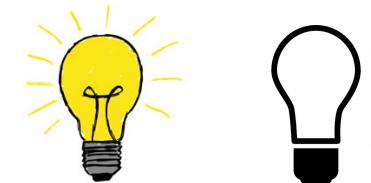
DNA
Segments
on
Genomes

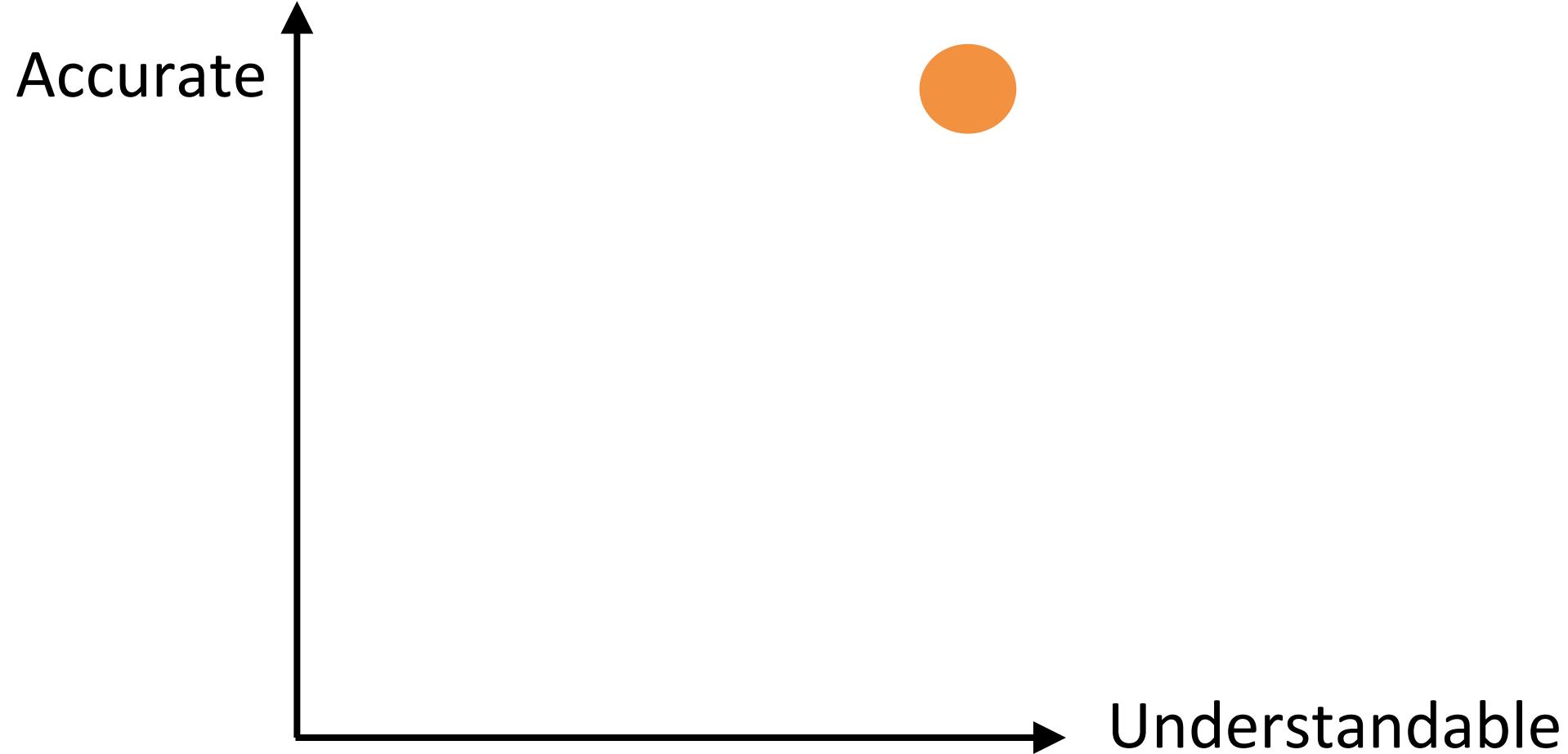
ATGCGATCAAGTCTG

TF Binding
Signals

Histone
Modification
Signals

Gene
Expression



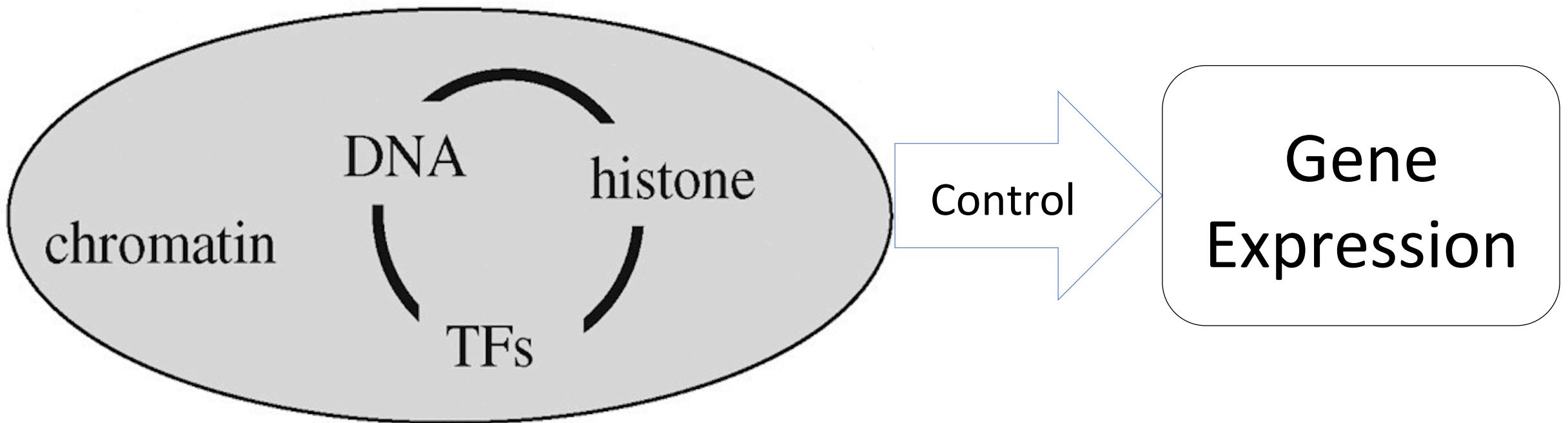


One main aim of such data analysis is to understand data and to discover knowledge.

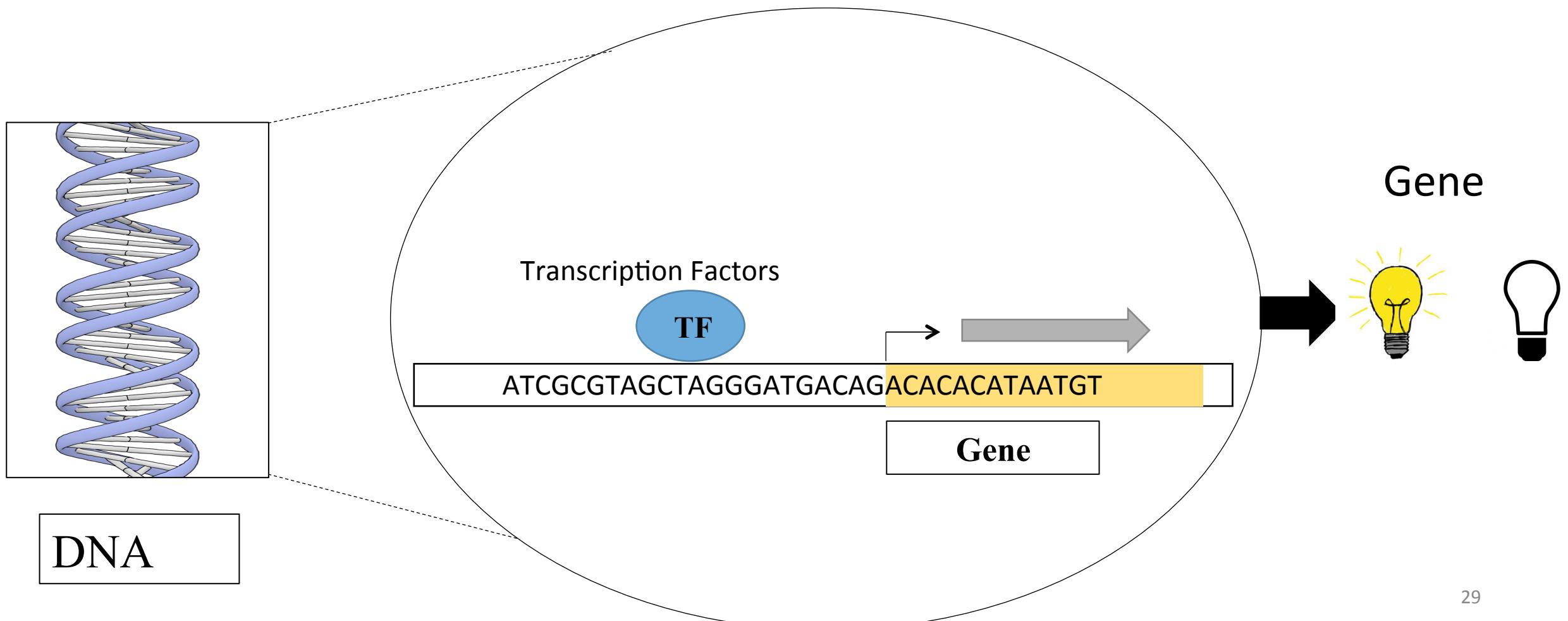
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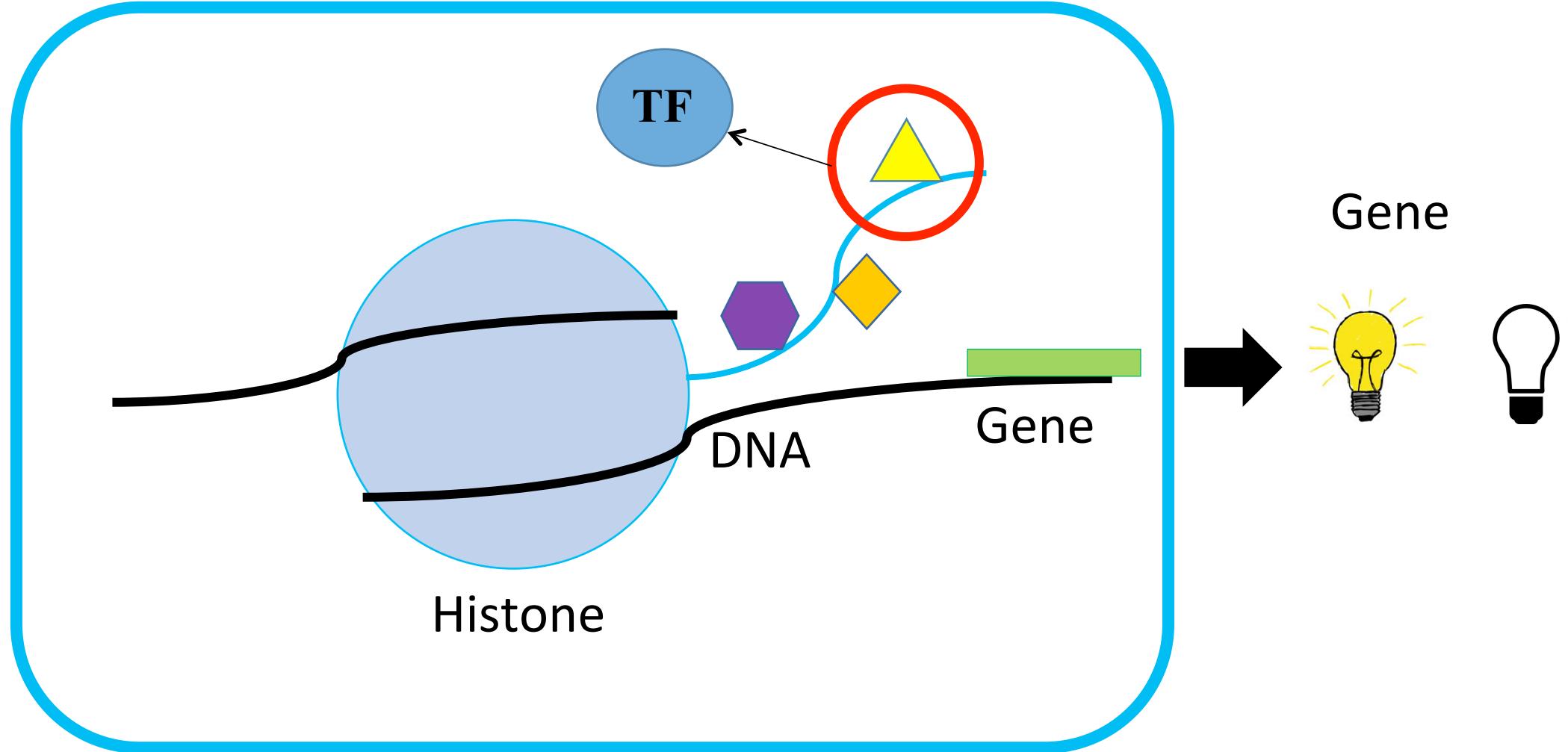
Chromatin



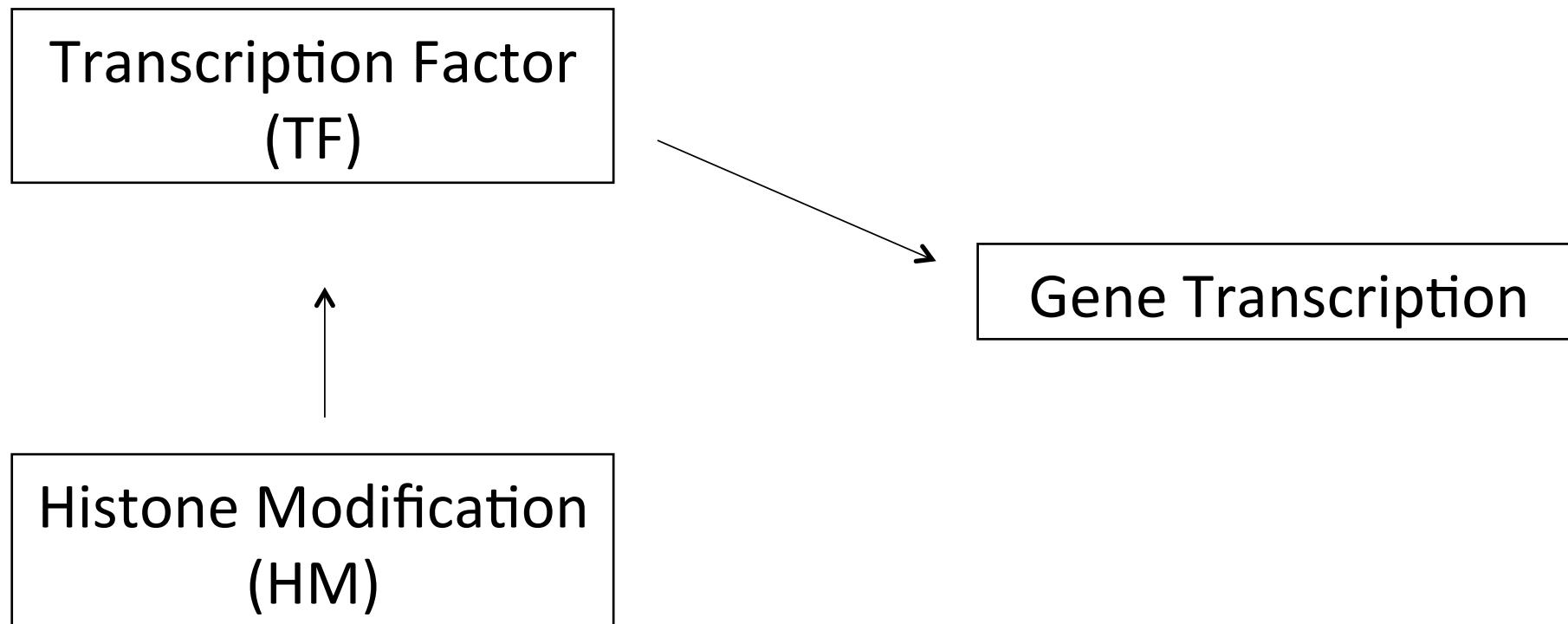
Transcription Factor Binding => Gene Transcription



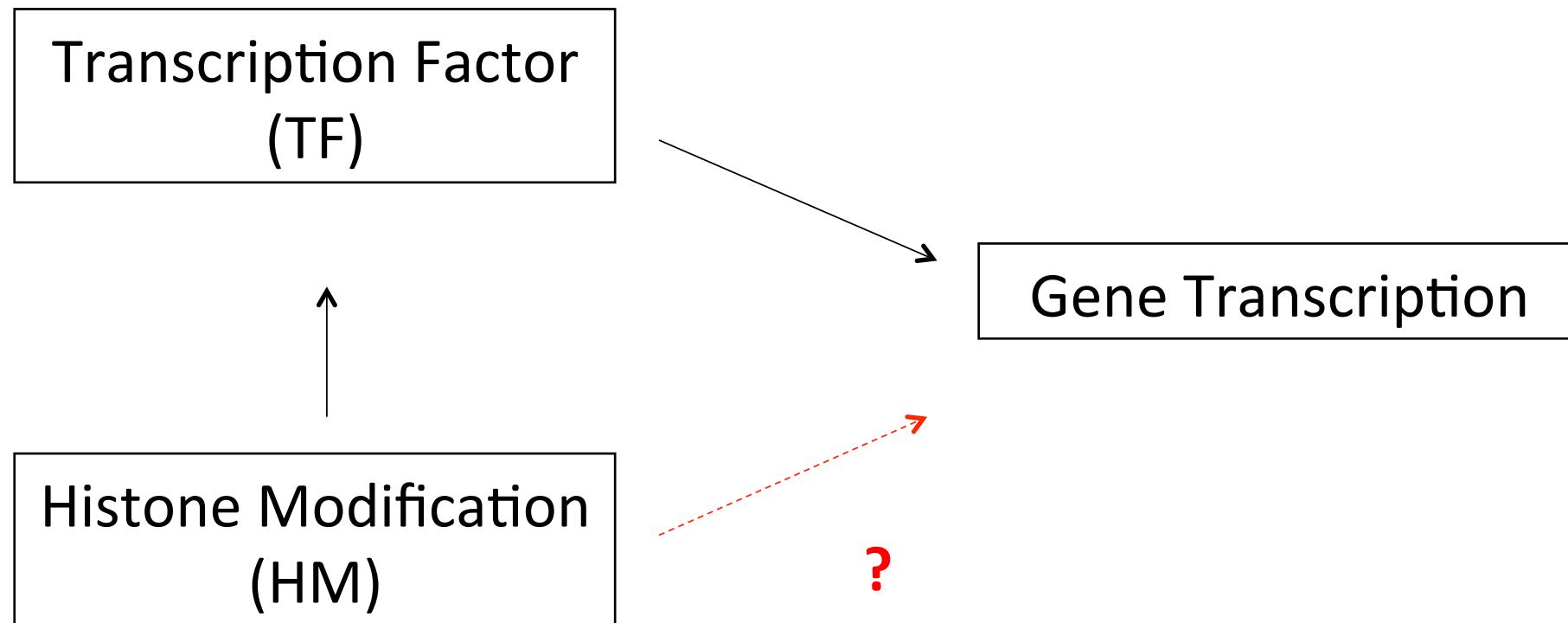
Histone Modifications (HM)



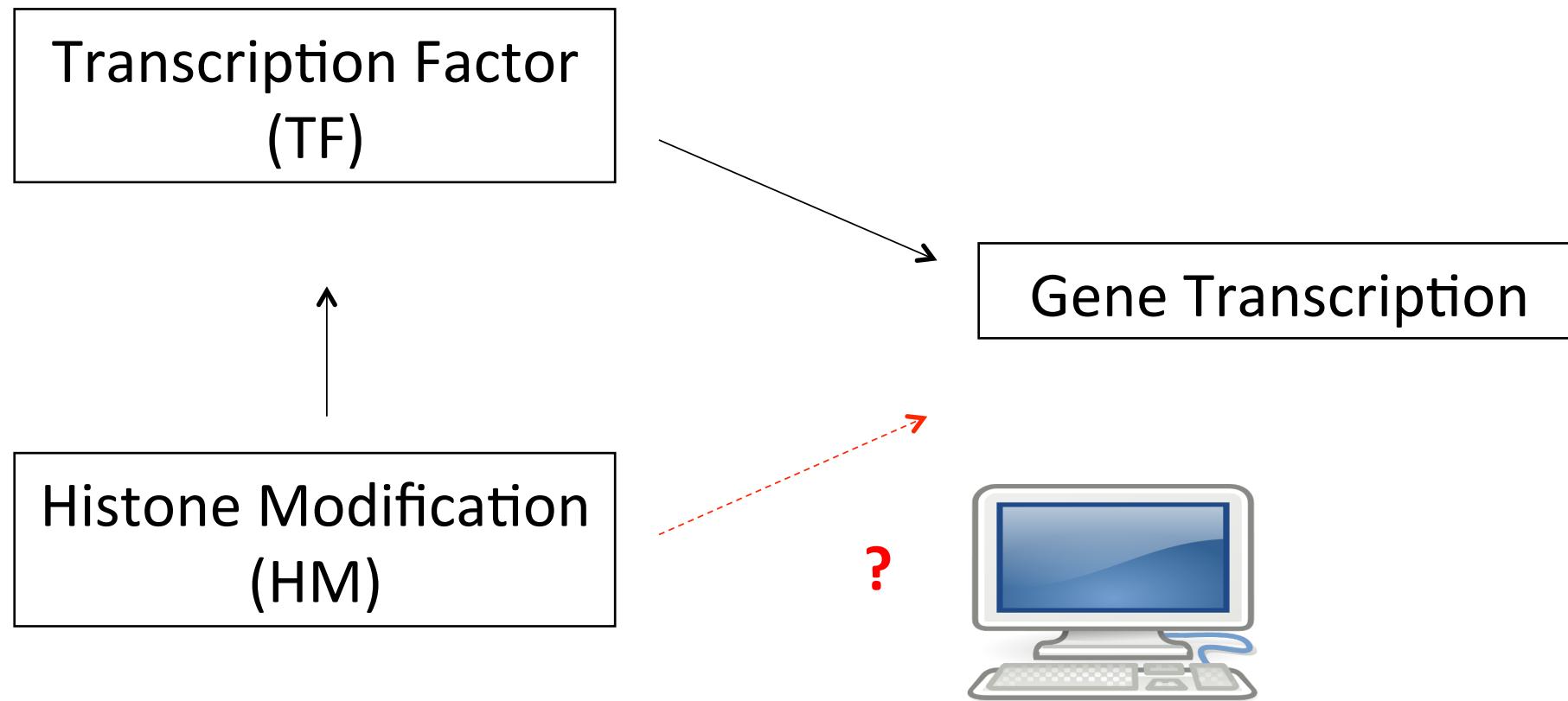
Histone Modification and Gene Transcription



Histone Modification and Gene Transcription



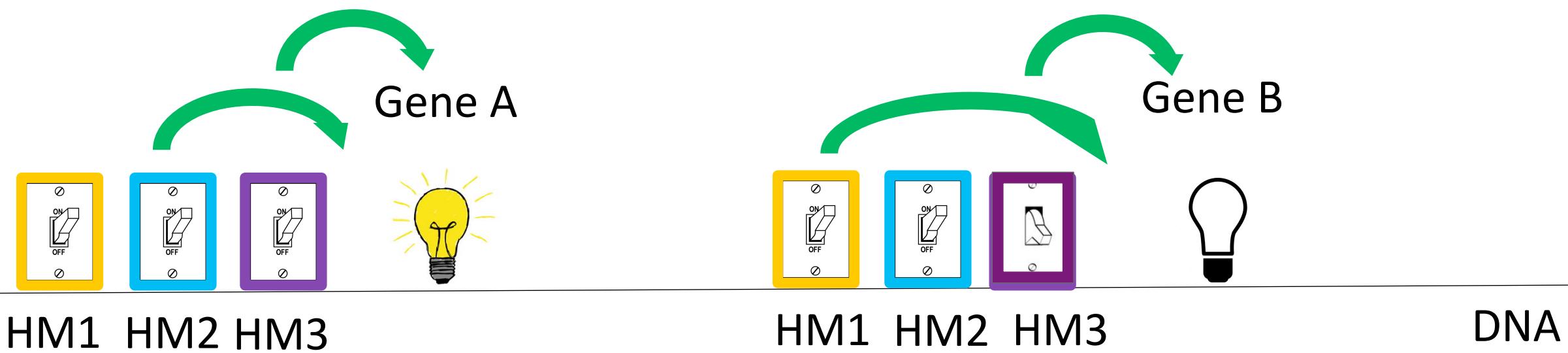
Histone Modification and Gene Transcription



Why Studying [HM => Gene Expression] ?

- Epigenomics:
 - Study of chemical changes in DNA and histones (without altering DNA sequence)
 - Inheritable and involved in regulating gene expression, development, tissue differentiation and suppression ...
- Modification in DNA/histones (changes in chromatin structure and function)
 - => influence how easily DNA can be accessed by TF
- Epigenome is dynamic
 - Can be altered by environmental conditions
 - Unlike genetic mutations, chromatin changes such as histone modifications are potentially reversible => Epigenome Drug for Cancer Cells?

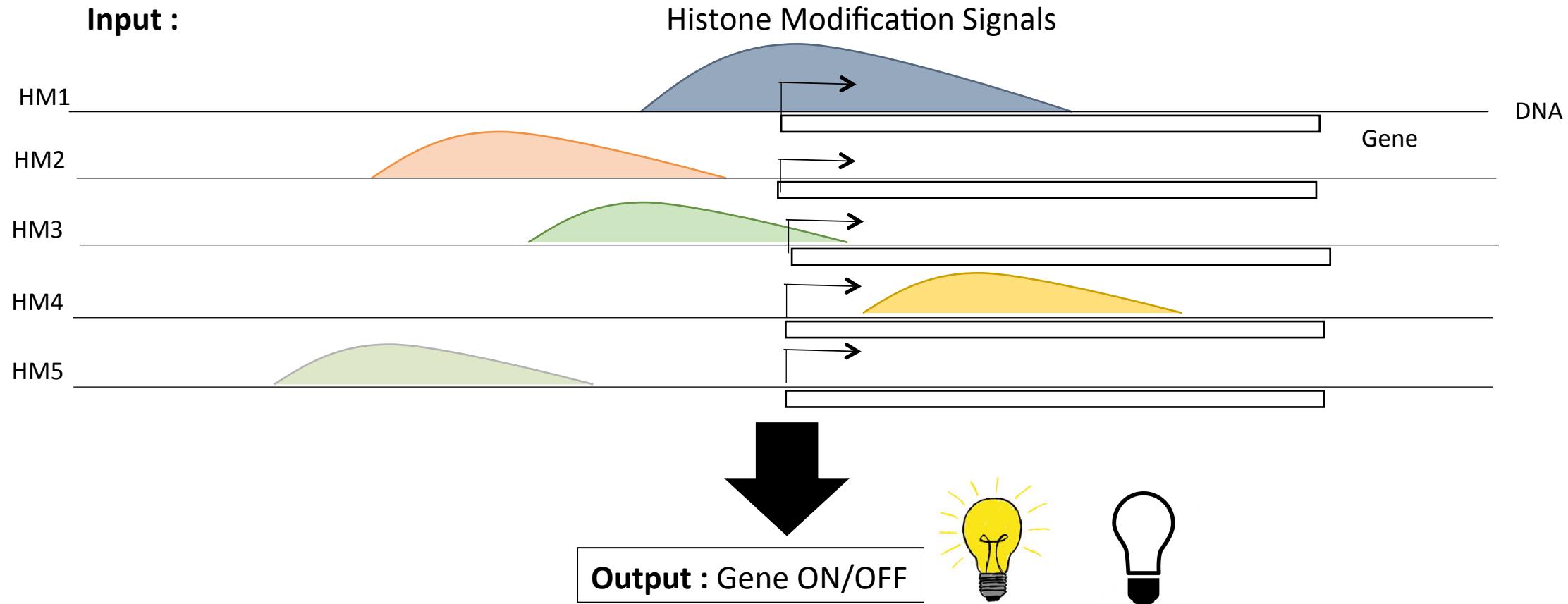
Study what HMs affect which genes in what cells?



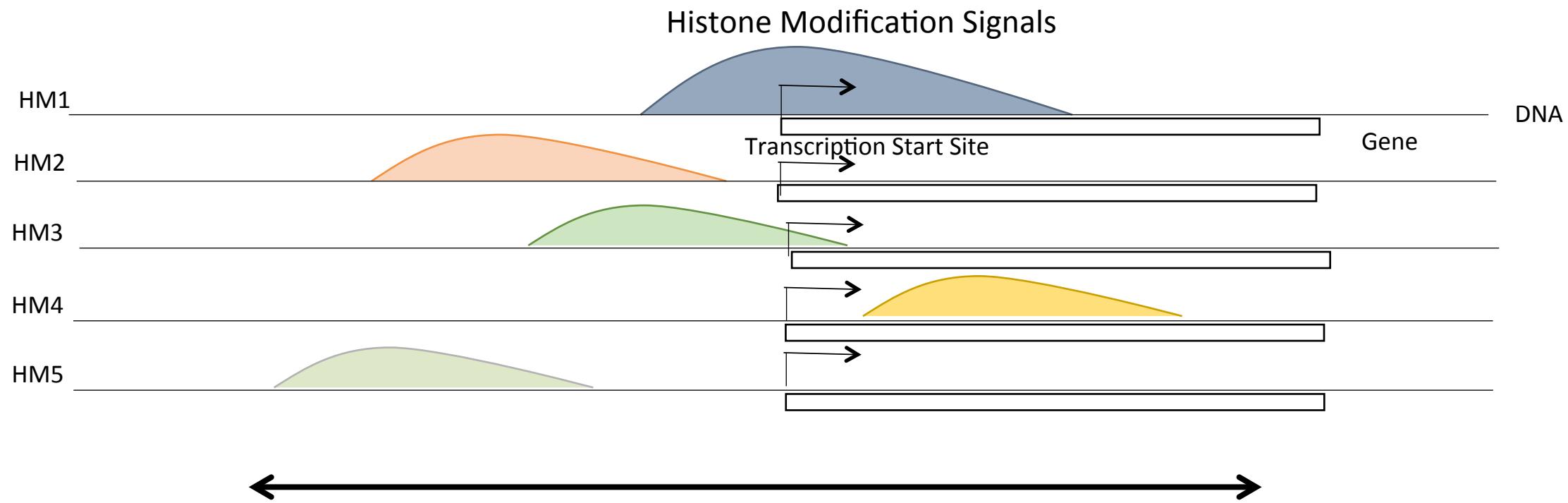
Task Formulation

Prediction Task

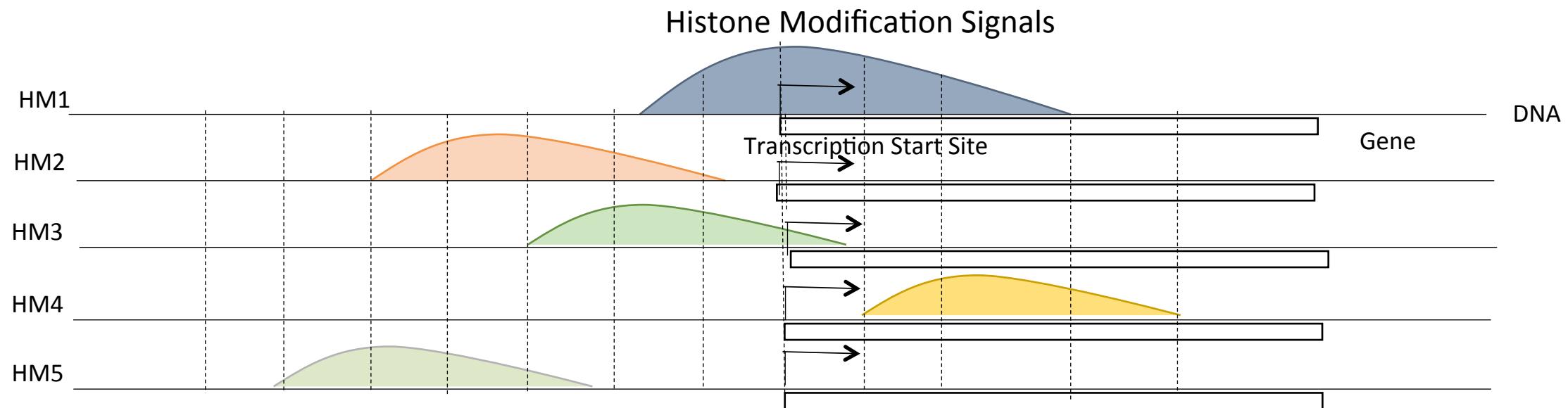
Input :



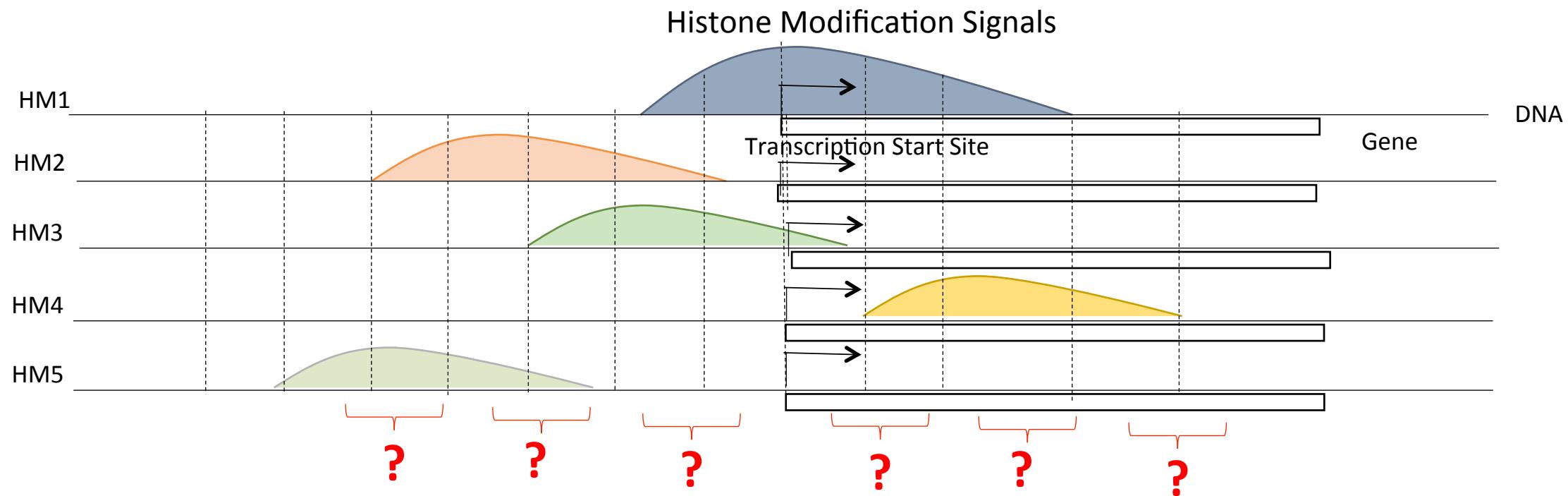
Input



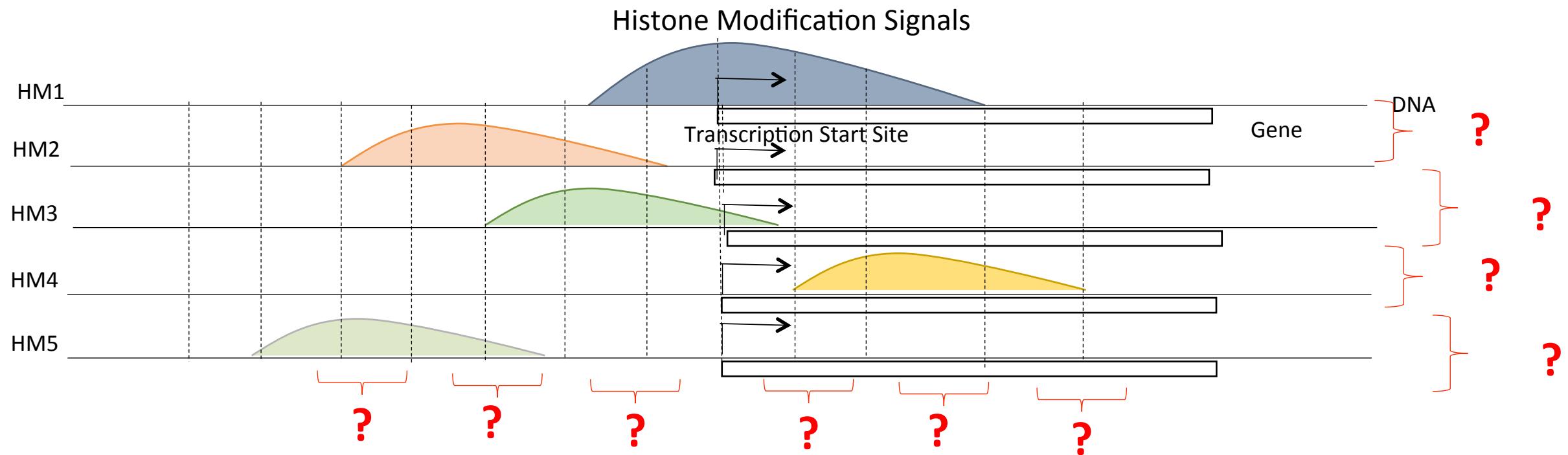
Input



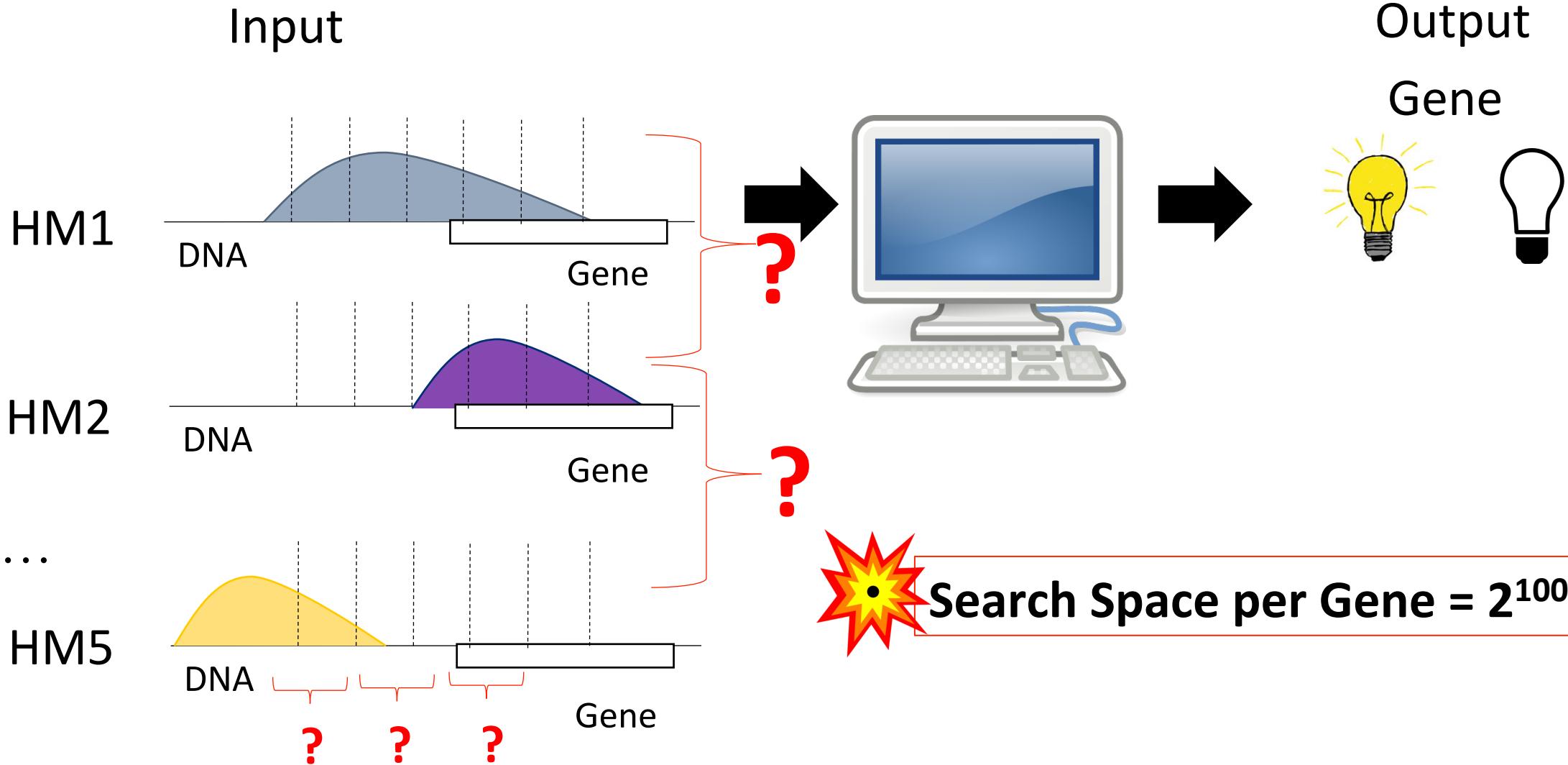
Challenge



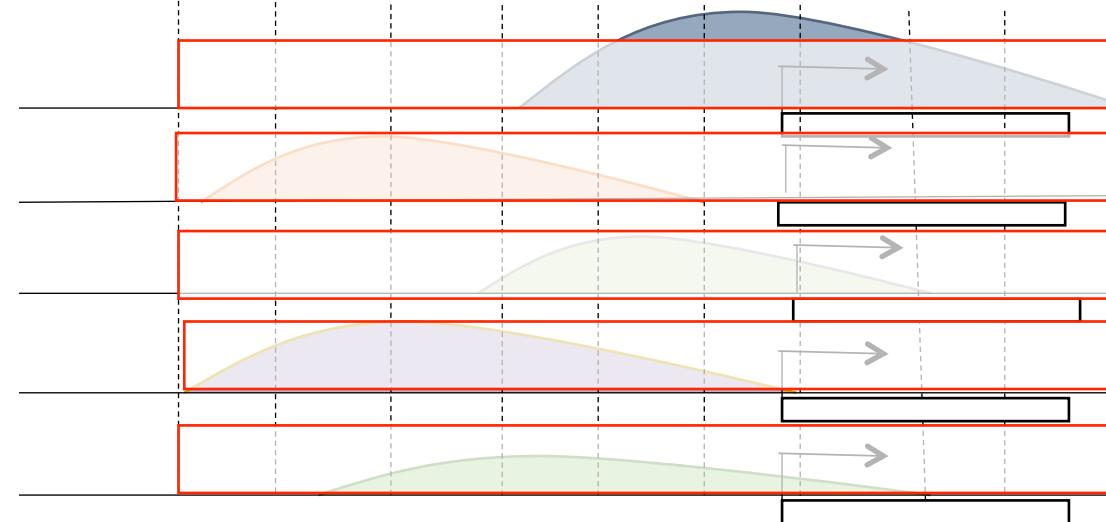
Challenge



Computational Challenge



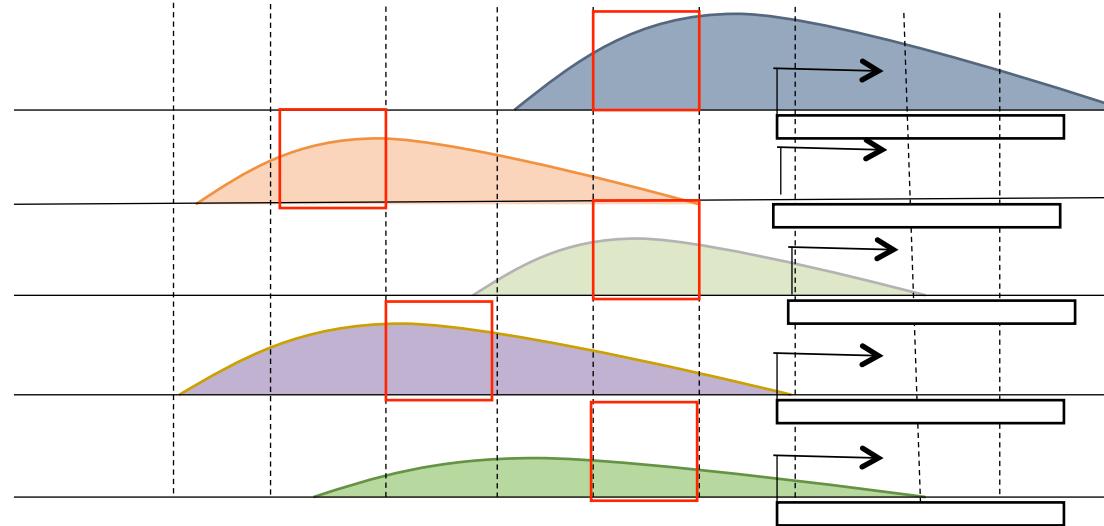
Related Work



**Linear Regression,
SVM,
Random Forest**

Gene ON/OFF

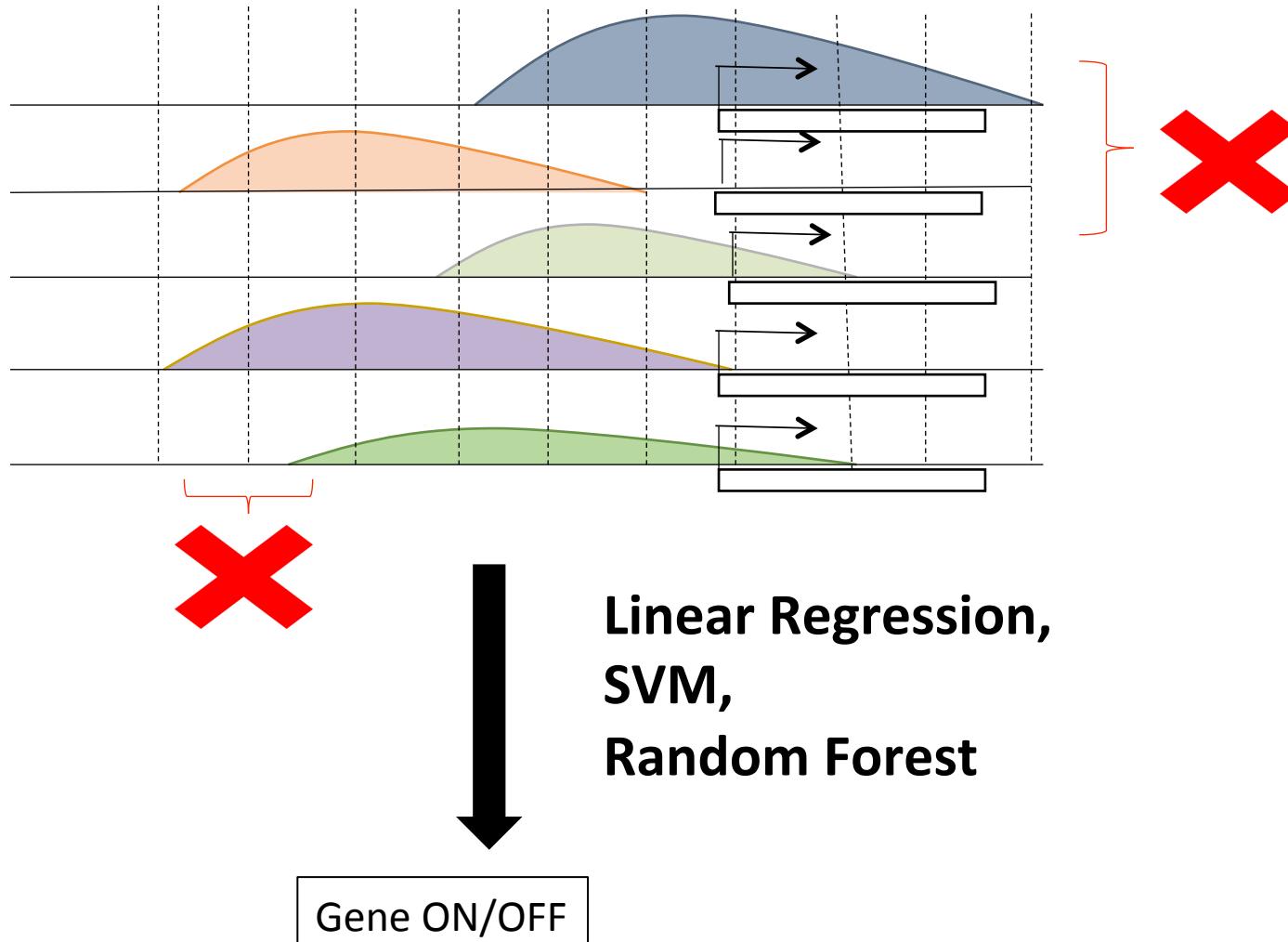
Related Work



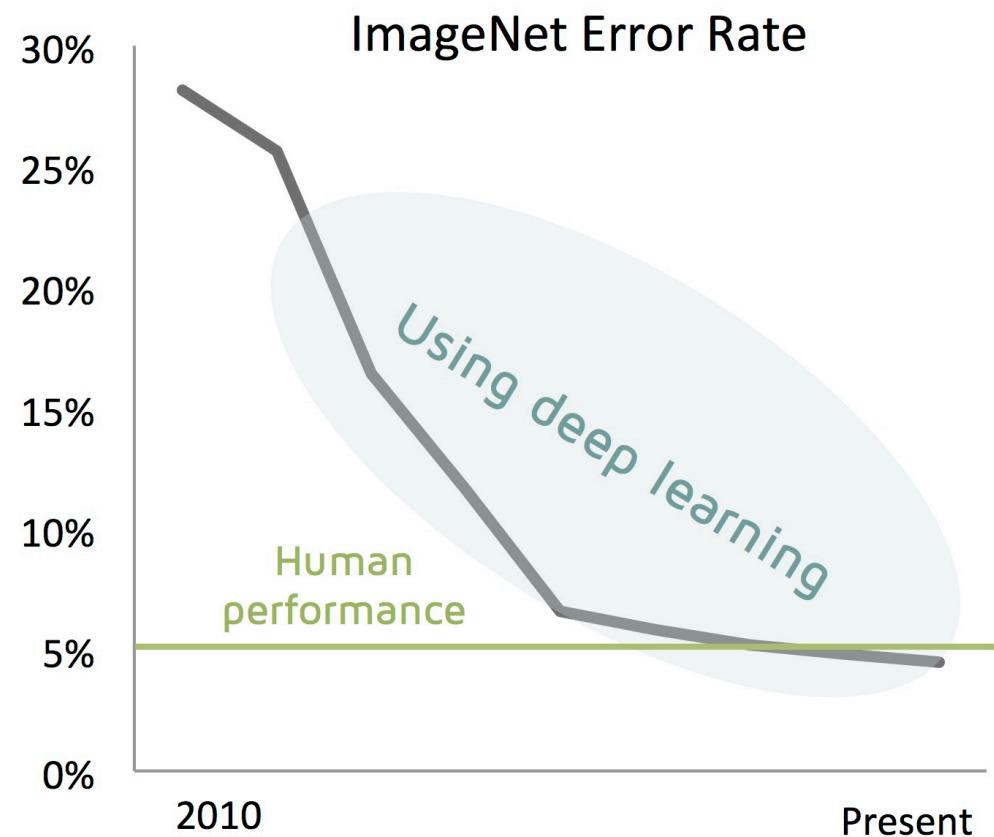
**Linear Regression,
SVM,
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Gene ON/OFF

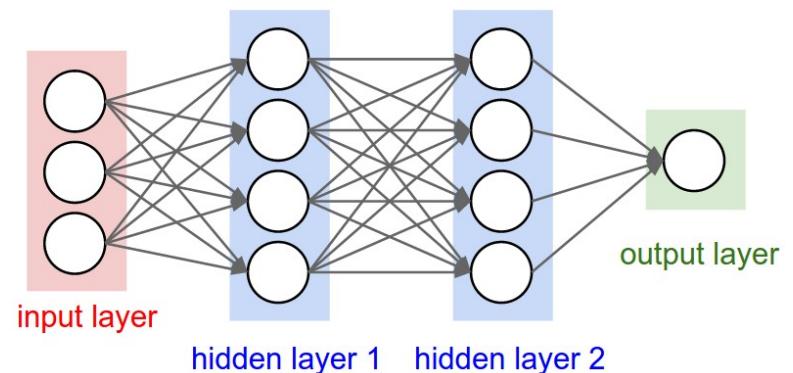
Drawback of Related Works



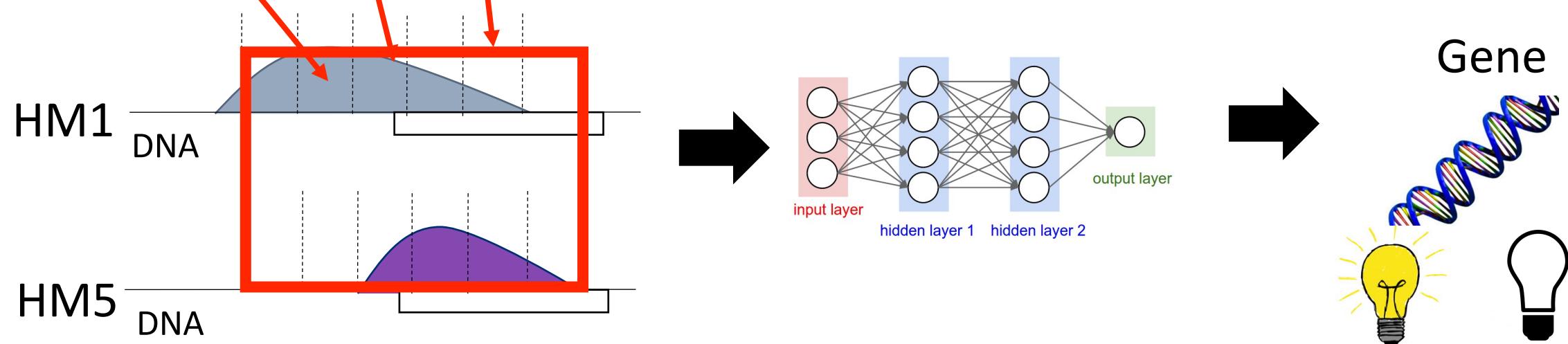
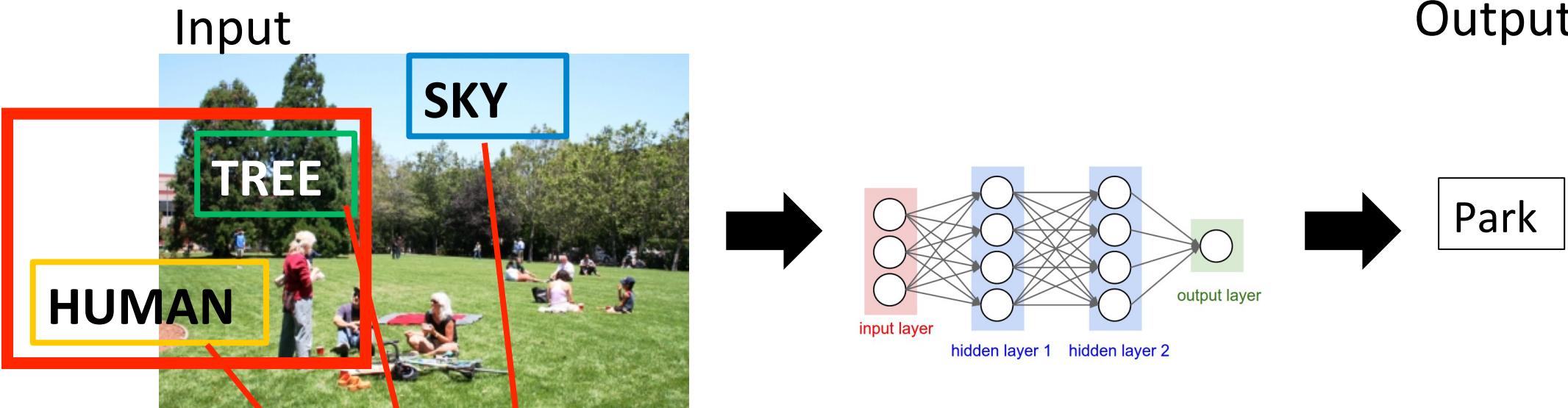
Deep Learning to Rescue:

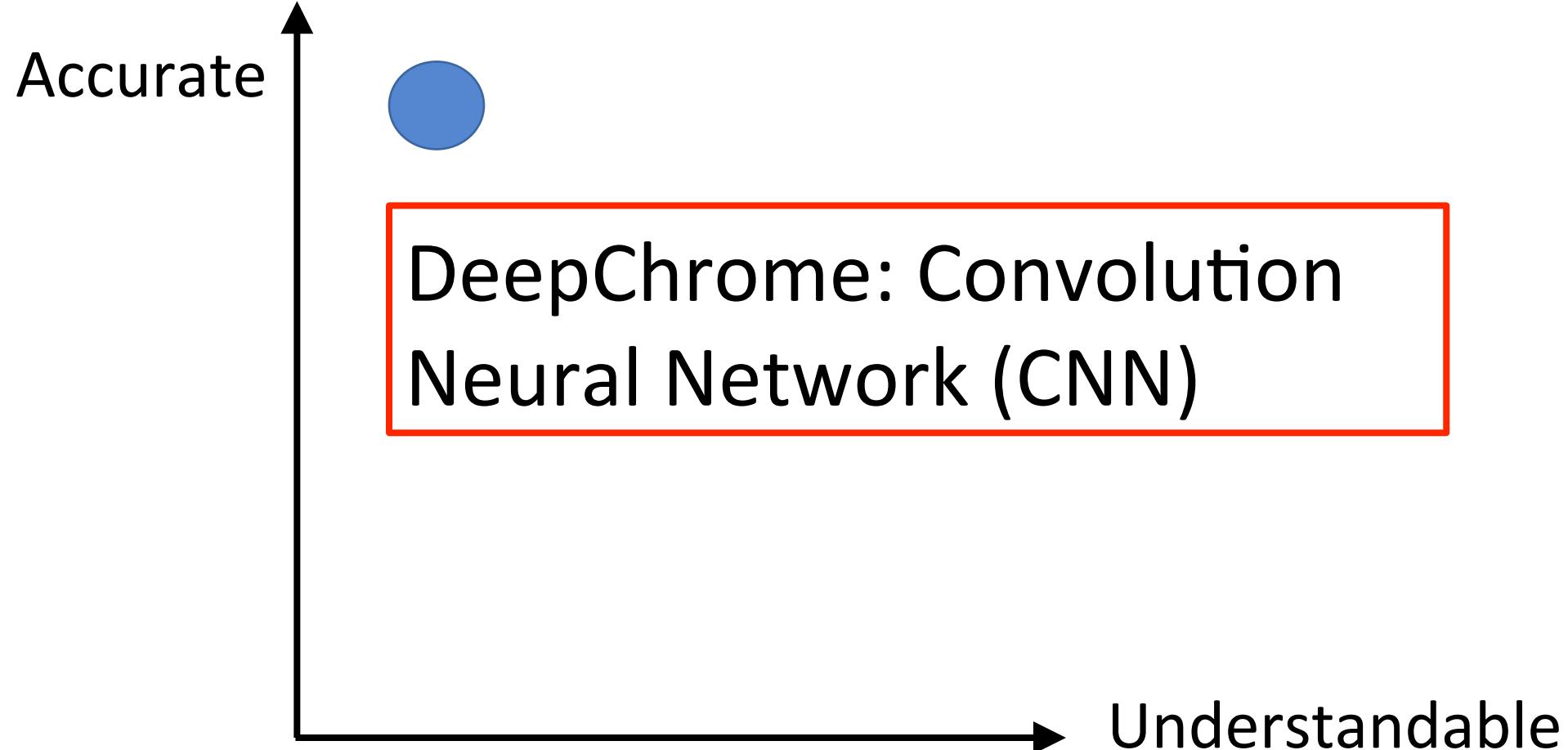


Deep Neural Network (DNN)

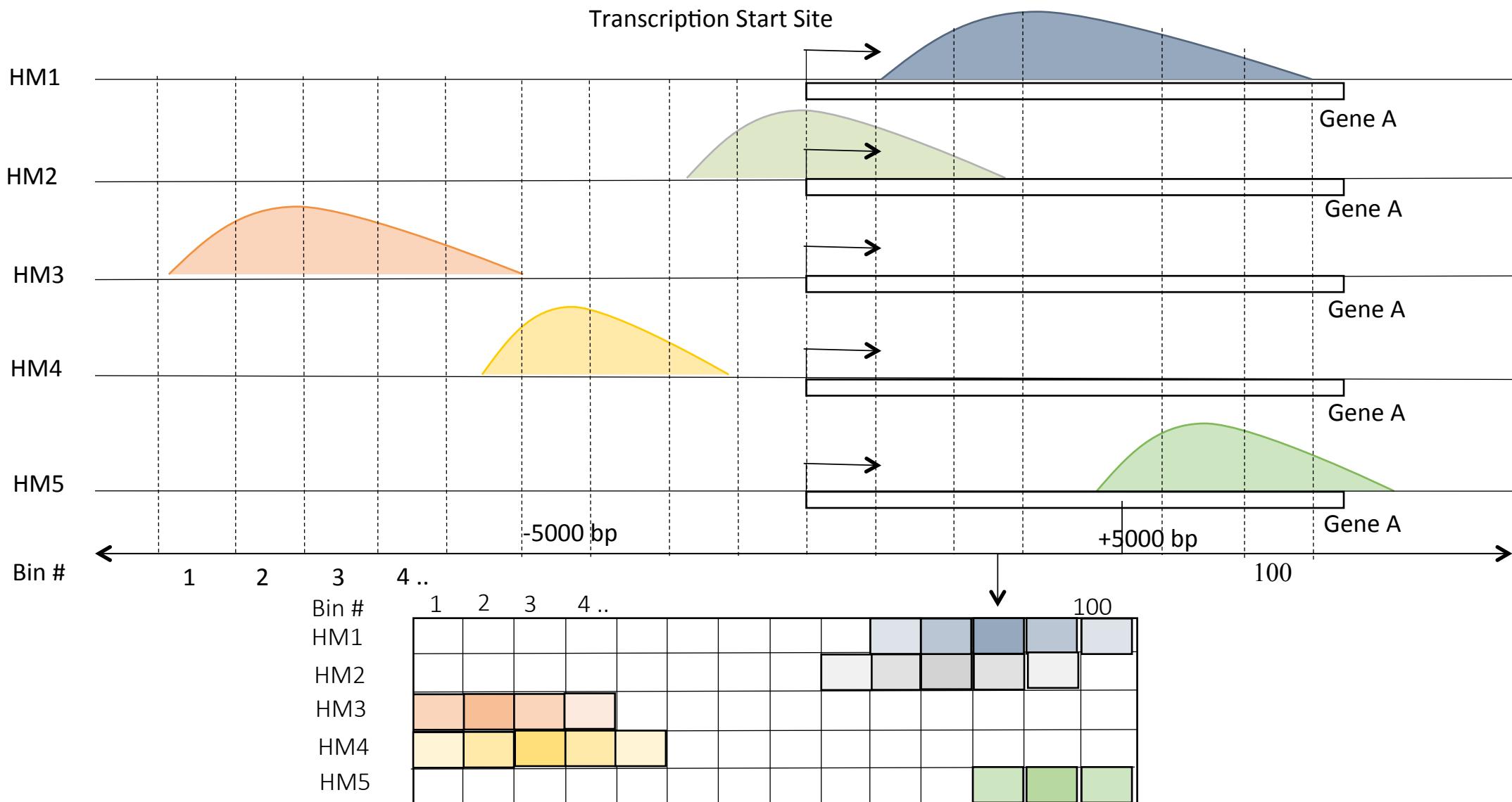


Deep Learning to Rescue:

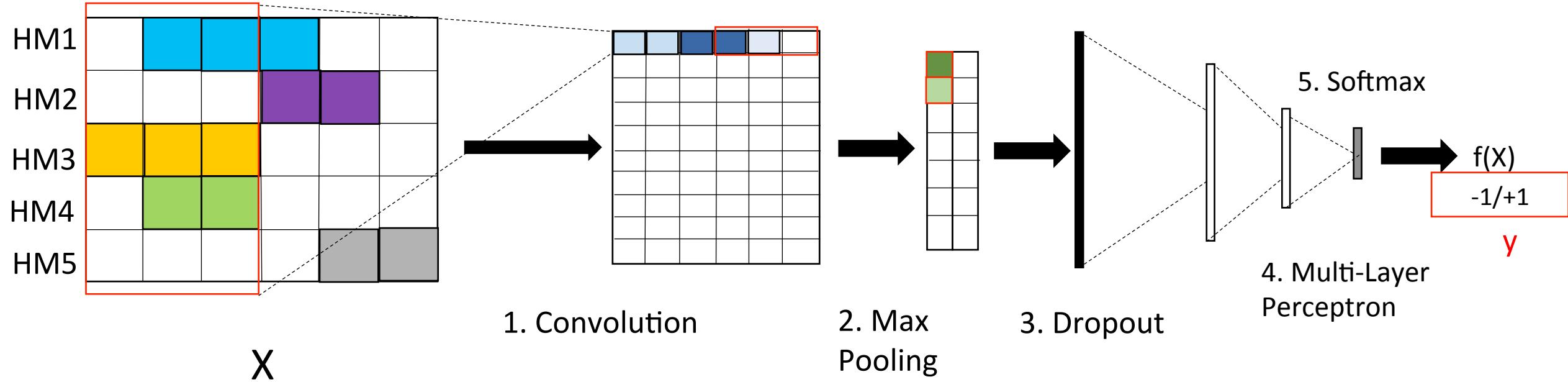




Data

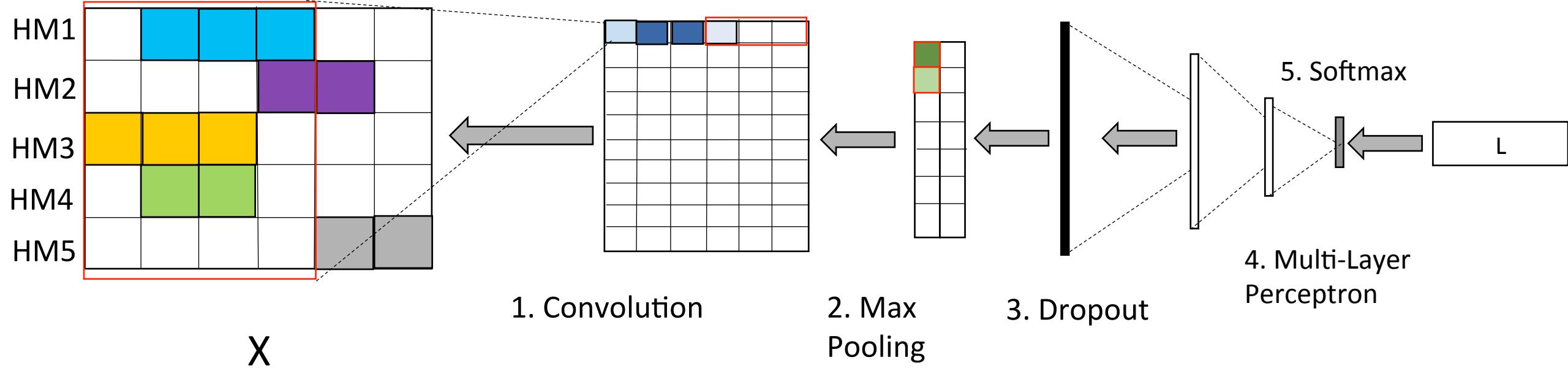


DeepChrome-Convolutional Neural Network (CNN)



$$L = \sum_{n=1}^{N_{\text{samp}}} \text{loss}(f(X^{(n)}), y^{(n)})$$

DeepChrome-Convolutional Neural Network (CNN)



Back-propagation:

$$\Theta \leftarrow \Theta - \eta \frac{\partial L}{\partial \Theta}$$

Experimental Setup

- **Cell-types:** 56
- **Input (HM):** ChIP-Seq Maps (REMC)
- **Output (Gene Expression):** Discretized RNA-Seq (REMC)

Histone Mark	Functional Category
H3K27me3	Repressor
H3K36me3	Promoter
H3K4me1	Distal Promoter
H3K4me3	Promoter
H3K9me3	Repressor

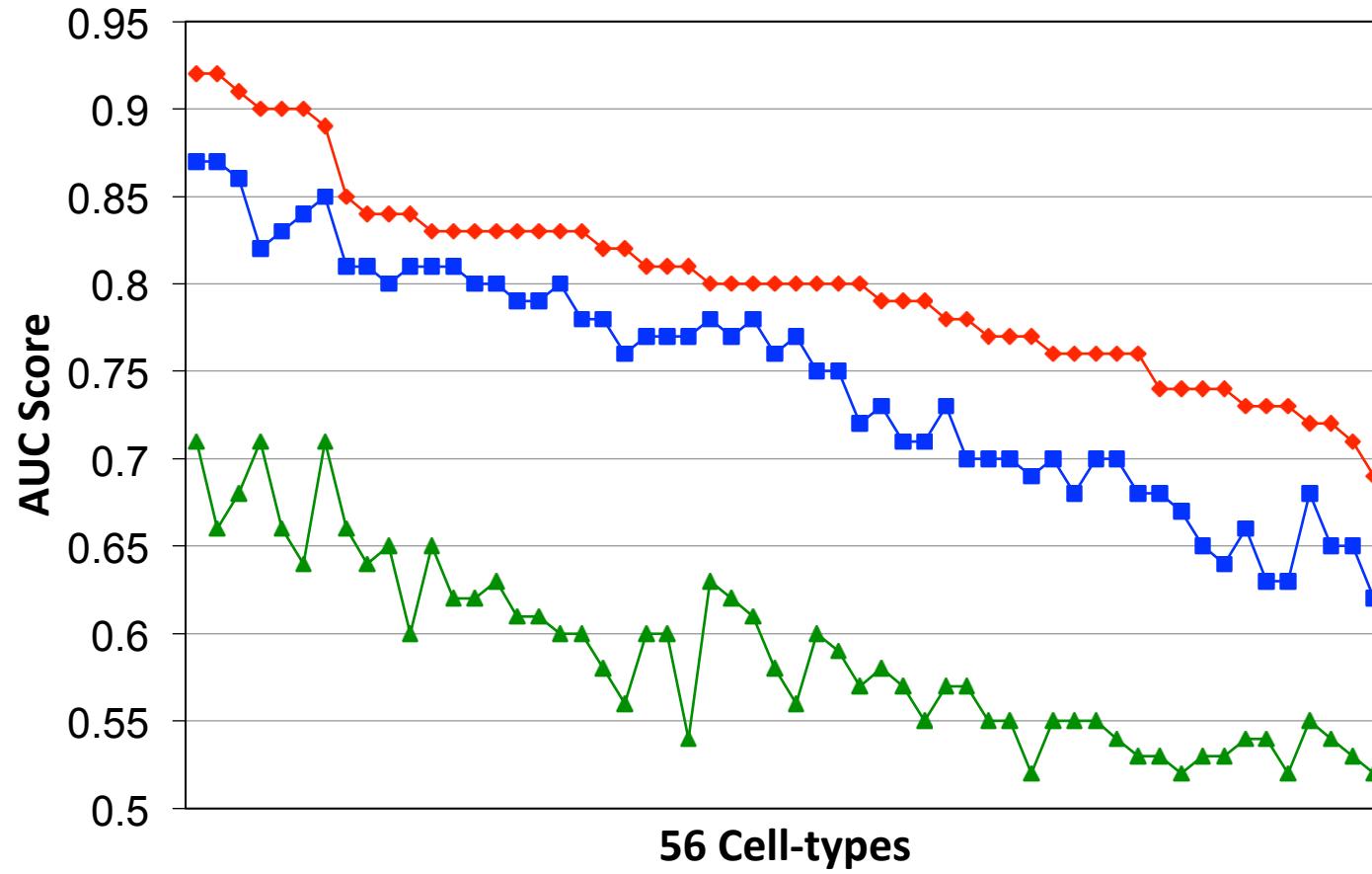
- **Baselines:** Support Vector Classifier (SVC) and Random Forest Classifier (RFC)

Training Set
6601 Genes

Validation Set
6601 Genes

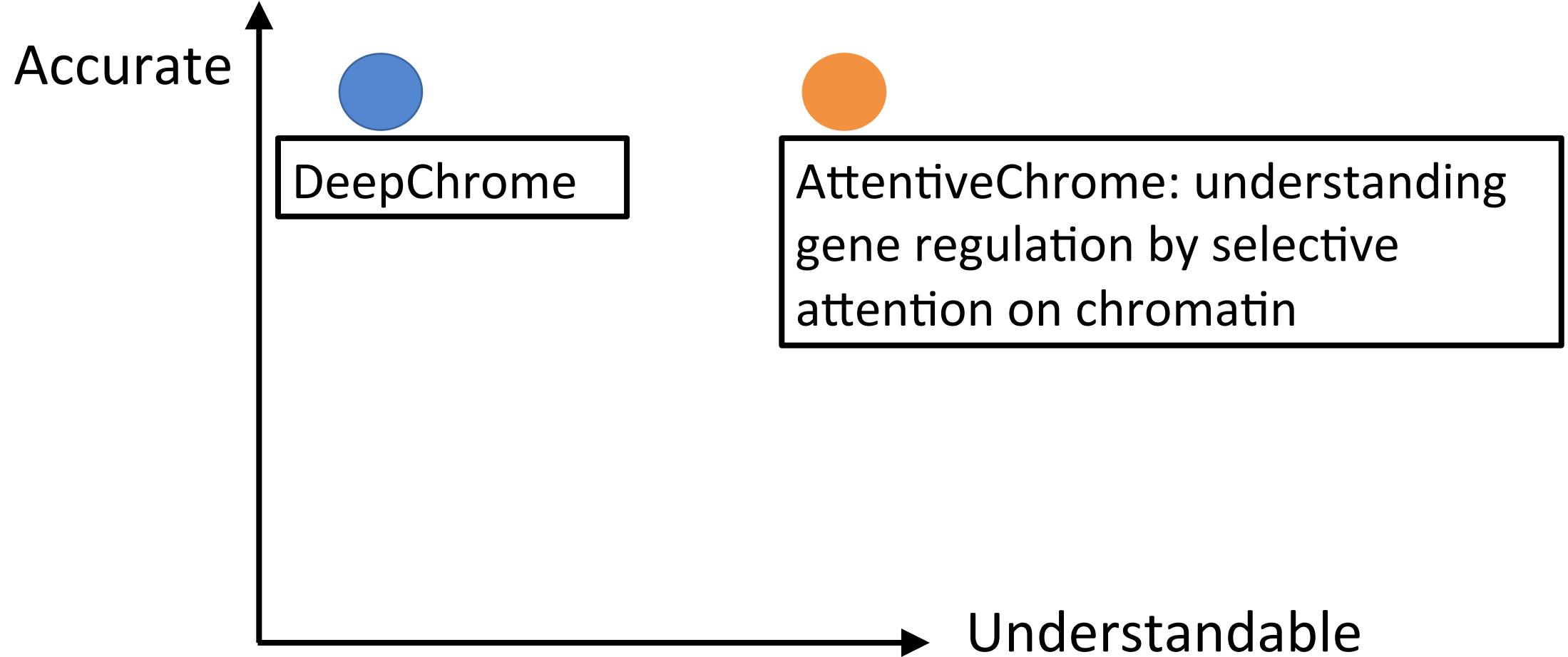
Test Set
6600 Genes

Results: Accuracy



- First deep learning implementation for gene expression prediction.
- But hard to interpret.

— DeepChrome — SVC — RFC



Goal: one DNN both accurate and interpretable

Interpretability by Attention

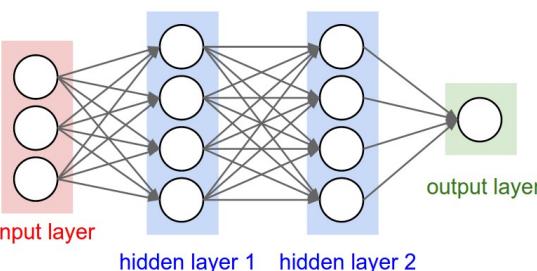
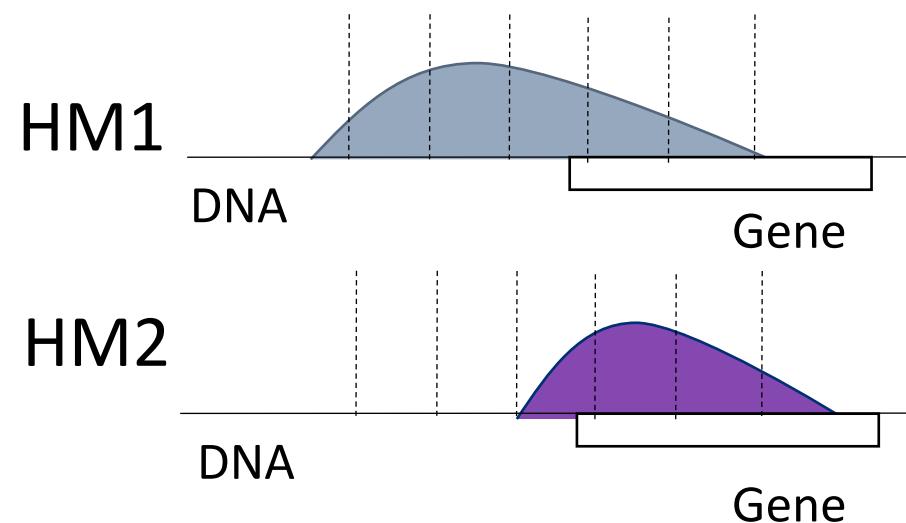
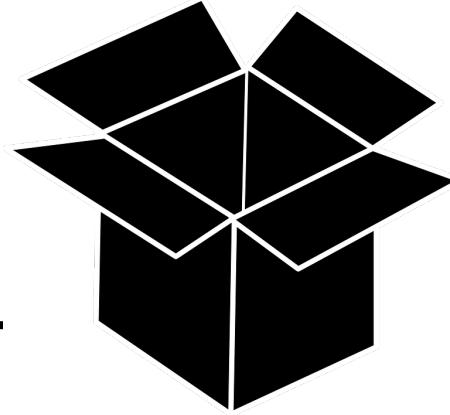
Input



Output

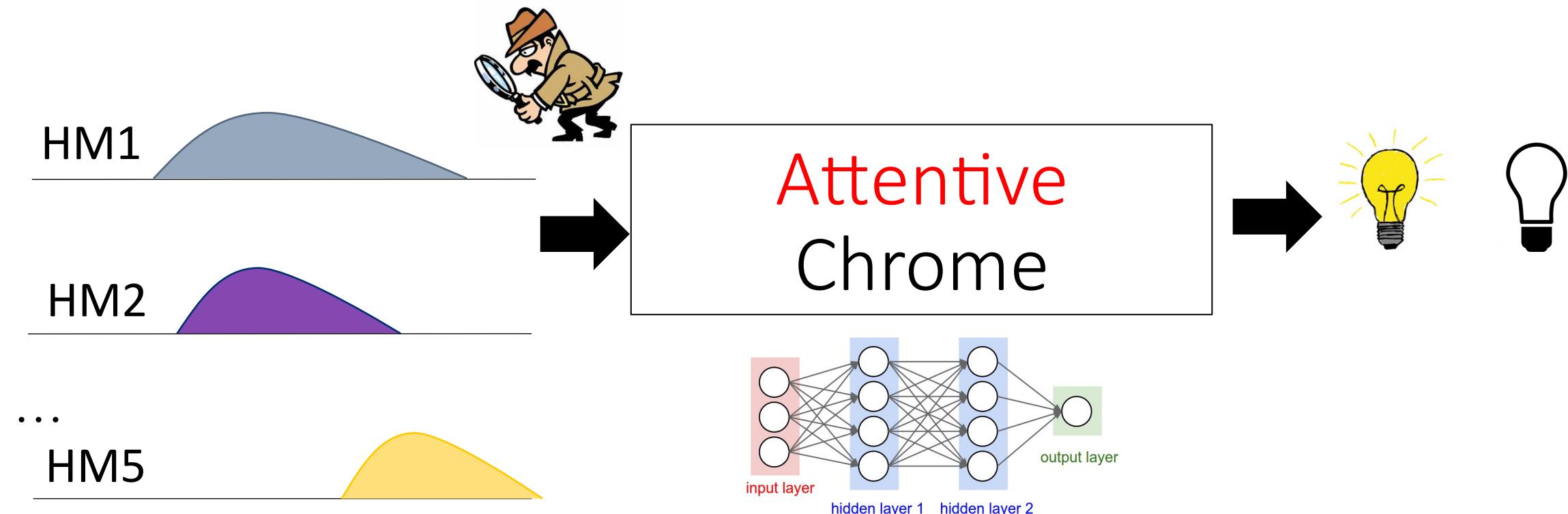
Park

Attention
Mechanism

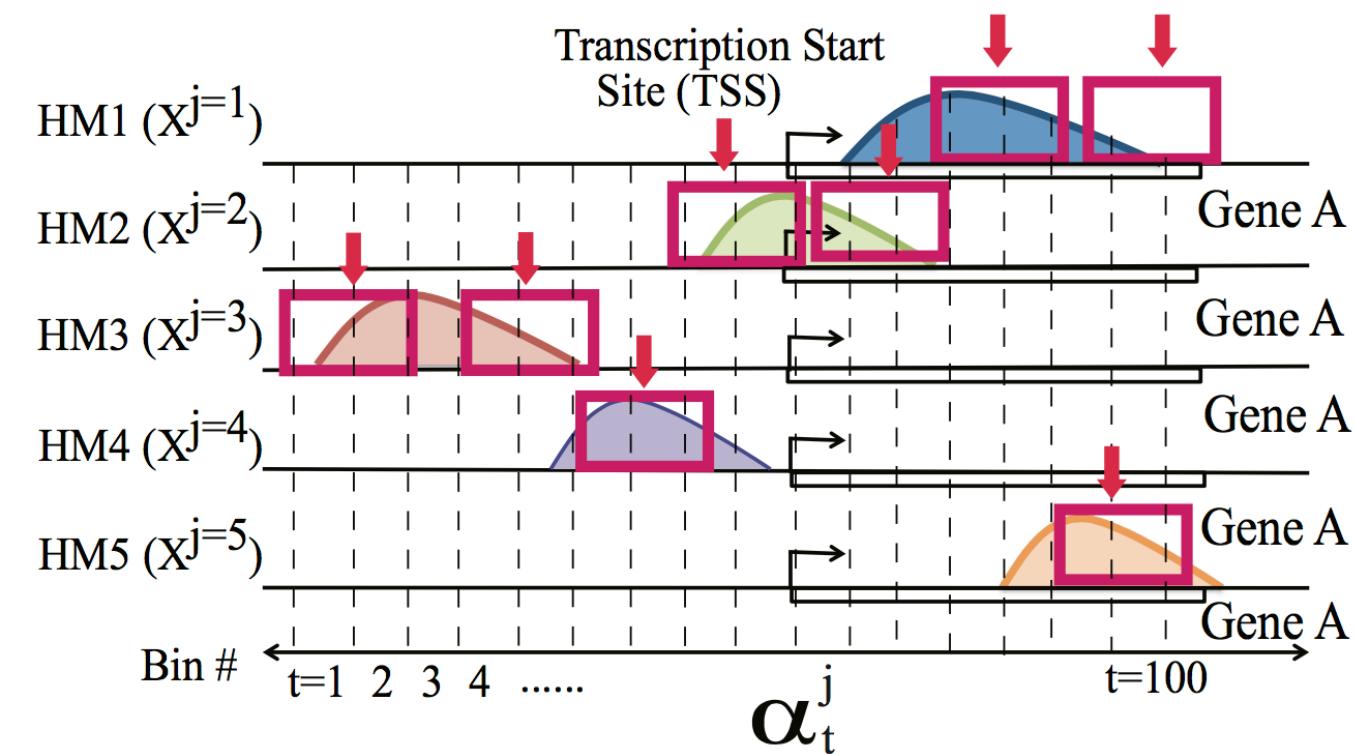


Gene

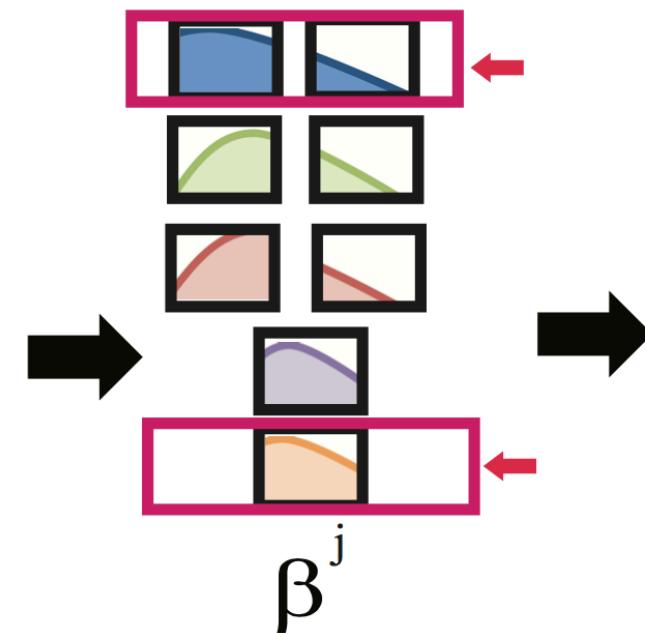




Two Levels of Attention



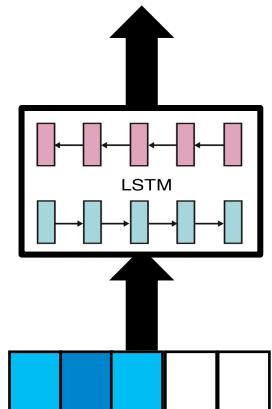
Bin-level Attention



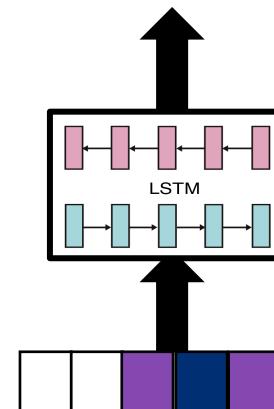
HM-level Attention

Classification

Input

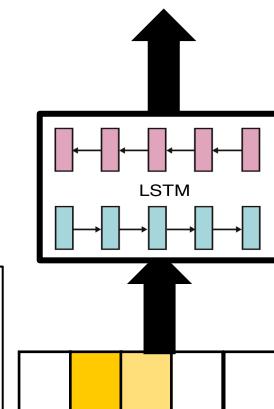


HM1



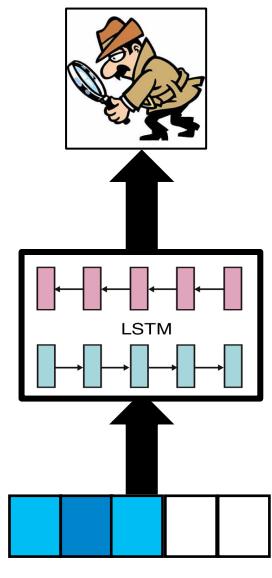
HM2

**LOCAL
LEVEL**

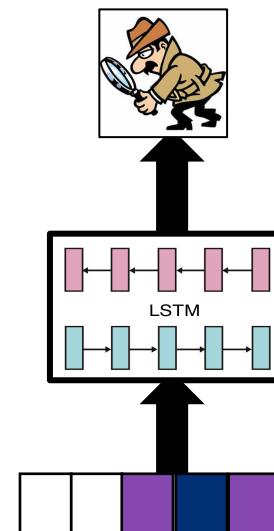


HM5

Input

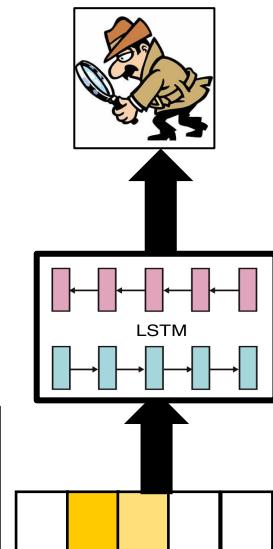


HM1



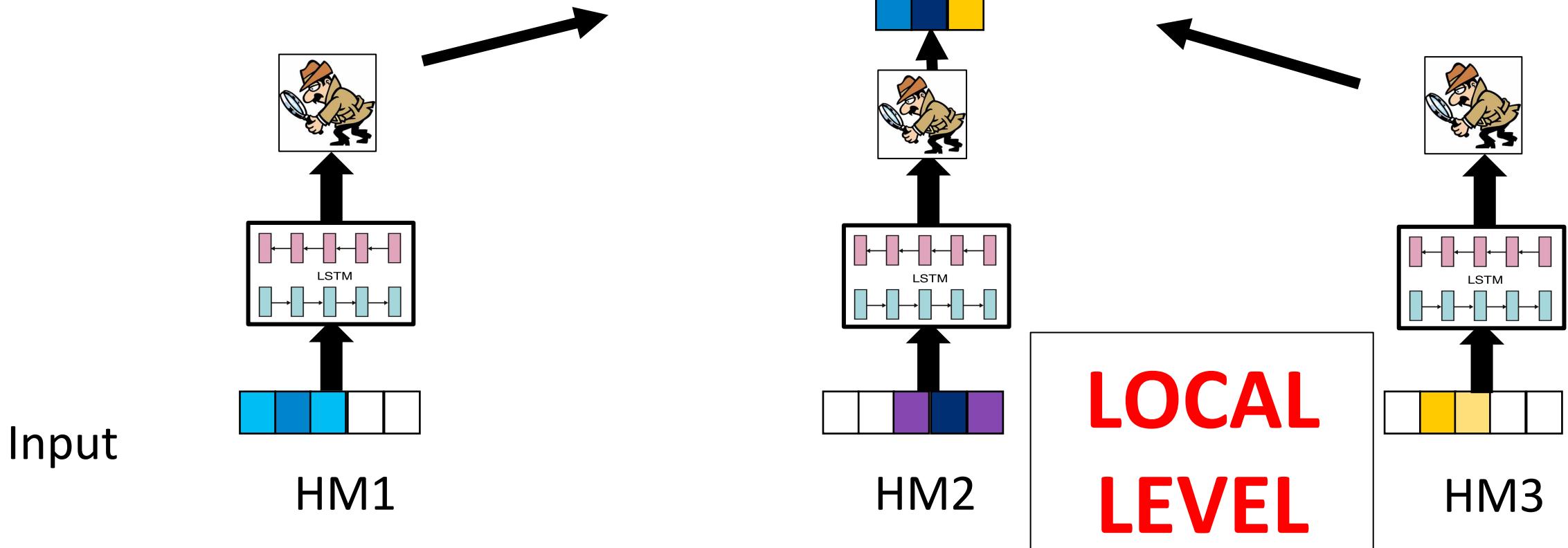
HM2

**LOCAL
LEVEL**

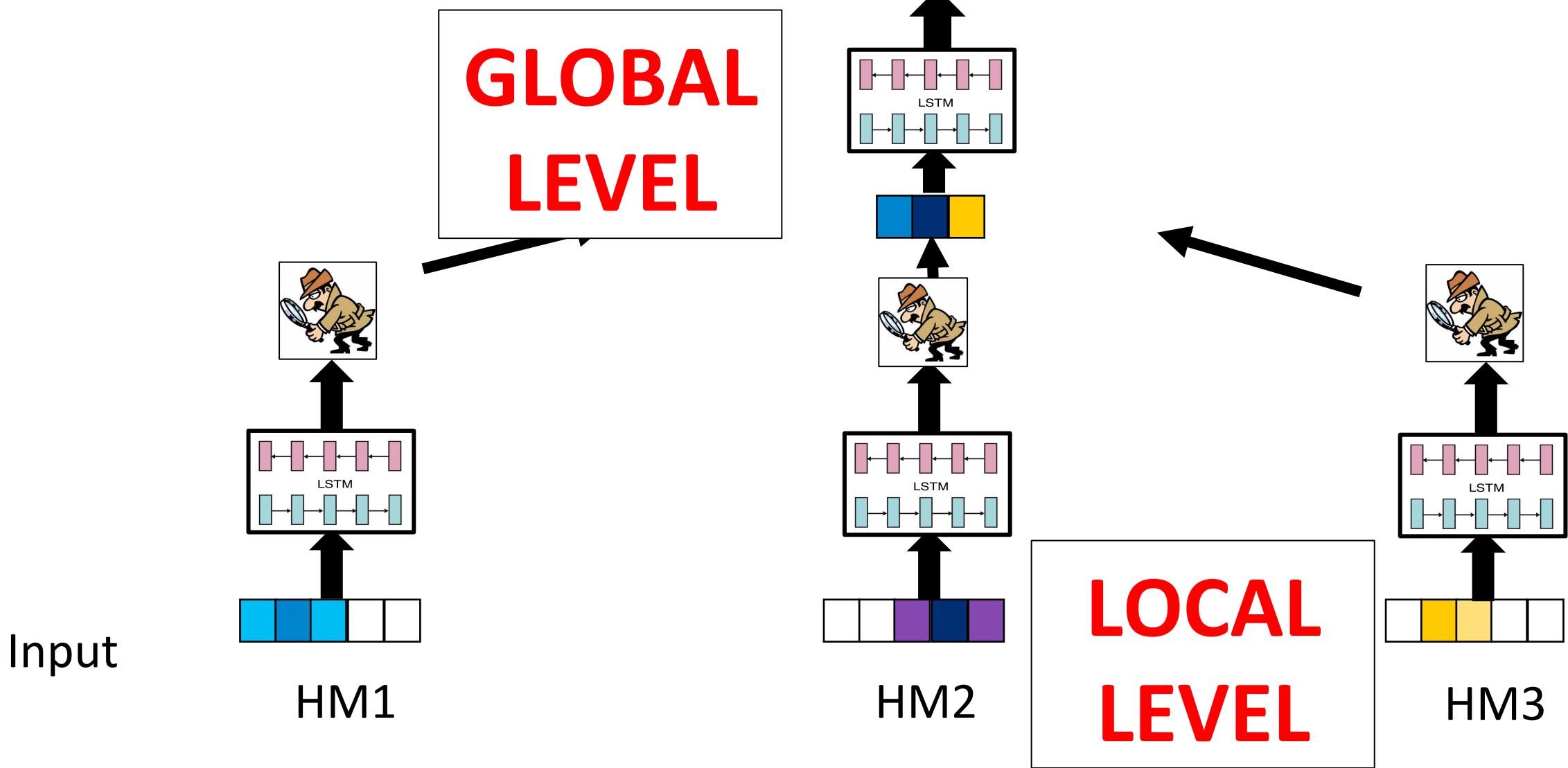


HM5

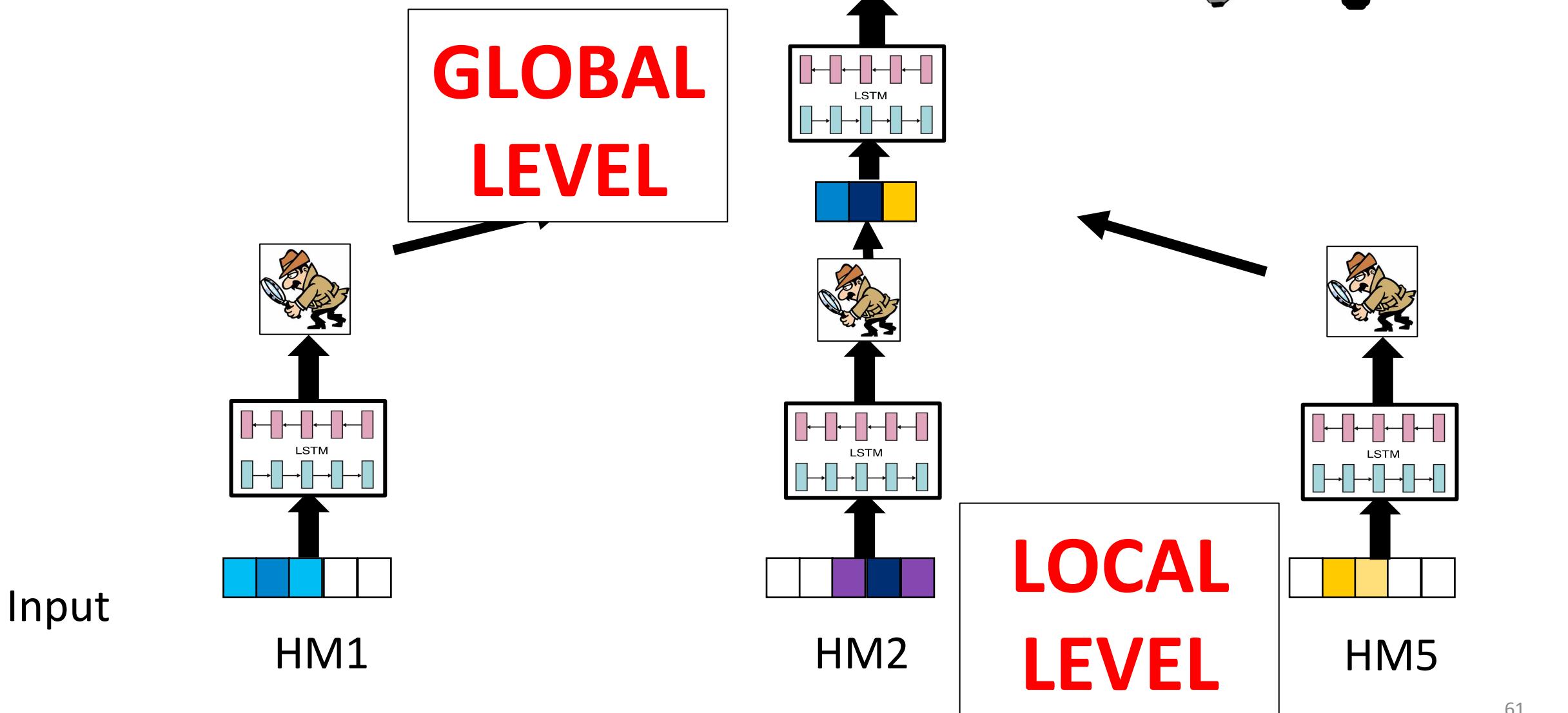
Overview



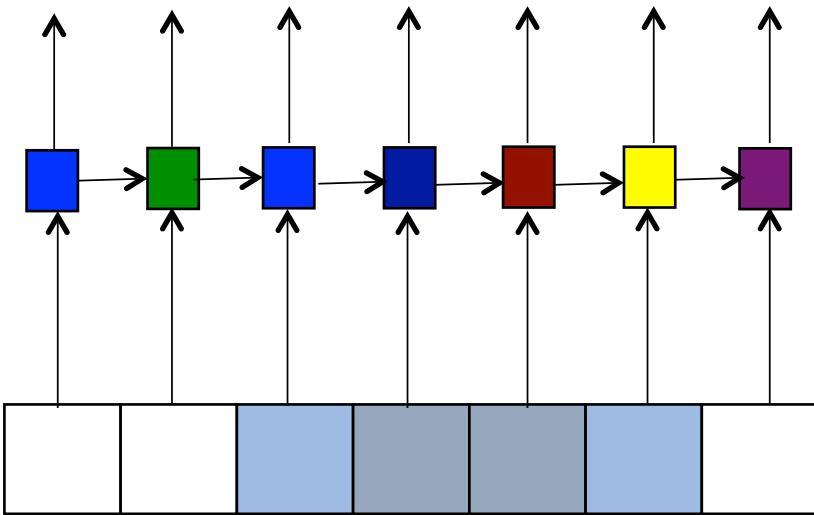
Overview



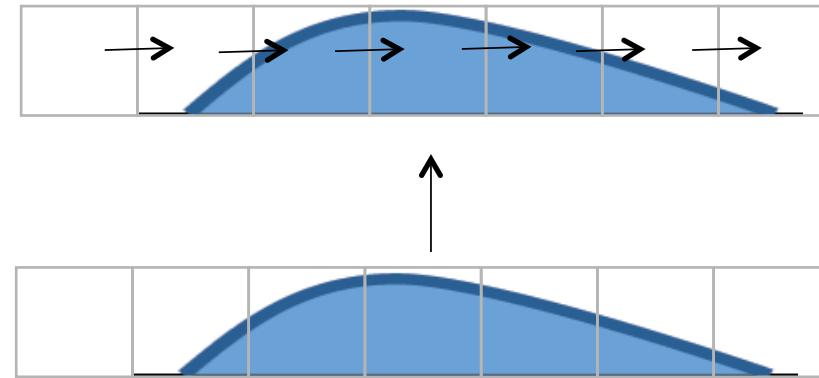
Overview



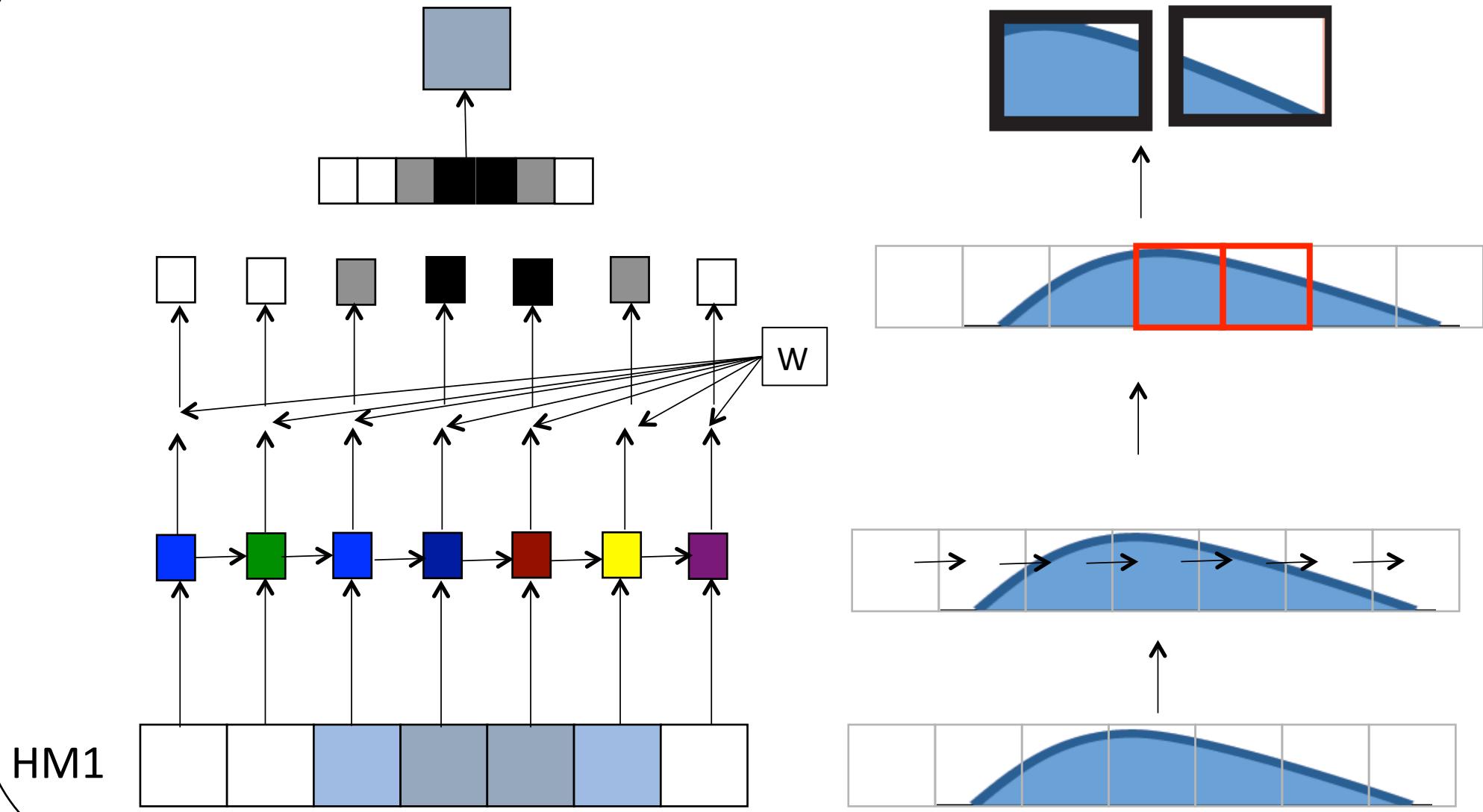
Recurrent Neural Network (RNN)



HM1



Attention Mechanism



Versus Baselines

Computational Study	Unified	Non-linear	Bin-Info	Representation Learning		Prediction	Feature Inter.	Interpretable
				Neighbor Bins	Whole Region			
Linear Regression ([14])	✗	✗	✗	✗	✓	✓	✗	✓
Support Vector Machine ([7])	✗	✓	Bin-specific	✗	✓	✓	✓	✗
Random Forest ([10])	✗	✓	Best-bin	✗	✓	✓	✗	✗
Rule Learning ([12])	✗	✓	✗	✗	✓	✗	✓	✓
DeepChrome-CNN [29]	✓	✓	Automatic	✓	✓	✓	✓	✗
AttentiveChrome	✓	✓	Automatic	✓	✓	✓	✓	✓

Experiments: Prediction Performance

- Same setup as DeepChrome
- AttentiveChrome is as accurate as (slightly better than) DeepChrome

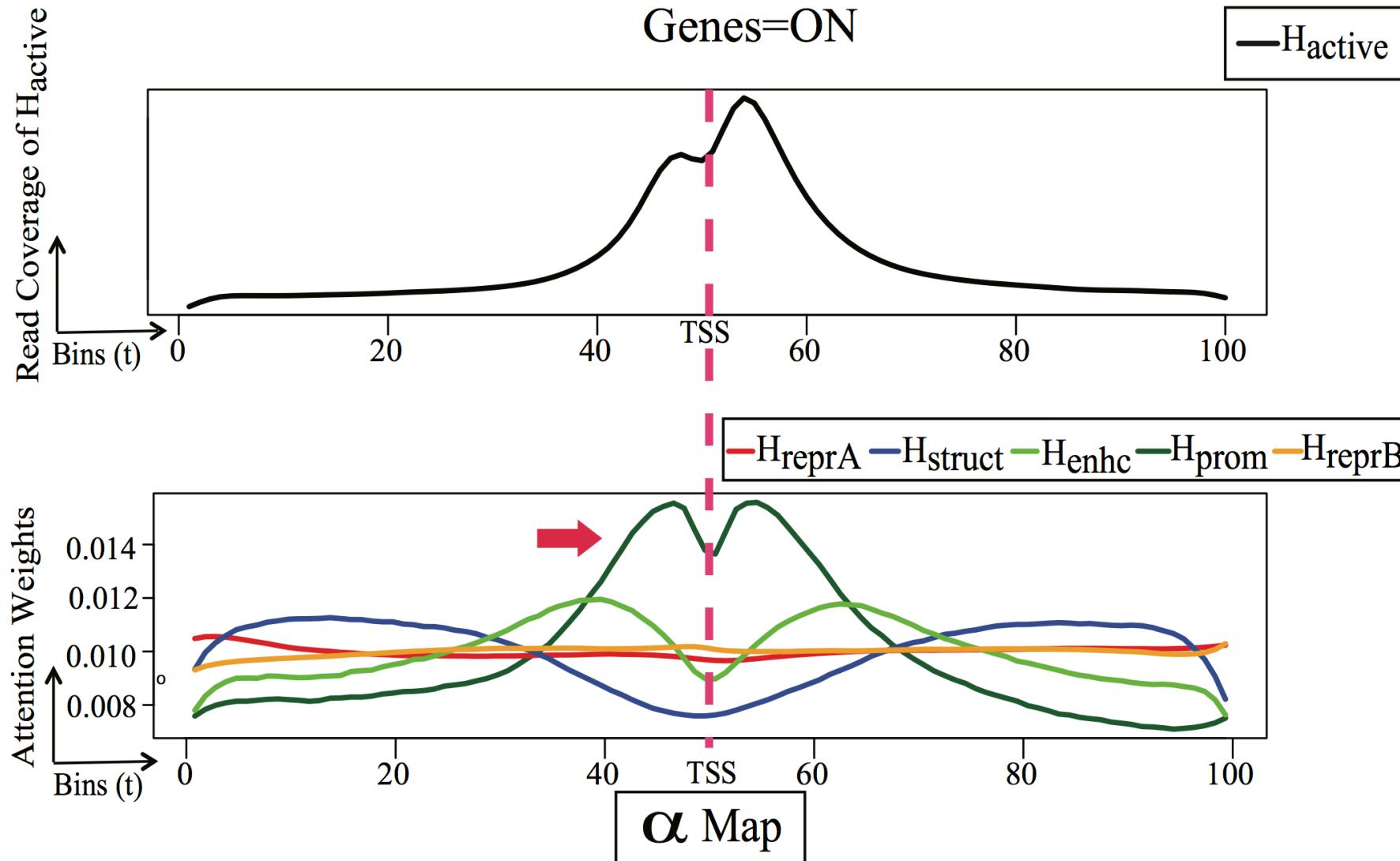
Models	Baselines		Our Model
	DeepChrome (CNN) [3]	LSTM	AttentiveChrome
Mean	0.8008	0.8052	0.8115
Median	0.8009	0.8036	0.8123
Max	0.9225	0.9185	0.9177
Min	0.6854	0.7073	0.7215
Improvement over DeepChrone [3] (out of 56 cell types)		36	49

Experiments: Interpretability

- Local-level (HM-level) Attention
- Global-level (HM interactions) Attention

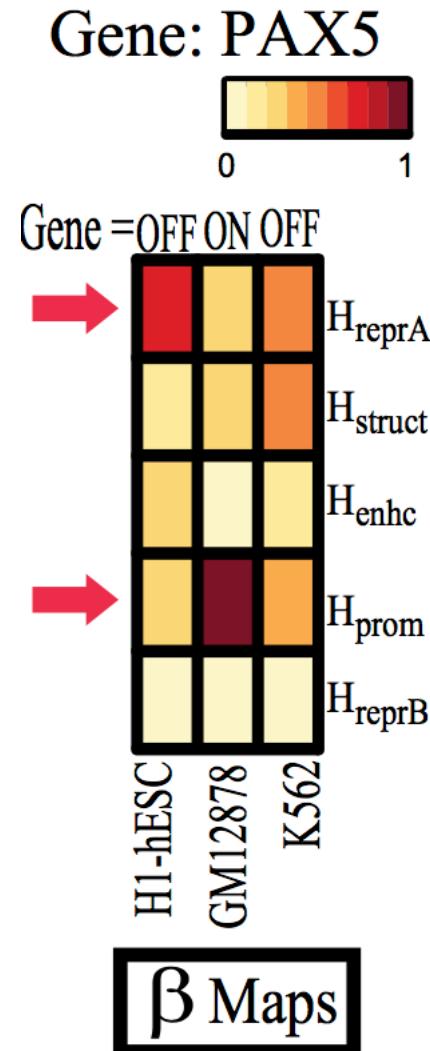
Histone Modification (HM) Mark	Renamed as	Functional Category
H3K4me3	H_{prom}	Promoter mark
H3K4me1	H_{enhc}	Distal Enhancer mark
H3K36me3	H_{struct}	Structural mark
H3K9me3	H_{reprA}	Repressor mark
H3K27me3	H_{reprB}	Repressor mark

(1) Visualization of Local Attention Weights (Learned from Data)



- Additional signal - H3K27ac (H-Active) from REMC
- Average local attention weights of gene=ON correspond well with H-active
- Indicating AttentiveChrome is focusing on the correct bin positions

(2) Visualization of Global Attention Weights (Learned from Data)



- An important differentially regulated gene (PAX5) across three blood lineage cell types:
 - H1-hESC (stem cell),
 - GM12878 (blood cell),
 - K562 (leukemia cell).
- Trend of its global weights (beta) Verified through the literature.

(3) Comparison with State-of-Art Deep-Visualization Methods

Correlation between local-level (HM-level) attention weights and the additional signal - H3K27ac (H-Active) from REMC

Table 3: Pearson Correlation values between weights assigned for H_{prom} (active HM) by different visualization techniques and H_{active} read coverage (indicating actual activity near "ON" genes) for predicted "ON" genes across three major cell types.

Viz. Methods	H1-hESC	GM12878	K562
α Map (LSTM- α)	0.8523	0.8827	0.9147
α Map (LSTM- α, β)	0.8995	0.8456	0.9027
Class-based Optimization (CNN)	0.0562	0.1741	0.1116
Saliency Map (CNN)	0.1822	-0.1421	0.2238

Summary

code available at: deepchrome.org

➤ Attentive DeepChrome

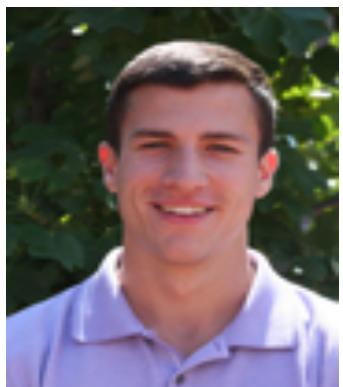
- Both accurate and interpretable
- Novel implementation of deep attention mechanism
- Importance analysis at both HM and HM-HM level



Acknowledgements



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Biochemistry and Molecular
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A scenic view of the University of Virginia's Rotunda building, a white neoclassical structure with a prominent dome, set against a backdrop of large, mature trees displaying vibrant autumn foliage in shades of orange, yellow, and red. The sky is a clear, pale blue with wispy white clouds.

Thank you