Making Deep Learning Understandable for Analyzing Sequential Data about Gene Regulation

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Tutorial @ ACM BCB-2018

Today

- Machine Learning: a quick review
- Deep Learning: a quick review
- Background Biology: a quick review
- Deep Learning for analyzing Sequential Data about Regulation:
    - DeepChrome
    - AttentiveChrome
    - DeepMotif

https://qdata.github.io/deep2Read/

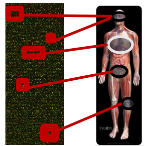
https://www.deepchrome.org

OUR DATA-RICH WORLD

- Biomedicine
    - Patient records, brain imaging, MRI & CT scans, …
    - Genomic sequences, bio-structure, drug effect info, …
- Science
    - Historical documents, scanned books, databases from astronomy, environmental data, climate records, …
- Social media
    - Social interactions data, twitter, facebook records, online reviews, …
- Business
    - Stock market transactions, corporate sales, airline traffic, …

Challenge of Data Explosion in Biomedicine

Molecular signatures of tumor / blood s

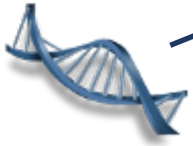


Signs & Symptoms

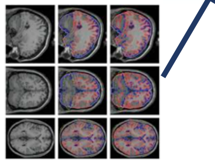
Patient Medical History & Demographics

Public Health Data

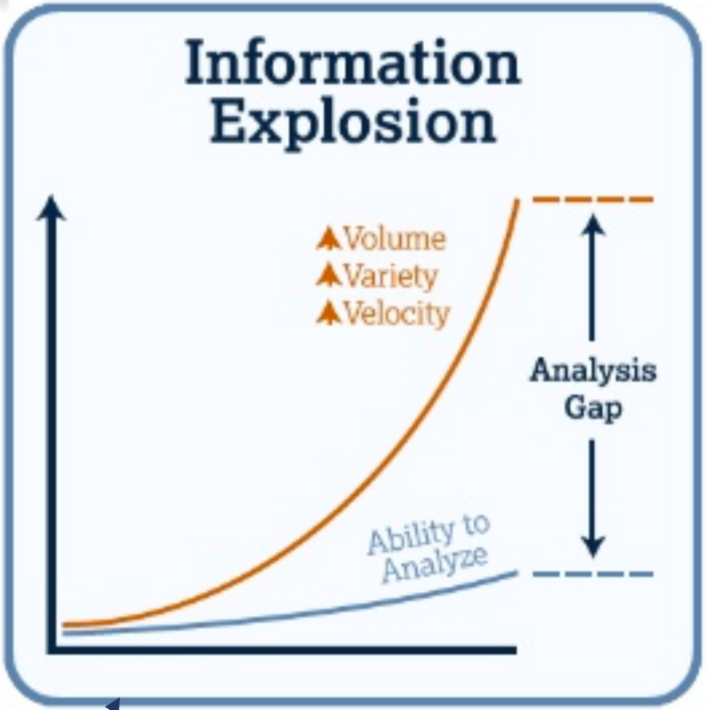
Genetic Data



Mobile medical sensor data



Medical Images



Traditional Approaches

Machine Learning

BASICS OF MACHINE LEARNING

- "The goal of machine learning is to build computer systems that can learn and adapt from their experience." – Tom Dietterich

- "Experience" in the form of available data examples (also called as instances, samples)

- Available examples are described with properties (data points in feature space X)

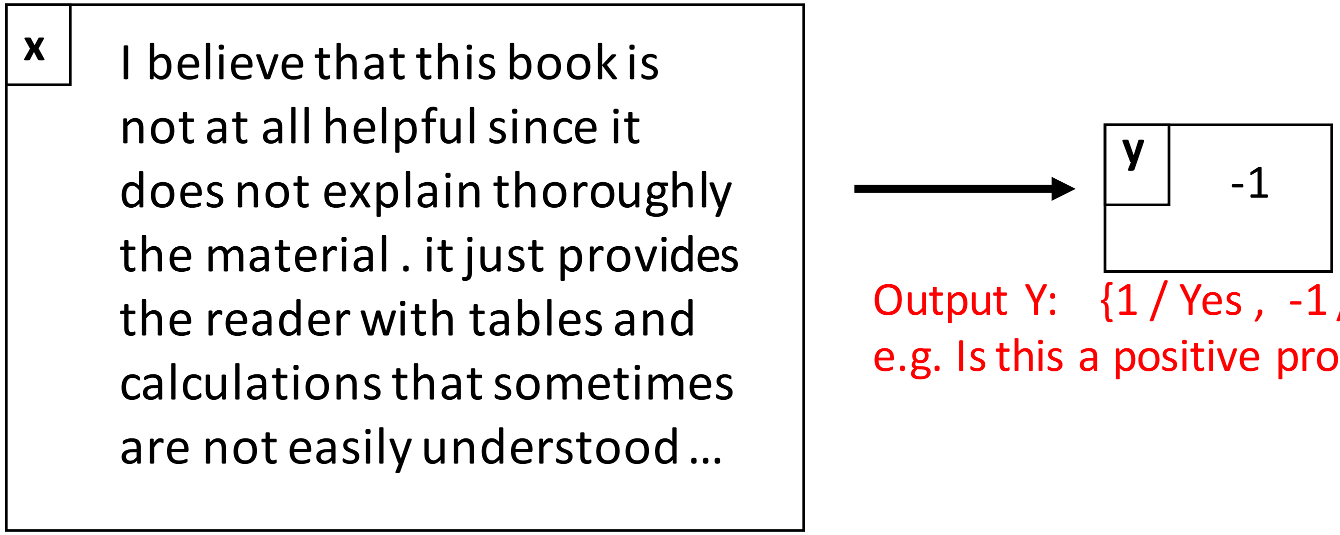
e.g. SUPERVISED LEARNING

- Find function to map input space X to output space Y

$$f : X \longrightarrow Y$$

- So that the difference between *y* and ***f(x)*** of each example ***x*** is small.

e.g.



x

I believe that this book is not at all helpful since it does not explain thoroughly the material . it just provides the reader with tables and calculations that sometimes are not easily understood …

y

-1

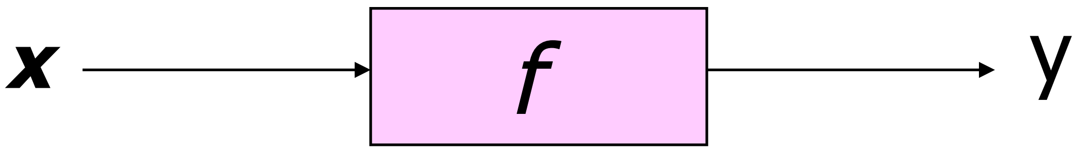
Input X : e.g. a piece of English text

Output Y: {1 / Yes , -1 / No }

e.g. Is this a positive product review ?

SUPERVISED Linear Binary Classifier

- Now let us check out a VERY SIMPLE case of



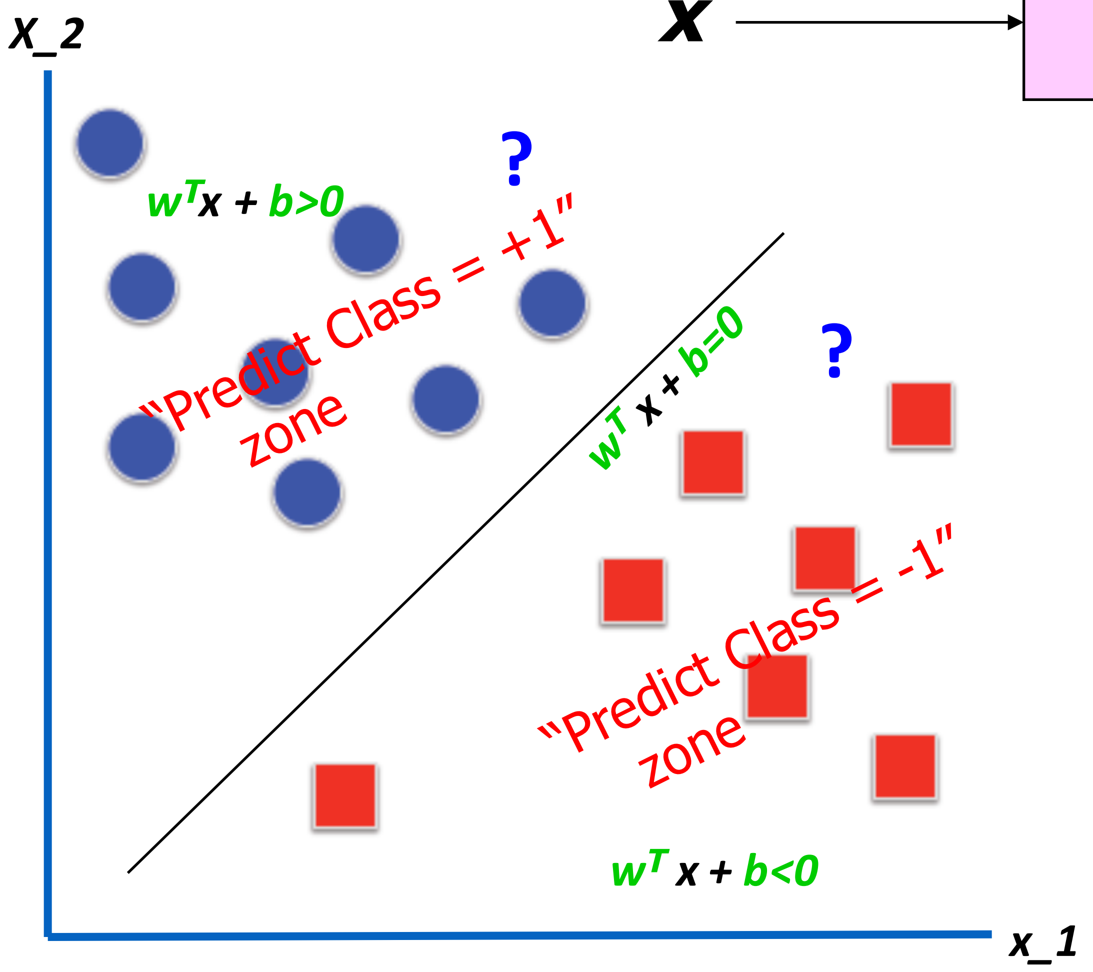
e.g.: Binary *y* / Linear *f* / X as R^2

$$\boldsymbol{f}(\mathbf{x},\mathbf{w},b) = sign(\mathbf{w}^T\, \mathbf{x} + b)$$

x =(x_1, x_2)

SUPERVISED Linear Binary Classifier

$$\mathbf{x} \longrightarrow \boxed{f} \longrightarrow y$$



$$f(\mathbf{x},\mathbf{w},b) = sign(\mathbf{w}^T \mathbf{x} + b)$$

$\mathbf{x} =(x\_1, x\_2)$

● denotes +1 point

🟥 denotes -1 point

? denotes future points

Courtesy slide from Prof. Andrew Moore's tutorial

Basic Concepts

- Training (i.e. learning parameters $\boxed{\mathbf{w},b}$)
  - Training set includes
    - available examples' feature represenation: $\mathbf{x}_1,\ldots,\mathbf{x}_L$
    - available corresponding labels $y_1,\ldots,y_L$

  - Find ($\mathbf{w}$,*b*) by minimizing loss (i.e. difference between *y* and *f*(**x**) *on available examples in training set*)

$$(\mathbf{W}, b) = \underset{\mathbf{w},\, b}{\operatorname{argmin}} \sum_{i=1}^{L} \ell(f(x_i), y_i)$$

Basic Concepts

- Testing (i.e. evaluating performance on "future" points)
  - Difference between true $y_?$ and the predicted $f(\boldsymbol{x}_?)$ on a set of testing examples (i.e. *testing set*)
  - Key: example $\boldsymbol{x}_?$ not in the training set

- Generalisation: learn function / hypothesis from past data in order to "explain", "predict", "model" or "control" new data examples

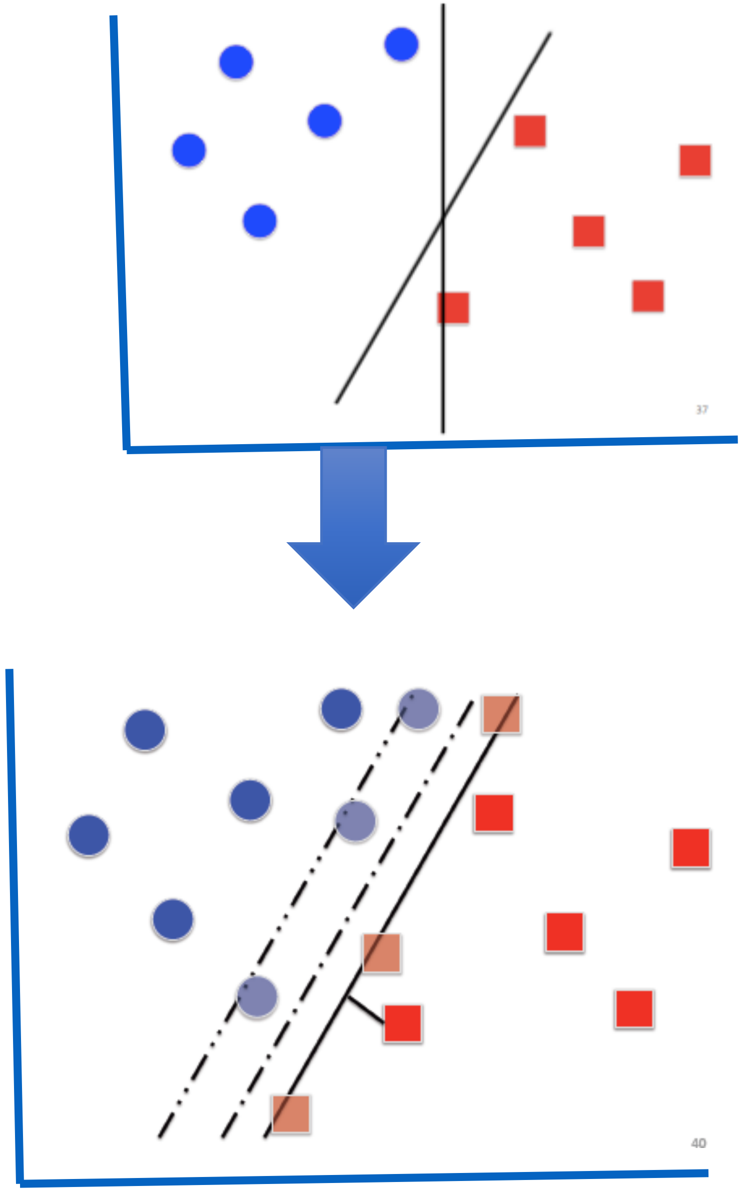
Basic Concepts

- Loss function
  - e.g. hinge loss for binary classification task

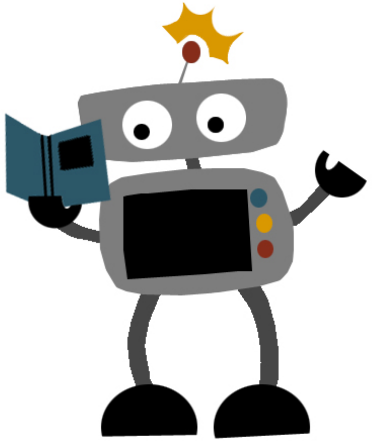
$$\sum_{i=1}^{L}\ell(f(x_i),y_i)=\sum_{i=1}^{L}\max(0,1-y_if(x_i)).$$

- Regularization
  - E.g. additional information added on loss function to control *f*

Maximize Separation Margin => Minimize $\|w\|^2$;

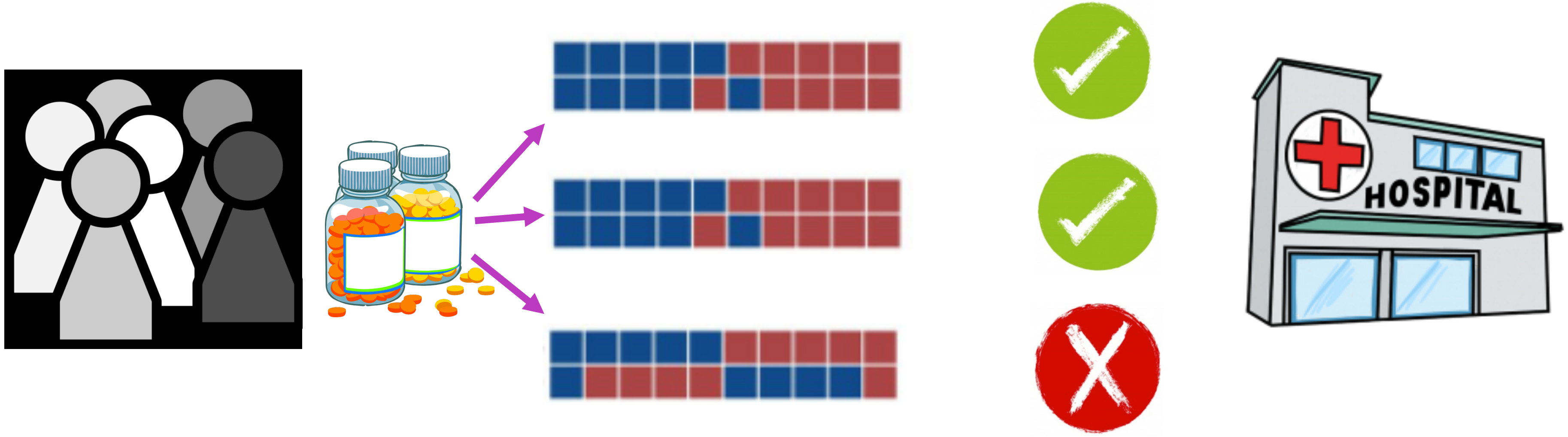


Basics of Machine Learning

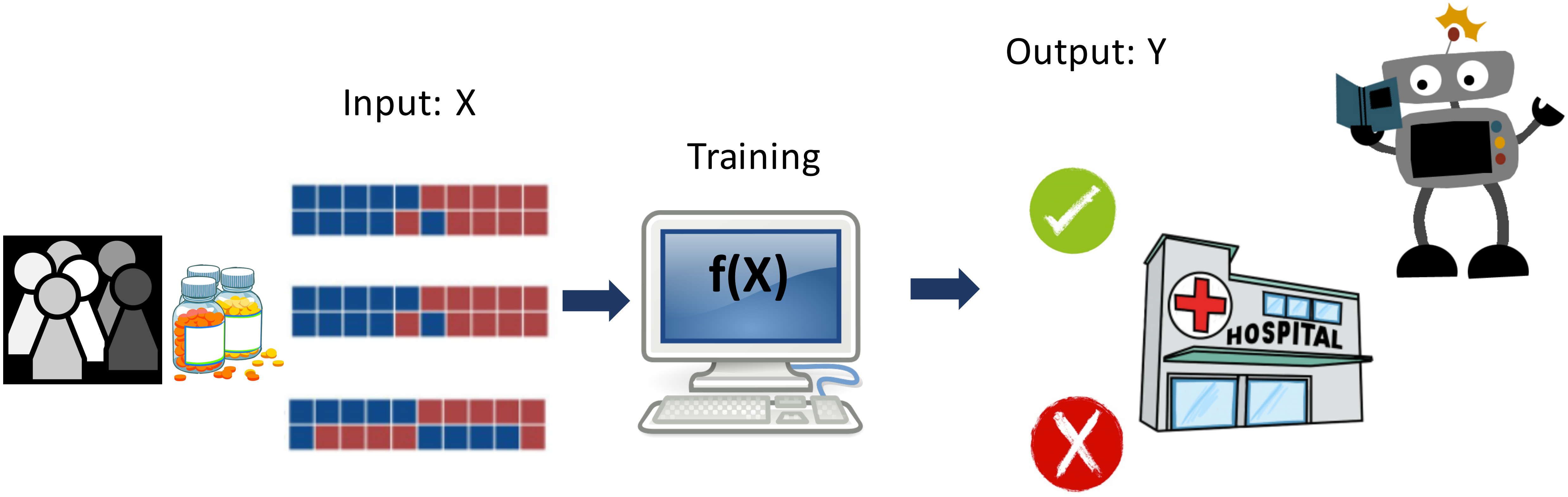


Input: X

Output: Y



Basics of Machine Learning



Input: X

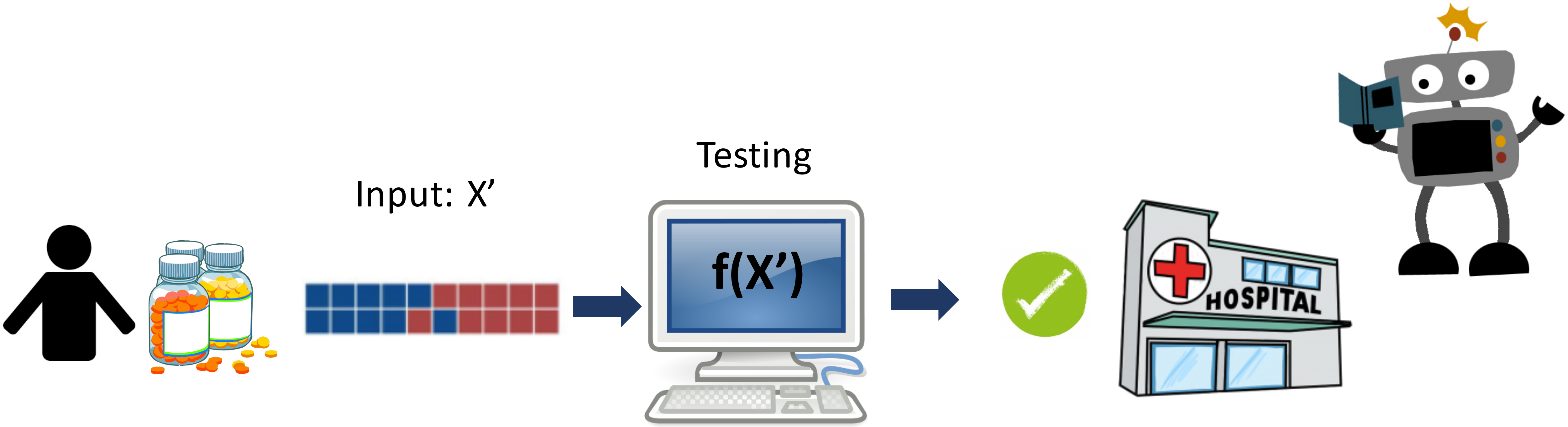
Training

f(X)

Output: Y

f(X)=Y

Basics of Machine Learning



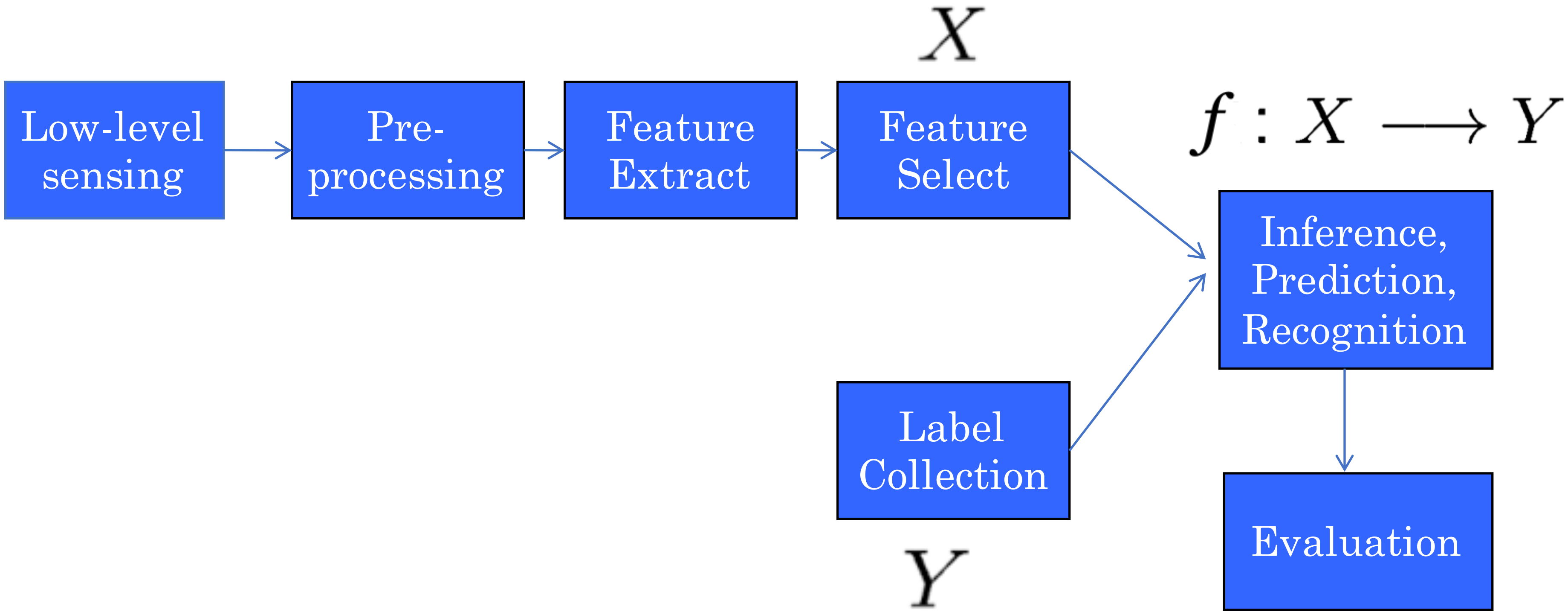
Testing

Input: X’

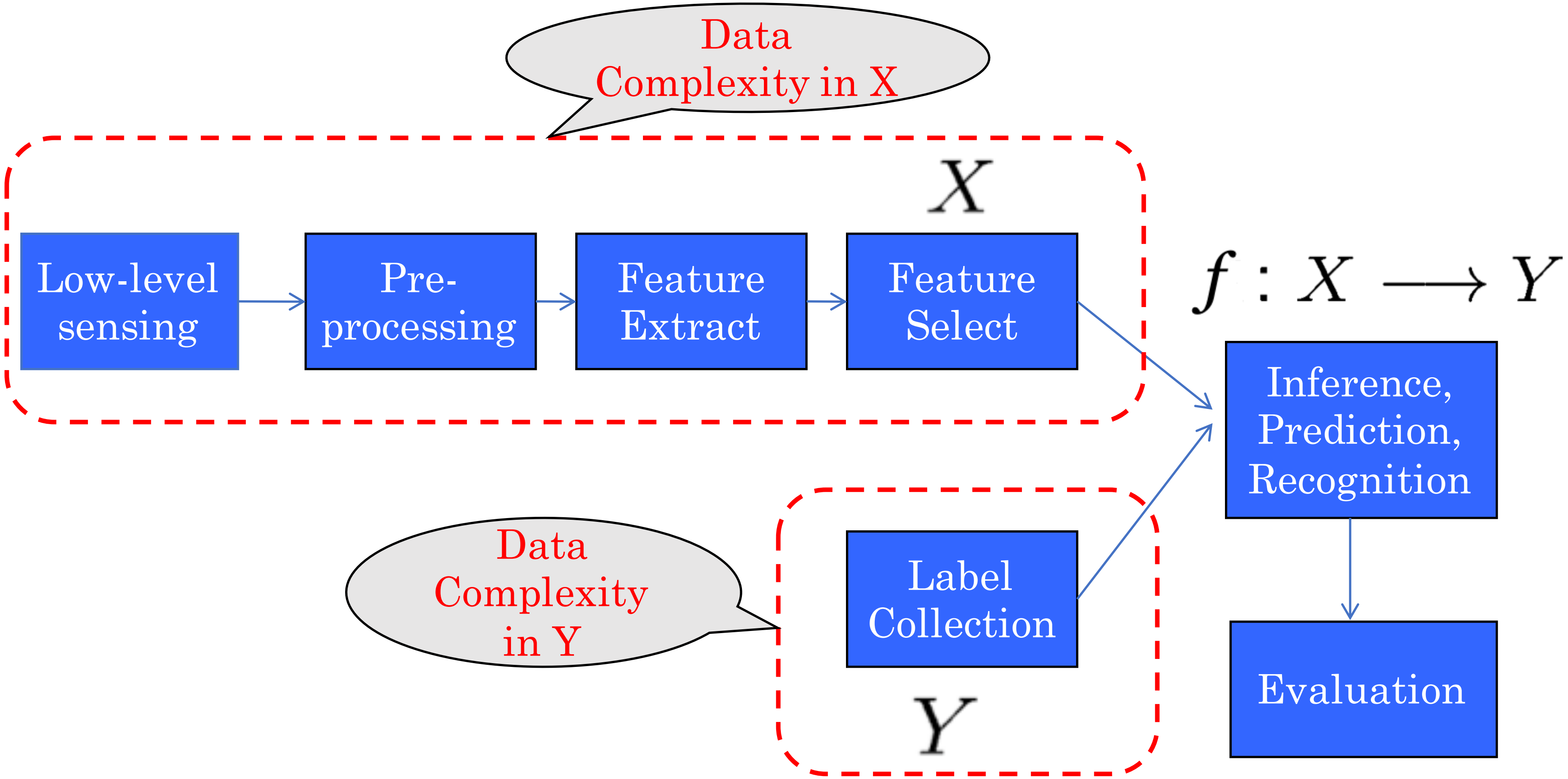
f(X’)

Supervised Classification

TYPICAL MACHINE LEARNING SYSTEM

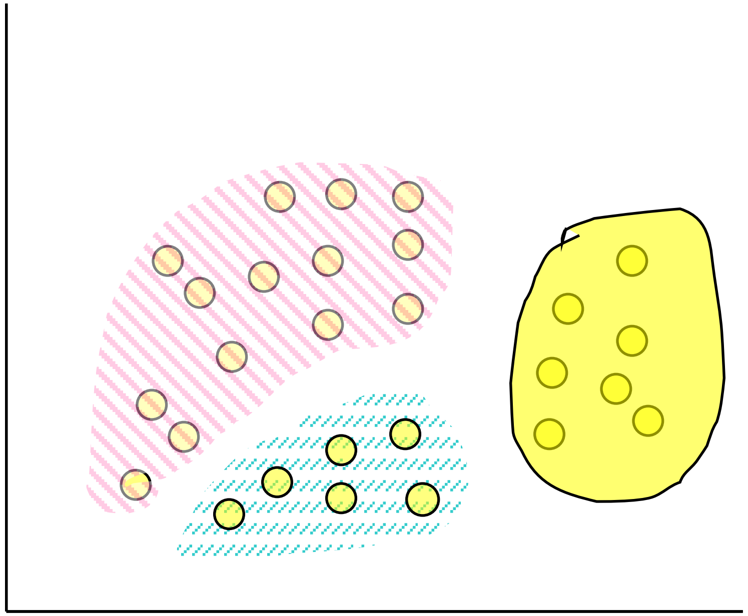


TYPICAL MACHINE LEARNING SYSTEM



UNSUPERVISED LEARNING : [COMPLEXITY OF Y]

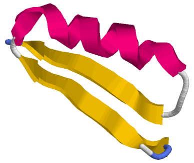
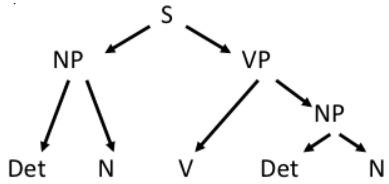
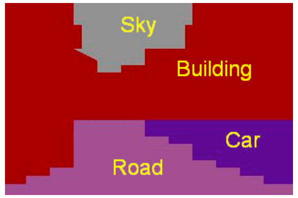
- No labels are provided (e.g. No Y provided)
- Find patterns from unlabeled data, e.g. clustering



e.g. clustering => to find "natural" grouping of instances given un-labeled data

Structured Output Prediction:
[COMPLEXITY in Y]

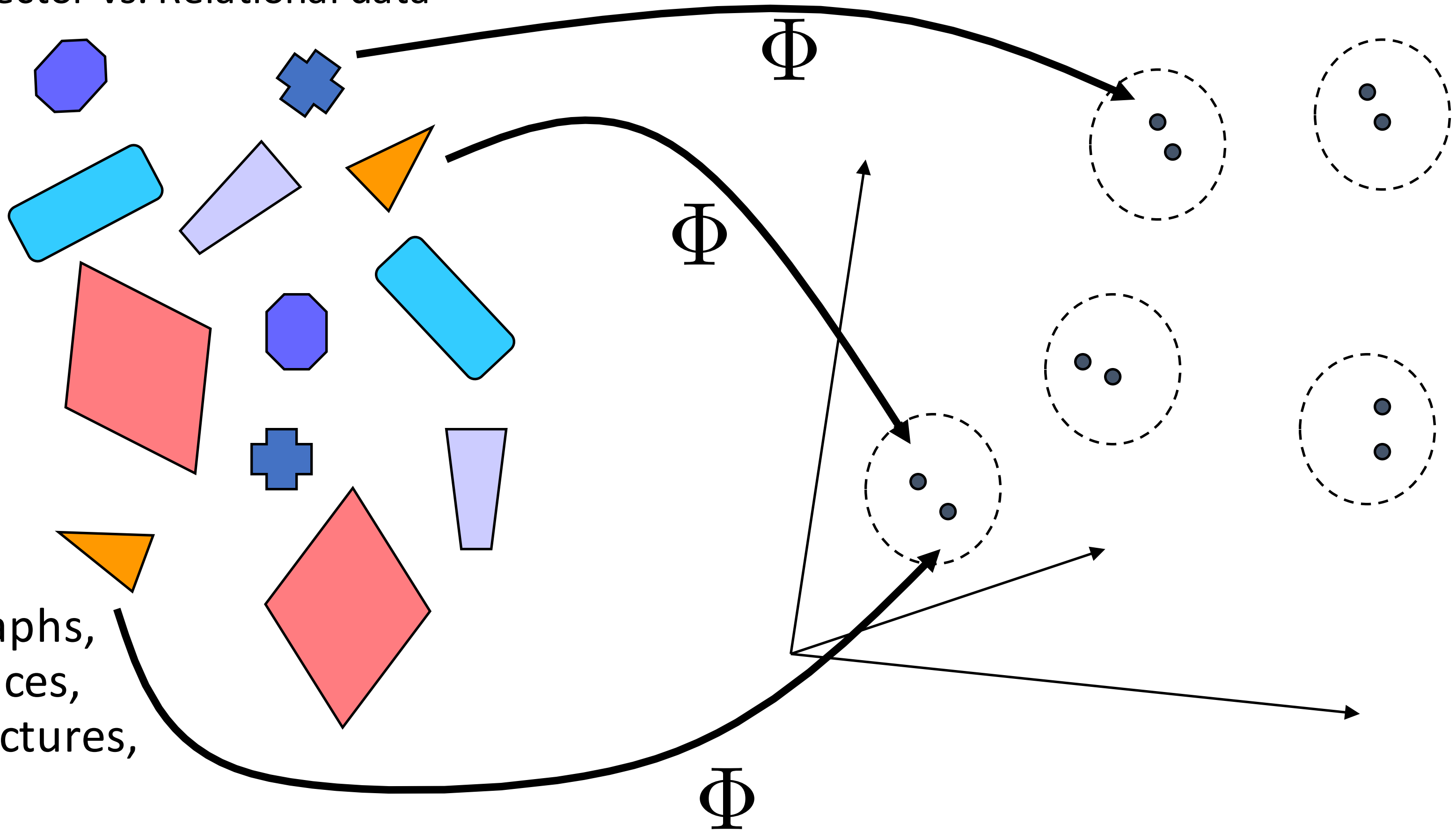
- Many prediction tasks involve output labels having structured correlations or constraints among instances

Structured Dependency between Examples' Y	Sequence	Tree	Grid
Input X	APAFSVSPASGACGPECA…	The dog chased the cat	
Output Y	 CCEEEEECCCCCHHHCCC…		

Many more possible structures between y_i , e.g. spatial , temporal, relational …

Structured Input: Kernel Methods
[COMPLEXITY OF X]

Vector vs. Relational data



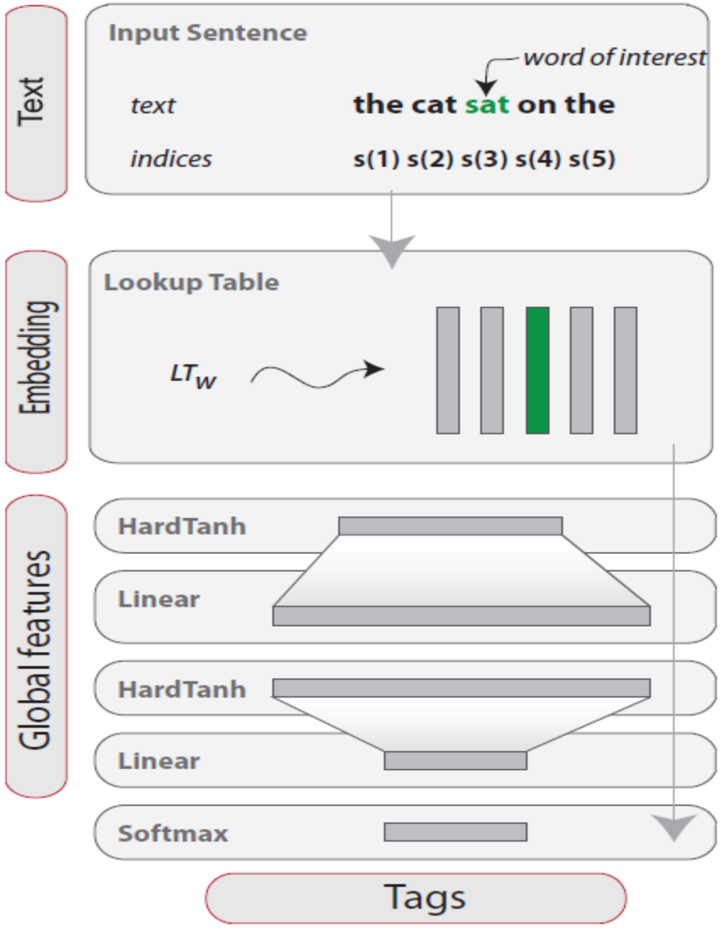
e.g. Graphs, Sequences, 3D structures,

Original Space

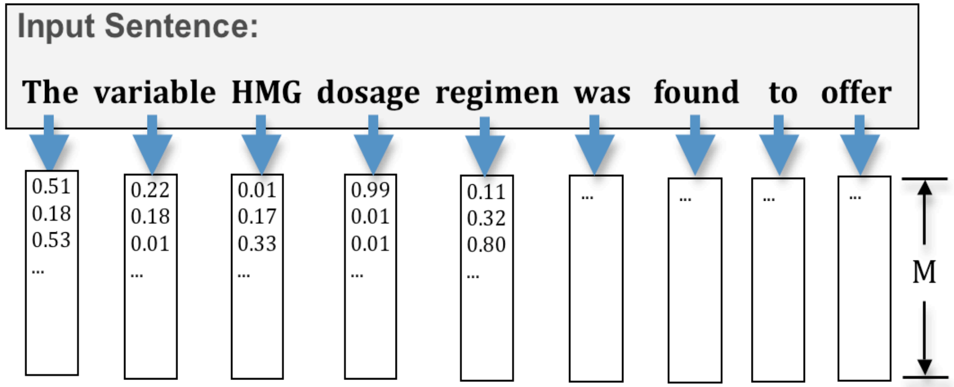
Feature Space

More Recent: Representation Learning
[COMPLEXITY OF X]

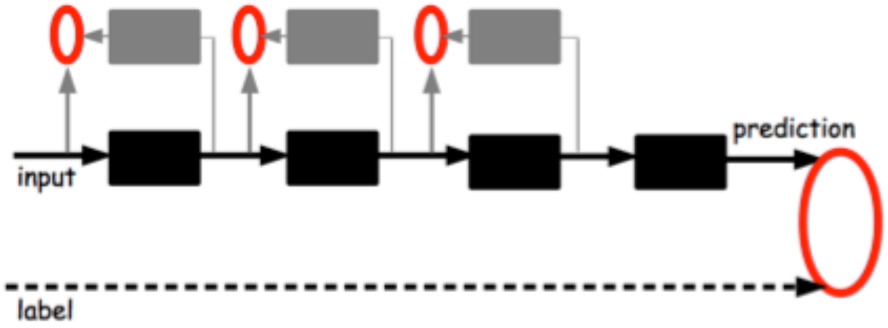
Deep Learning



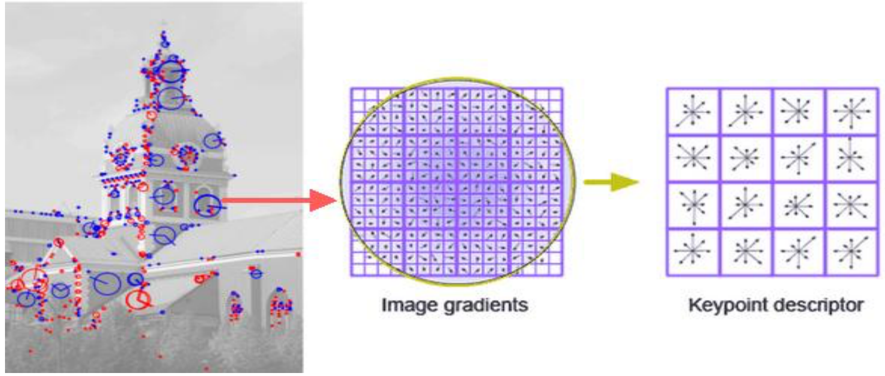
Supervised Embedding

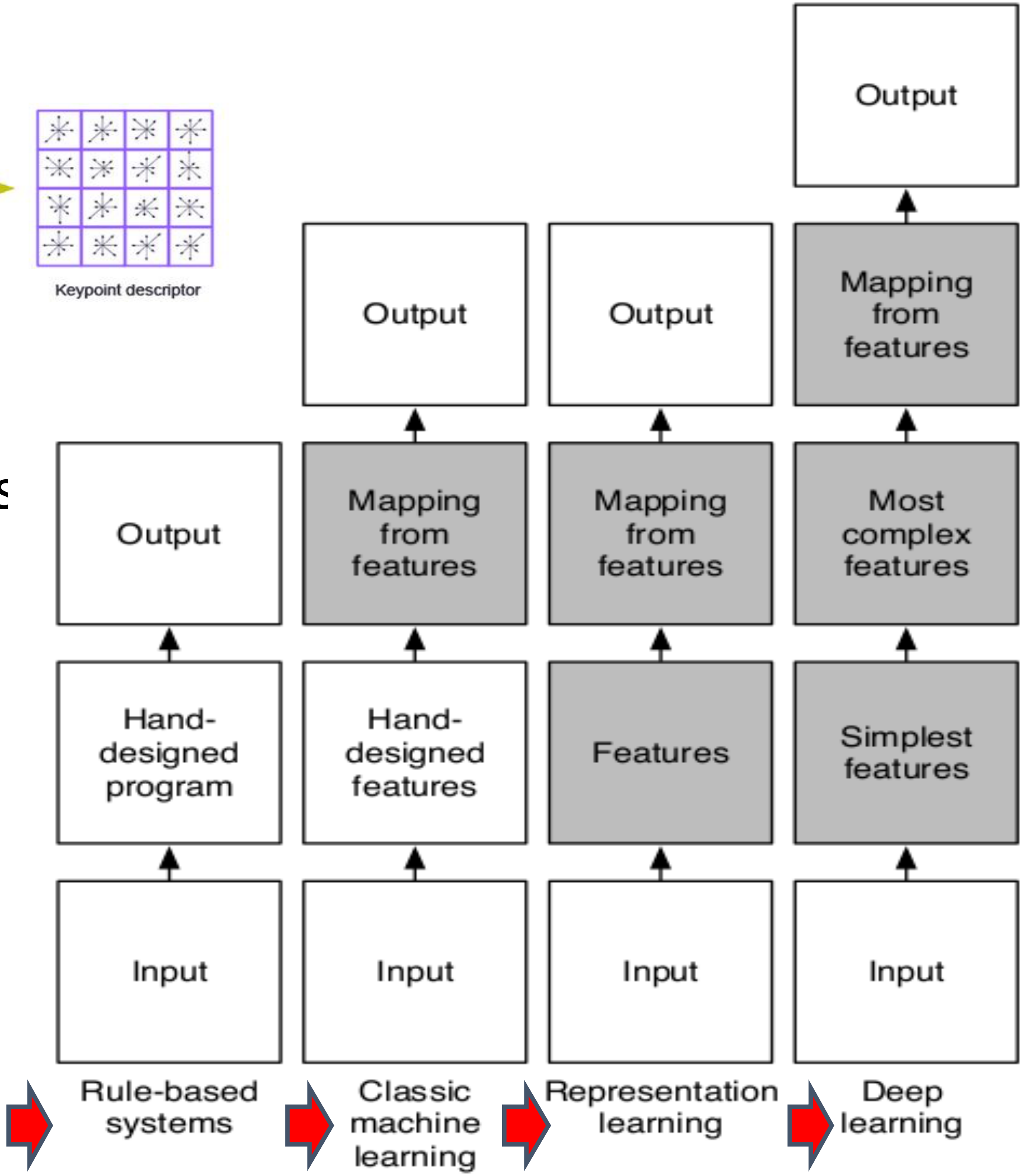


Layer-wise Pretraining



Why learn features





Rule-based systems: Input → Hand-designed program → Output

Classic machine learning: Input → Hand-designed features → Mapping from features → Output

Representation learning: Input → Features → Mapping from features → Output

Deep learning: Input → Simplest features → Most complex features → Mapping from features → Output

When to use Machine Learning ?

- 1. Extract knowledge from data
  - Relationships and correlations can be hidden within large amounts of data
  - The amount of knowledge available about certain tasks is simply too large for explicit encoding (e.g. rules) by humans
- 2. Learn tasks that are difficult to formalise
  - Hard to define well, except by examples (e.g. face recognition)
- 3. Create software that improves over time
  - New knowledge is constantly being discovered.
  - Rule or human encoding-based system is difficult to continuously re-design "by hand".

Recap

$$f : X \longrightarrow Y$$

- Goal of Machine Learning: Generalisation
- Training
- Testing
- Loss

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https://qdata.github.io/deep2Read/

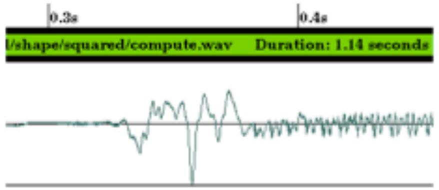
https://www.deepchrome.org

- Deep Learning
  - Why is this a breakthrough ?
  - Basics
  - History
  - A Few Recent trends

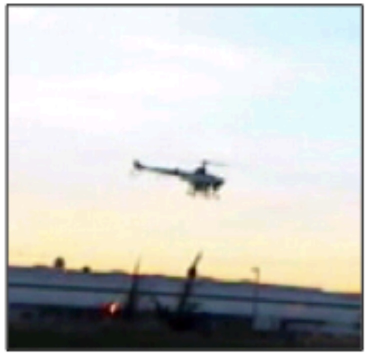
https://qdata.github.io/deep2Read/

Deep Learning is Changing the World

How may I help you, human?

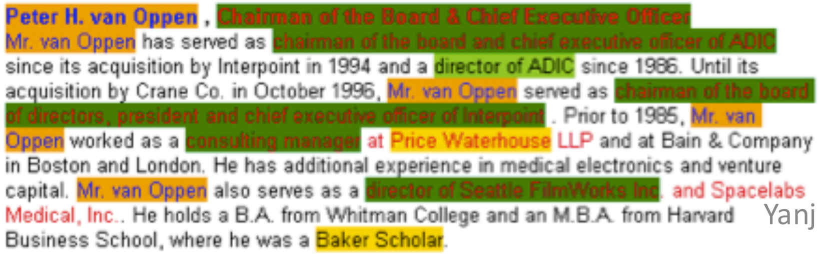


Speech Recognition



Control learning

Text analysis



Peter H. van Oppen , Chairman of the Board & Chief Executive Officer
Mr. van Oppen has served as chairman of the board and chief executive officer of ADIC since its acquisition by Interpoint in 1994 and a director of ADIC since 1986. Until its acquisition by Crane Co. in October 1996, Mr. van Oppen served as chairman of the board of directors, president and chief executive officer of Interpoint . Prior to 1985, Mr. van Oppen worked as a consulting manager at Price Waterhouse LLP and at Bain & Company in Boston and London. He has additional experience in medical electronics and venture capital. Mr. van Oppen also serves as a director of Seattle FilmWorks Inc. and Spacelabs Medical, Inc.. He holds a B.A. from Whitman College and an M.B.A. from Harvard Business School, where he was a Baker Scholar.

Object recognition

Many more !

MIT
Technology
Review

10 Breakthrough Technologies 2013

Think of the most frustrating, intractable, or simply annoying problems you can imagine. Now think about what technology is doing to fix them. That's what we did in coming up with our annual list of 10 Breakthrough Technologies. We're looking for technologies that we believe will expand the scope of human possibilities.

Deep Learning

10 Breakthrough Technologies 2017

These technologies all have staying power. They will affect the economy and our politics, improve medicine, or influence our culture. Some are unfolding now; others will take a decade or more to develop. But you should know about all of them right now.

Deep Reinforcement Learning

Generative Adversarial Network (GAN)

Why breakthrough ?

Breakthrough from 2012 Large-Scale Visual Recognition Challenge (ImageNet)

10% improve with deepCNN

72%, 2010

74%, 2011

85%, 2012

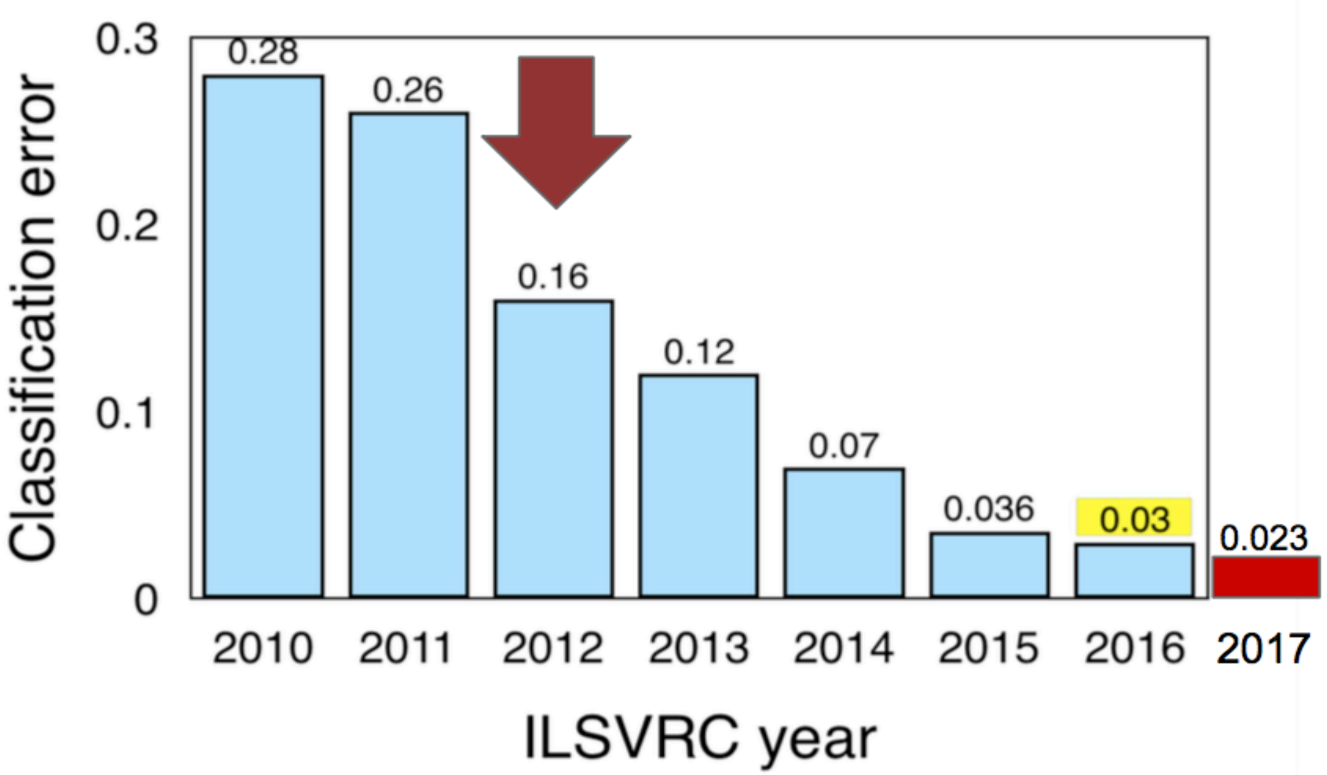
In one "very large-scale" benchmark competition

(1.2 million images [X] vs.1000 different word labels [Y])

ImageNet Challenge

Arch

- 2010-11: hand-crafted computer vision pipelines
- 2012-2016: ConvNets
  - 2012: AlexNet
    - major deep learning success
  - 2013: ZFNet
    - improvements over AlexNet
  - 2014
    - VGGNet: deeper, simpler
    - InceptionNet: deeper, faster
  - 2015
    - ResNet: even deeper
  - 2016
    - ensembled networks
  - 2017
    - Squeeze and Excitation Network

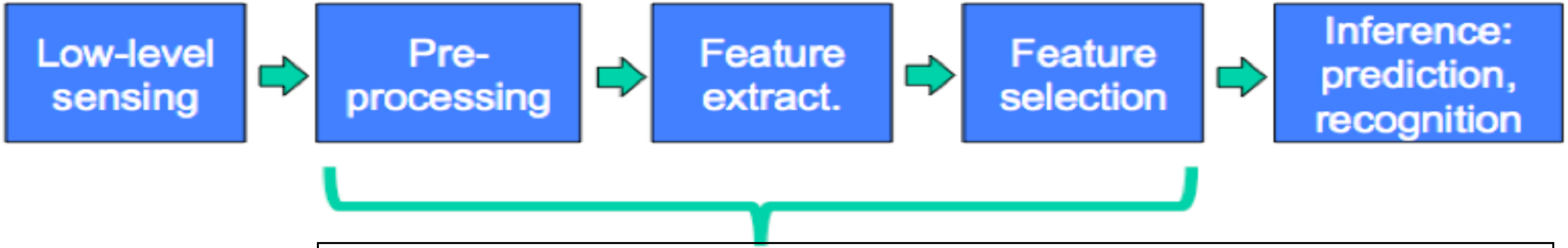


Adapt from From NIPS 2017 DL Trend Tutorial

DNNs help us build more intelligent computers

- Perceive the world,
  - e.g., objective recognition, speech recognition, …
- Understand the world,
  - e.g., machine translation, text semantic understanding
- Interact with the world,
  - e.g., AlphaGo, AlphaZero, self-driving cars, …
- Being able to think / reason,
  - e.g., learn to code programs, learn to search deepNN, …
- Being able to imagine / to make analogy,
  - e.g., learn to draw with styles, ……

Deep Learning Way: Learning Representation from data



Low-level sensing → Pre-processing → Feature extract. → Feature selection → Inference: prediction, recognition

Feature Engineering

- ✓ Most critical for accuracy
- ✓ Account for most of the computation
- ✓ Most time-consuming in development cycle
- ✓ Often hand-craft and task dependent in practice

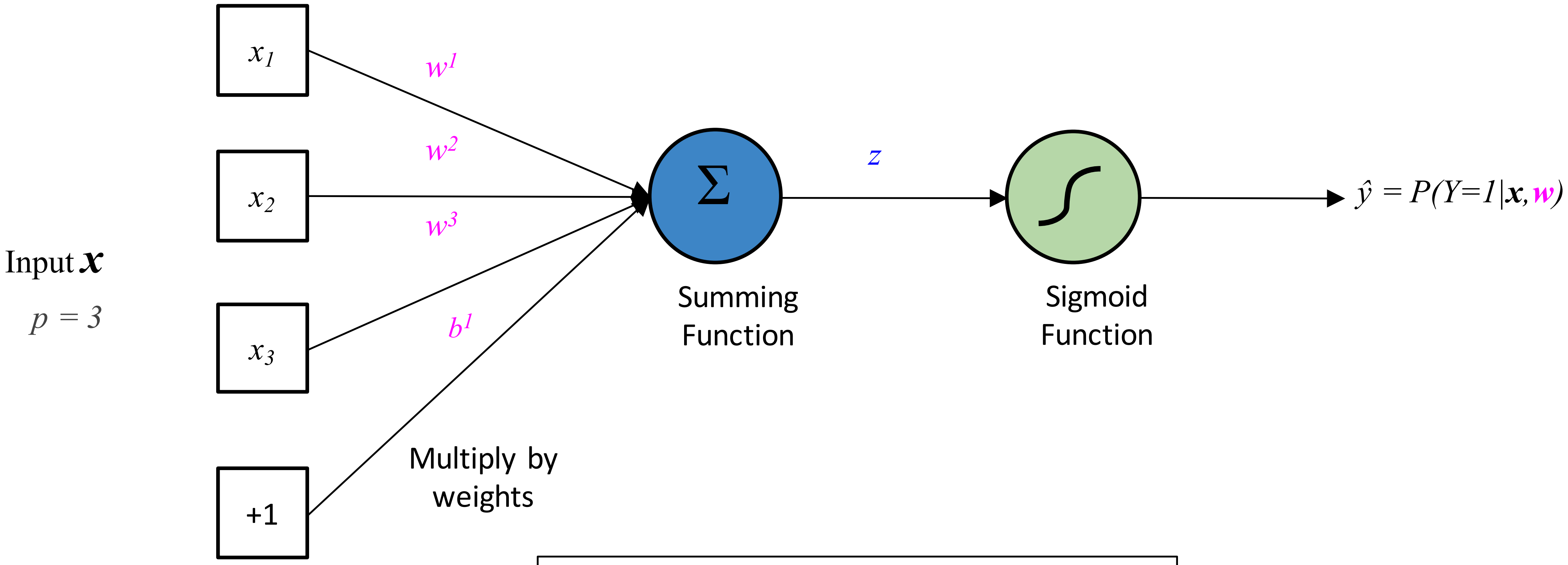
Feature Learning

- ✓ Easily adaptable to new similar tasks
- ✓ Learn layerwise representation from data

Basics

- Basic Neural Network (NN)
  - single neuron, e.g. logistic regression unit
  - multilayer perceptron (MLP)
  - various loss function
    - E.g., when for multi-class classification, softmax layer
  - training NN with backprop algorithm

One “Neuron”: Expanded Logistic Regression

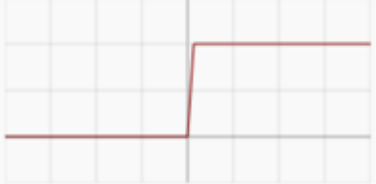
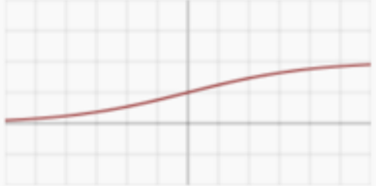
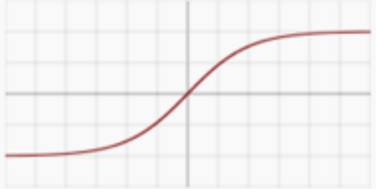
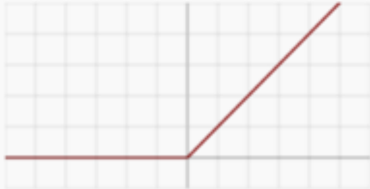


$$z = \boldsymbol{w}^T \cdot \boldsymbol{x} + \boldsymbol{b}$$

$$y = sigmoid(z) = \frac{e^z}{1 + e^z}$$

E.g., Many Possible Nonlinearity Functions

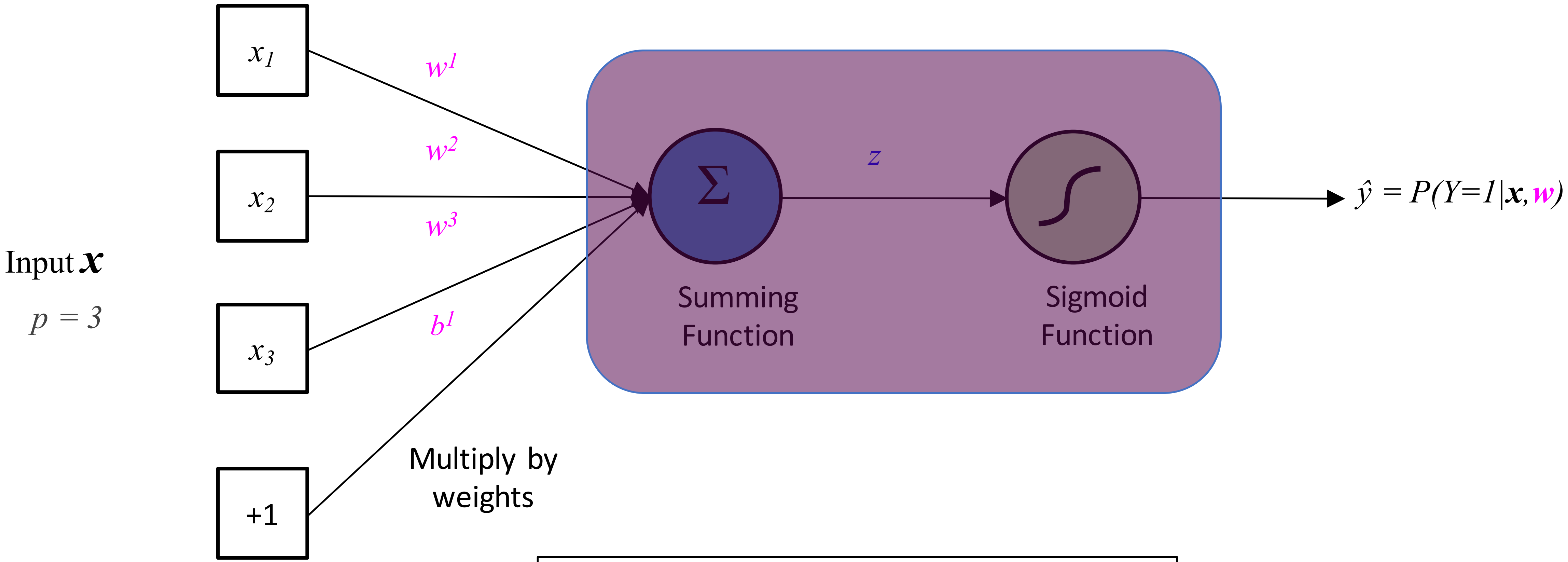
(aka transfer or activation functions)

Name	Plot	Equation	Derivative (w.r.t x)
Binary step		$f(x) = \begin{cases} 0 & \text{for} \quad x < 0 \\ 1 & \text{for} \quad x \geq 0 \end{cases}$	$f'(x) = \begin{cases} 0 & \text{for} \quad x \neq 0 \\ ? & \text{for} \quad x = 0 \end{cases}$
Logistic (a.k.a Soft step)		$f(x) = \frac{1}{1+e^{-x}}$	$f'(x) = f(x)(1-f(x))$
TanH		$f(x) = \tanh(x) = \frac{2}{1+e^{-2x}} - 1$	$f'(x) = 1 - f(x)^2$
Rectifier (ReLU)[9]		$f(x) = \begin{cases} 0 & \text{for} \quad x < 0 \\ x & \text{for} \quad x \geq 0 \end{cases}$	$f'(x) = \begin{cases} 0 & \text{for} \quad x < 0 \\ 1 & \text{for} \quad x \geq 0 \end{cases}$

usually works best in practice

https://en.wikipedia.org/wiki/Activation_function#Comparison_of_activation_functions

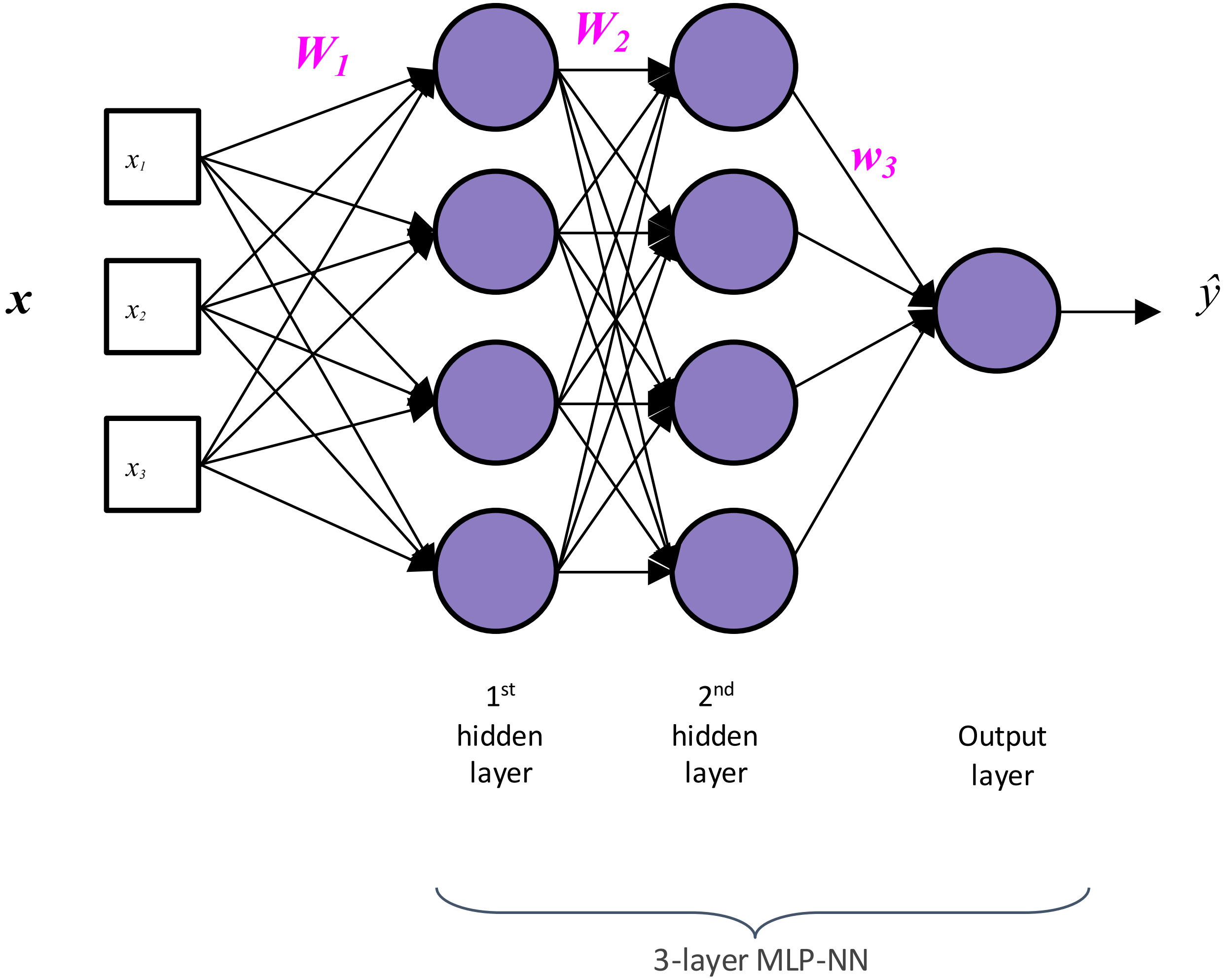
One "Neuron": Expanded Logistic Regression => "Neuron View"



$$z = \boldsymbol{w}^T \cdot \boldsymbol{x} + \boldsymbol{b}$$

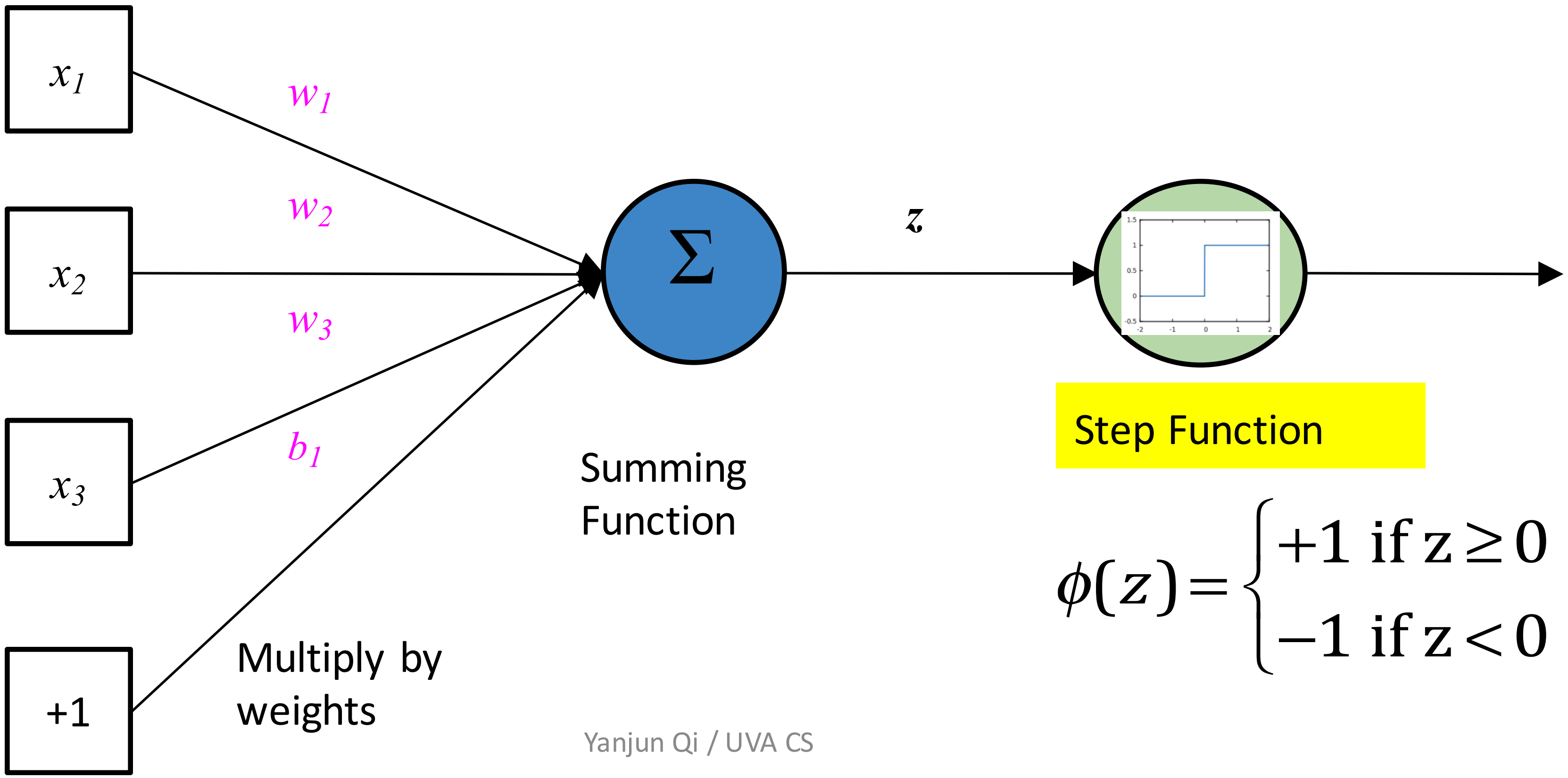
$$y = sigmoid(z) = \frac{e^z}{1 + e^z}$$

Multi-Layer Perceptron (MLP)- (Feed-Forward NN)



History ➔ Perceptron: 1-Neuron Unit with Step

- First proposed by Rosenblatt (1958)
- A simple neuron that is used to classify its input into one of two categories.
- A perceptron uses a **step function**



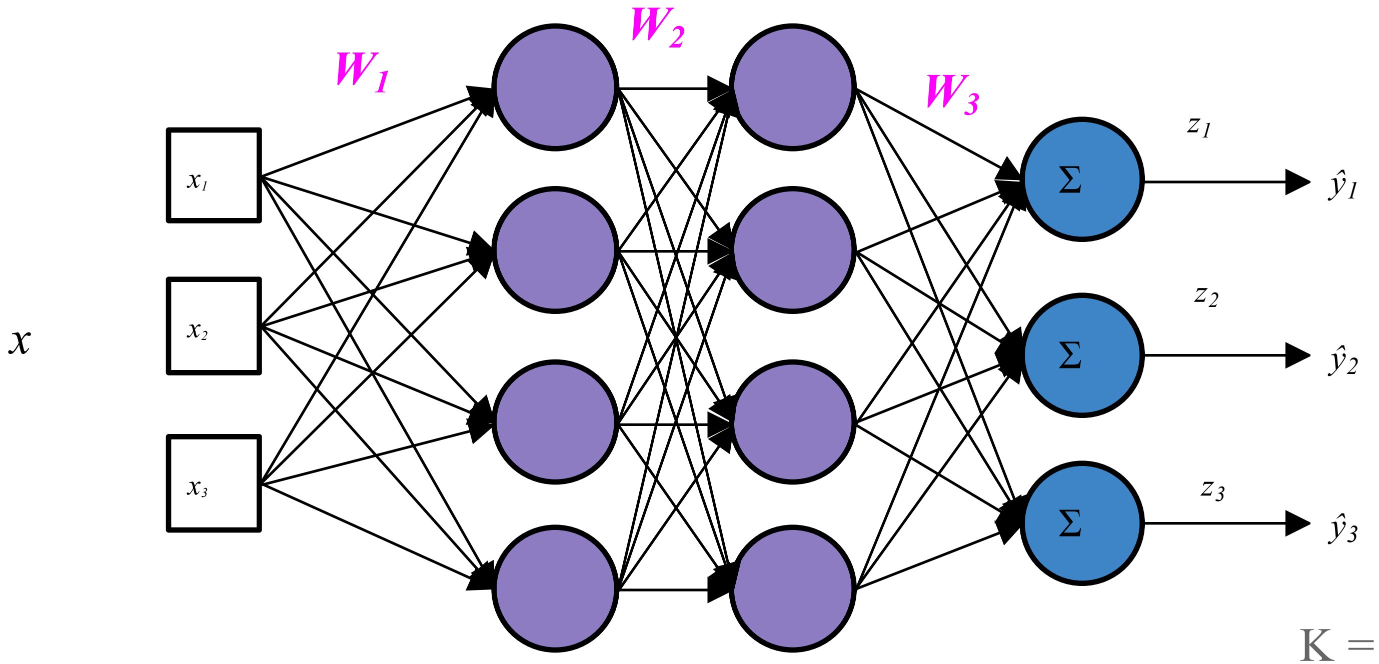
Multiply by weights

Summing Function

Step Function

$$\phi(z) = \begin{cases} +1 \text{ if } z \geq 0 \\ -1 \text{ if } z < 0 \end{cases}$$

E.g., Cross-Entropy Loss for Multi-Class Classification

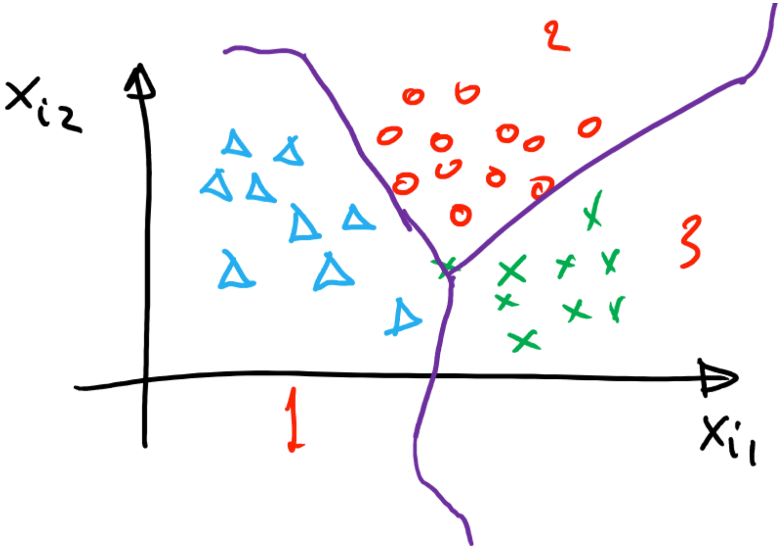


$$\hat{y}_i = \frac{e^{z_i}}{\sum_j e^{z_j}} = P(\hat{y}_i = 1 \mid \boldsymbol{x})$$

"Softmax" function. Normalizing function which converts each class output to a probability.

K = 3

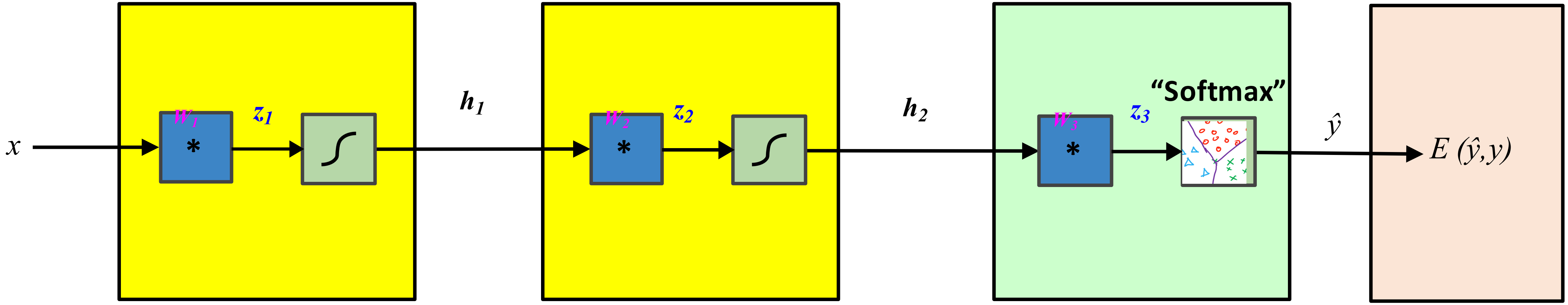
Y_{i1}	Y_{i2}	Y_{i3}	
0	1	0	Class 2
1	0	0	Class 1
0	0	1	Class 3



$$E_W(\hat{y},y) = \text{loss} = \sum_{j=1...K} y_j \ln \hat{y}_j$$

Cross-entropy loss

“Block View”



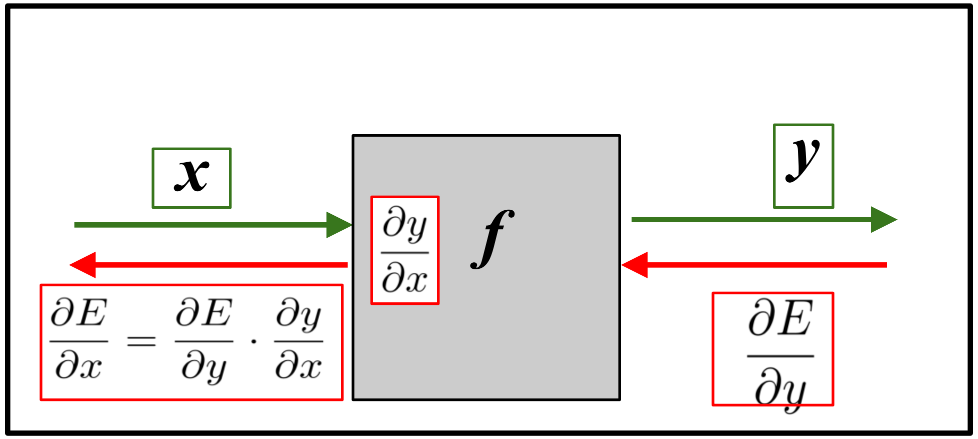
1st
hidden layer

2nd
hidden layer

Output layer

Loss Module

Building Deep Neural Nets



x
y
f
$\frac{\partial y}{\partial x}$
$\frac{\partial E}{\partial x} = \frac{\partial E}{\partial y} \cdot \frac{\partial y}{\partial x}$
$\frac{\partial E}{\partial y}$

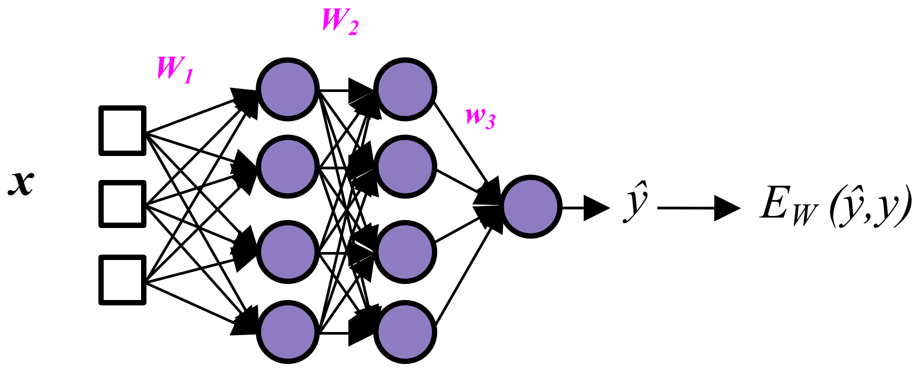
http://cs231n.stanford.edu/slides/winter1516_lecture5.pdf

Training Neural Networks

How do we learn the optimal weights W_L for our task??

- **Stochastic Gradient descent:**

$$W_L^{\,t} = W_L^{\,t-1} - \eta \frac{\partial E}{\partial W_L}$$



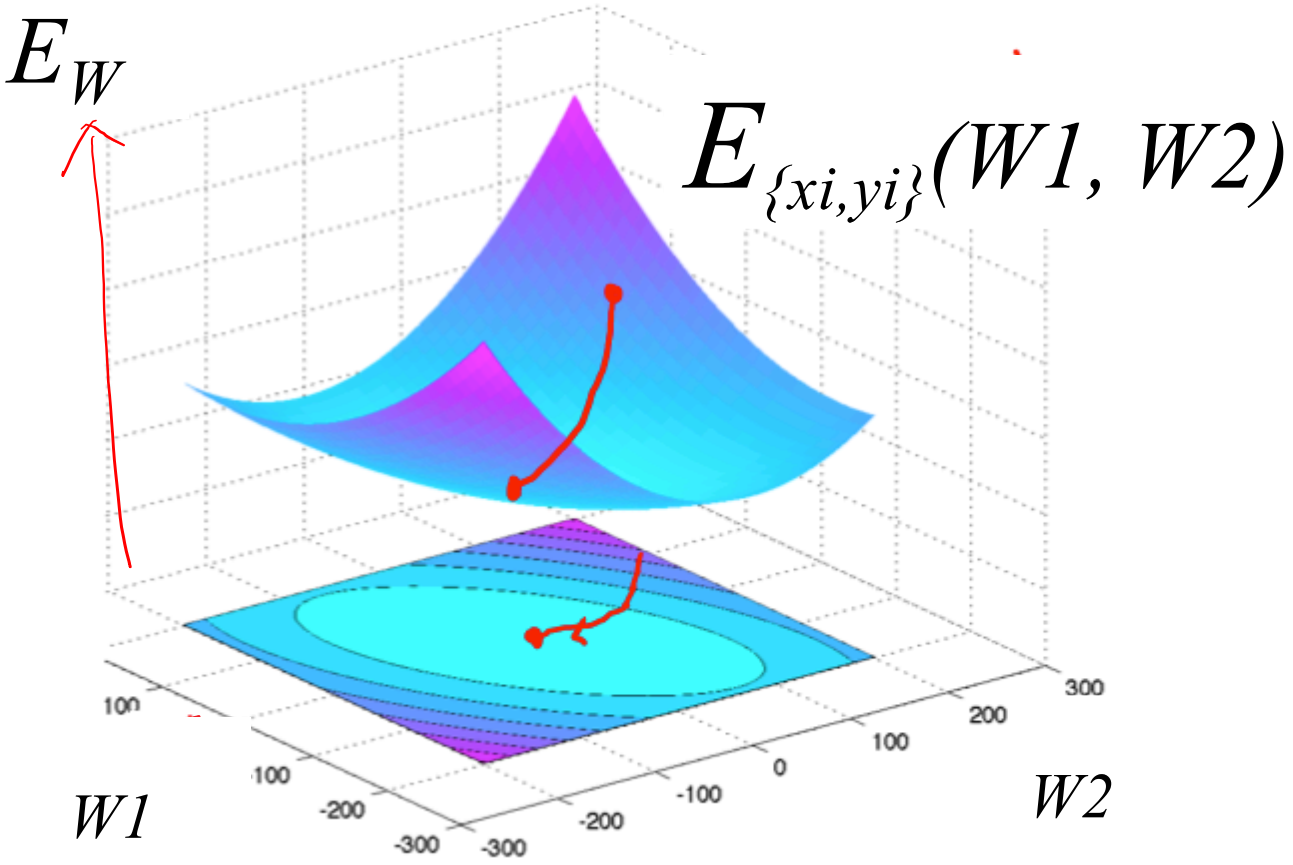
But how do we get gradients of lower layers?

- **Backpropagation!**
  - Repeated application of chain rule of calculus
  - Locally minimize the objective
  - Requires all “blocks” of the network to be differentiable

– Main Idea: error in hidden layers

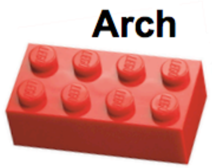
LeCun et. al. *Efficient Backpropagation*. 1998

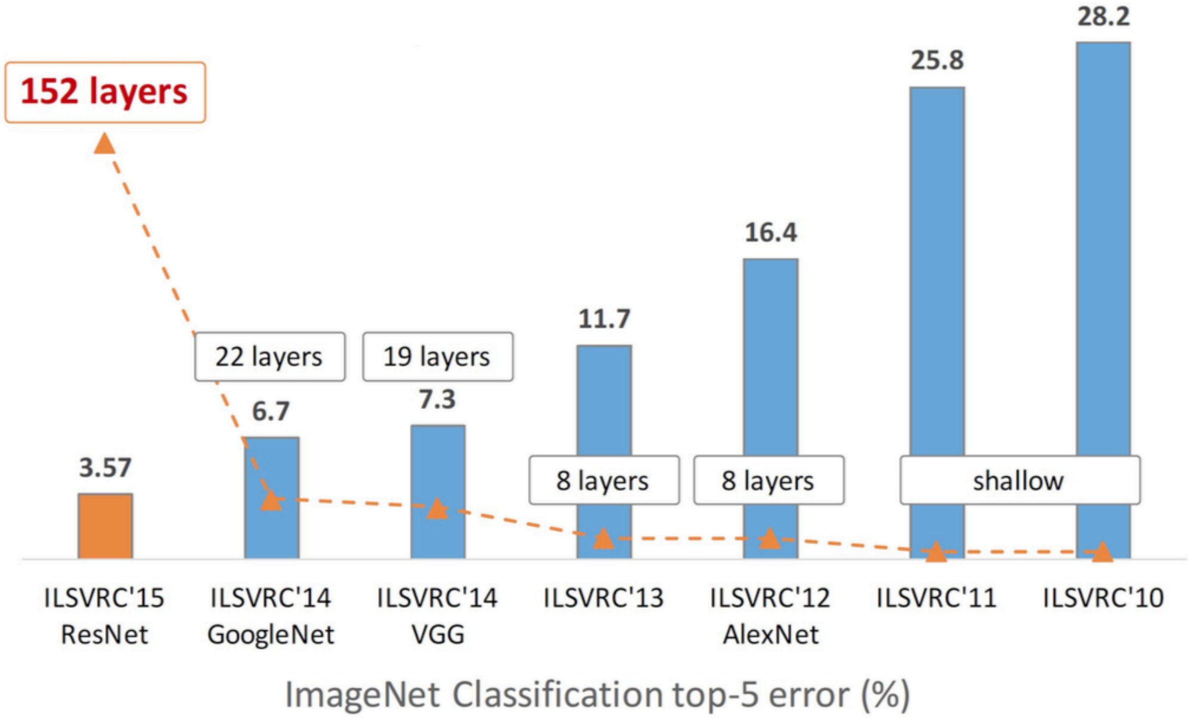
Illustrating Objective Loss Function (extremely simplified) and Gradient Descent (2D case)



The gradient points in the direction (in the variable space) of the greatest rate of increase of the function and its magnitude is the slope of the surface graph in that direction

Revolution of Depth



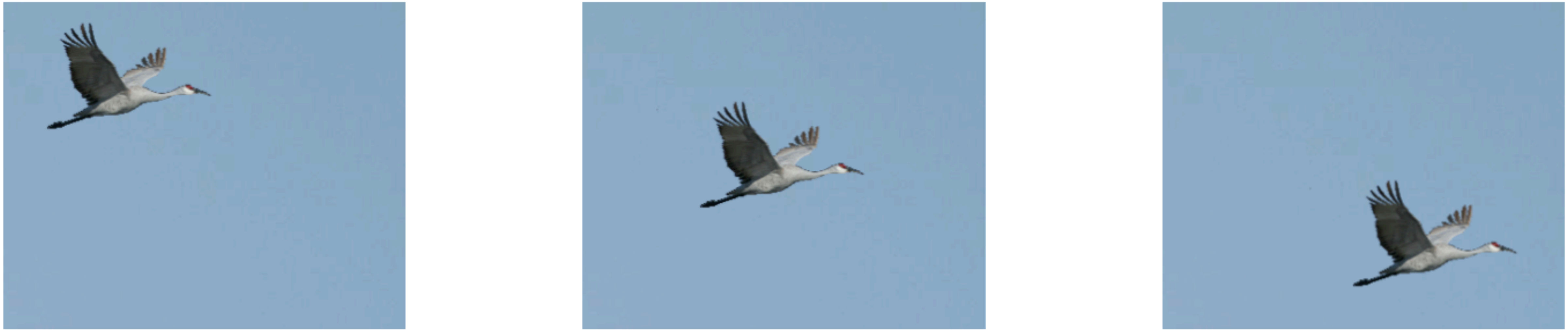


Kaiming He, Xiangyu Zhang, Shaoqing Ren, & Jian Sun. "Deep Residual Learning for Image Recognition". CVPR 2016.

Adapt from From NIPS 2017 DL Trend Tutorial

Important Block: Convolutional Neural Networks (CNN)

- Prof. Yann LeCun invented CNN in 1998
- First NN successfully trained with many layers

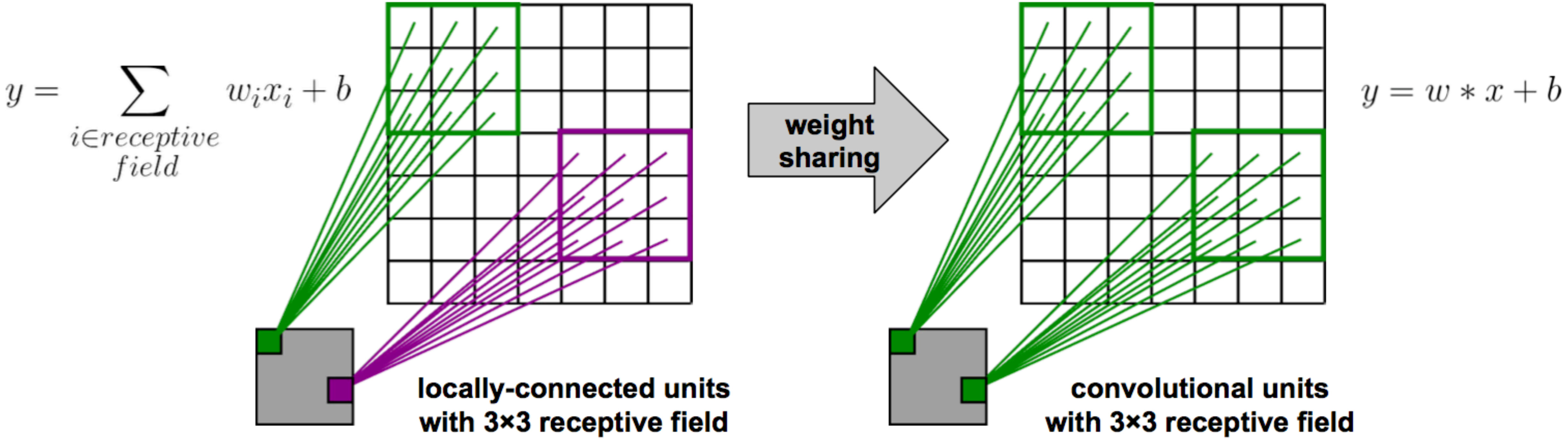


The bird occupies a local area and looks the same in different parts of an image.
We should construct neural nets which exploit these properties!

Y. LeCun, L. Bottou, Y. Bengio, and P. Haffner, Gradient-based learning applied to document recognition, Proceedings of the IEEE 86(11): 2278–2324, 1998.

CNN models Locality and Translation Invariance

Make fully-connected layer locally-connected and sharing weight



$$y = \sum_{i \in receptive\ field} w_i x_i + b$$

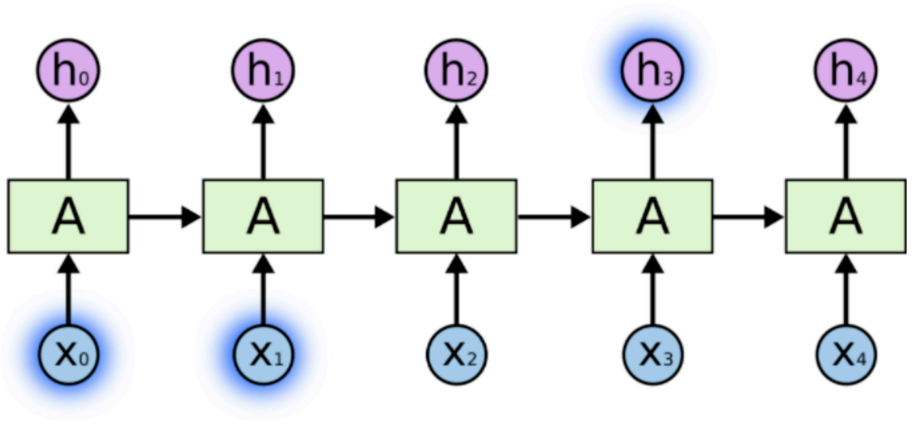
$$y = w * x + b$$

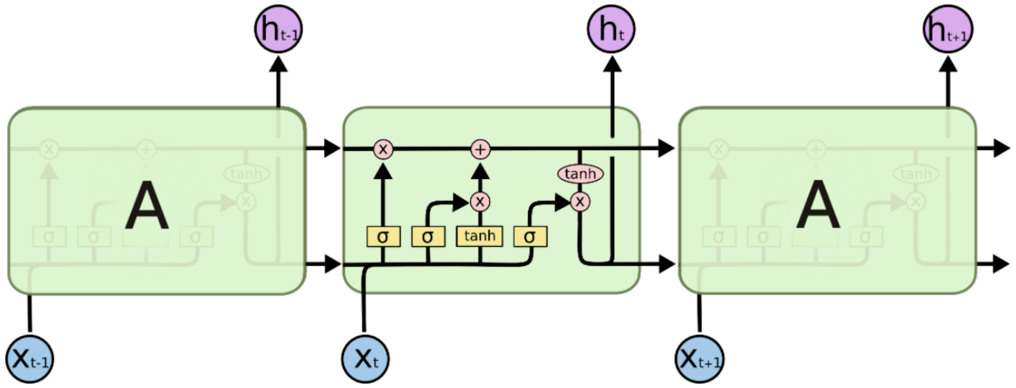
weight sharing
locally-connected units with 3×3 receptive field
convolutional units with 3×3 receptive field

Adapt from From NIPS 2017 DL Trend Tutorial

Important Block: Recurrent Neural Networks (RNN)

- Prof. Schmidhuber invented "Long short-term memory" – Recurrent NN (LSTM-RNN) model in 1997





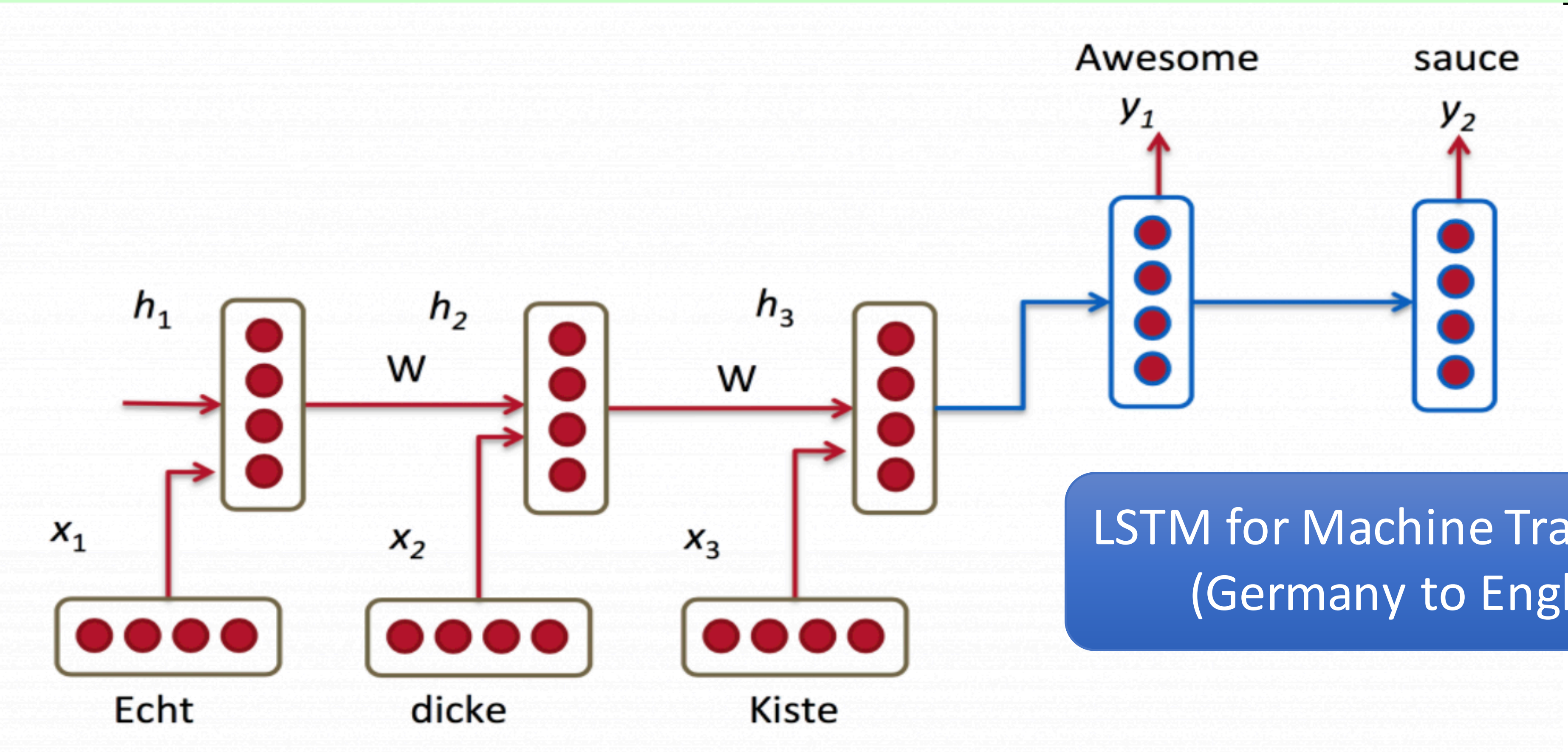
The repeating module in an LSTM contains four interacting layers.

Sepp Hochreiter; Jürgen Schmidhuber (1997). "Long short-term memory". Neural Computation. 9 (8): 1735–1780.

Image Credits from Christopher Olah

RNN models dynamic temporal dependency

- Make fully-connected layer model each unit recurrently
- Units form a directed chain graph along a sequence
- Each unit uses recent history and current input in modeling



LSTM for Machine Translation (Germany to English)

Image credit : wildML

- Deep Learning
  - Why is this a breakthrough ?
  - Basics
  - History
  - A Few Recent trends

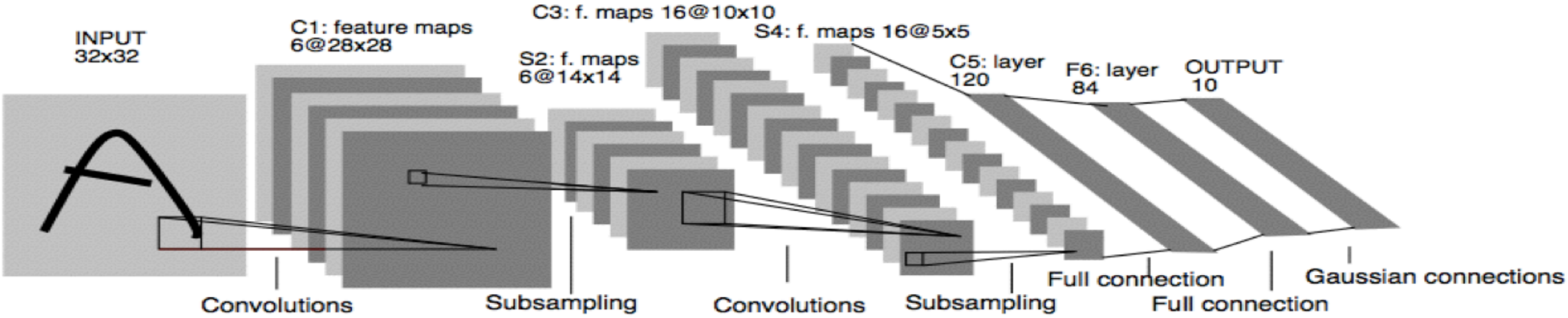
https://qdata.github.io/deep2Read/

Many classification models invented since late 80's

- Neural networks
- Boosting
- Support Vector Machine
- Maximum Entropy
- Random Forest
- ……

Deep Learning (CNN) in the 90's

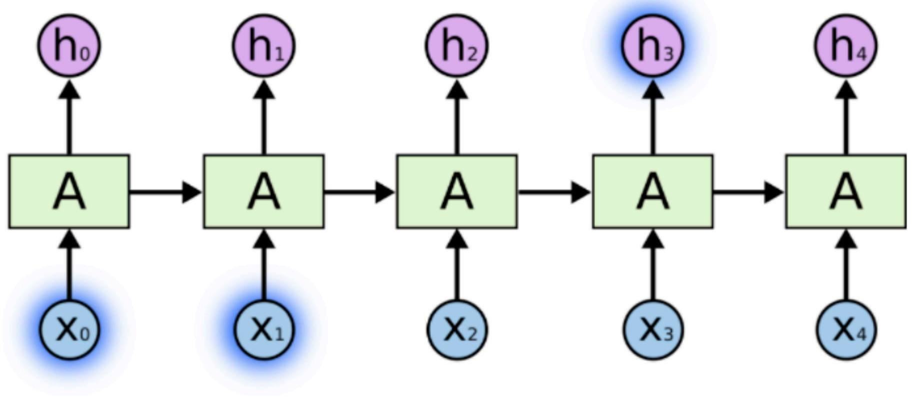
- Prof. Yann LeCun invented Convolutional Neural Networks (CNN) in 1998
- First NN successfully trained with many layers

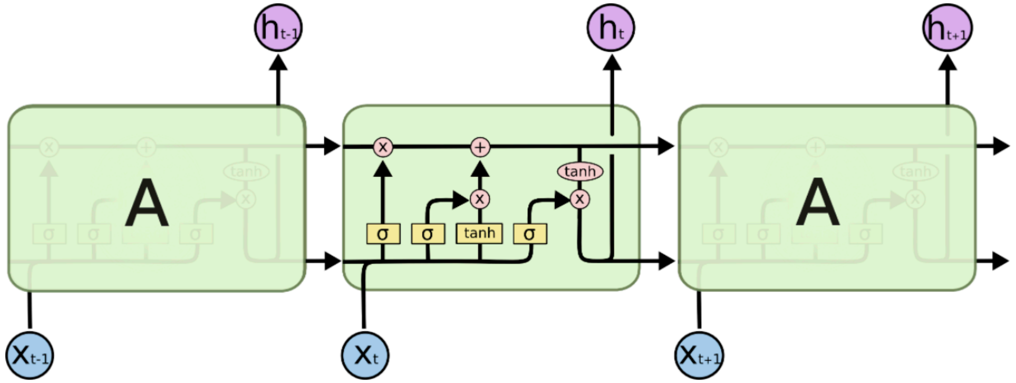


Y. LeCun, L. Bottou, Y. Bengio, and P. Haffner, Gradient-based learning applied to document recognition, Proceedings of the IEEE 86(11): 2278–2324, 1998.

Deep Learning (RNN) in the 90’s

- Prof. Schmidhuber invented "Long short-term memory” – Recurrent NN (LSTM-RNN) model in 1997





The repeating module in an LSTM contains four interacting layers.

Sepp Hochreiter; Jürgen Schmidhuber (1997). "Long short-term memory". Neural Computation. 9 (8): 1735–1780.

Image Credits from Christopher Olah

Between ~2000 to ~2011
Machine Learning Field Interest

- Learning with Structures ! + Convex Formulation!
  - Kernel learning
  - Manifold Learning
  - Sparse Learning
  - Structured input-output learning …
  - Graphical model
  - Transfer Learning
  - Semi-supervised
  - Matrix factorization
  - ……

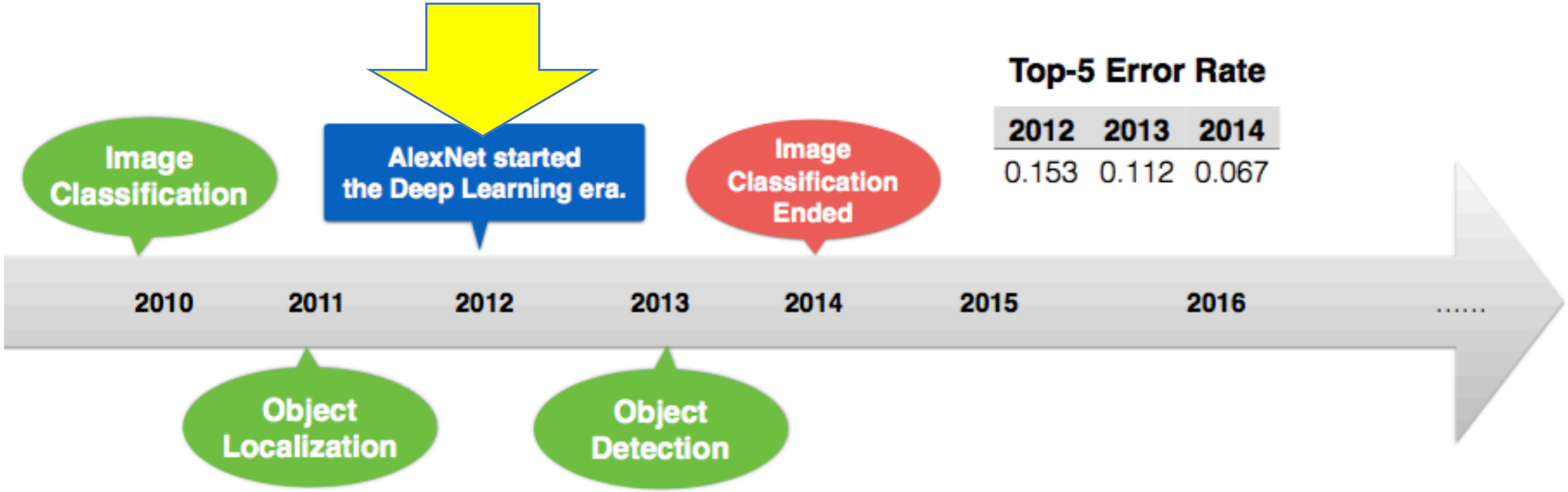
“Winter of Neural Networks” Since 90’s to ~2011

- Non-convex

- Need a lot of tricks to play with
  - How many layers ?
  - How many hidden units per layer ?
  - What topology among layers ? …….

- Hard to perform theoretical analysis

Breakthrough in 2012 Large-Scale Visual Recognition Challenge (ImageNet) : Milestones in Recent Vision/AI Fields



Top-5 Error Rate

2012	2013	2014
0.153	0.112	0.067

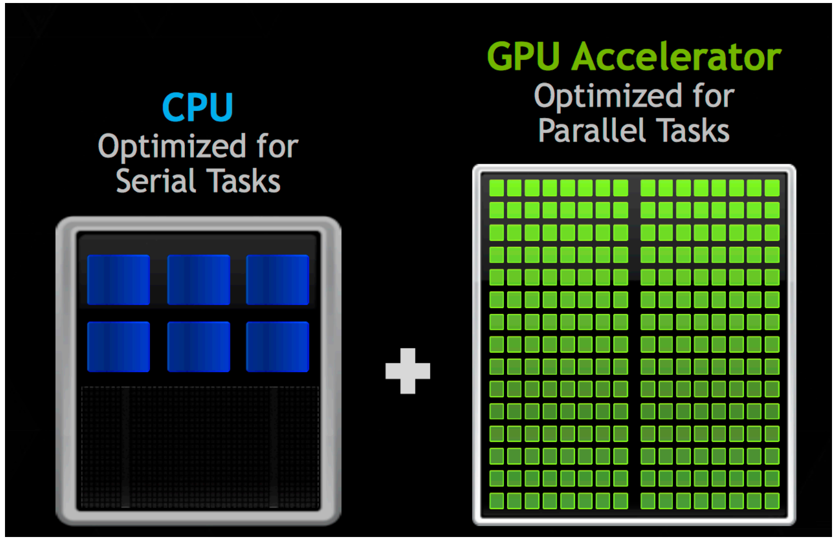
- 2013, Google Acquired Deep Neural Networks Company headed by Utoronto “Deep Learning” Professor Hinton
- 2013, Facebook Built New Artificial Intelligence Lab headed by NYU “Deep Learning” Professor LeCun
- 2016, Google's DeepMind defeats legendary Go player Lee Se-dol in historic victory / 2017 Alpha Zero

Reason: Plenty of (Labeled) Data

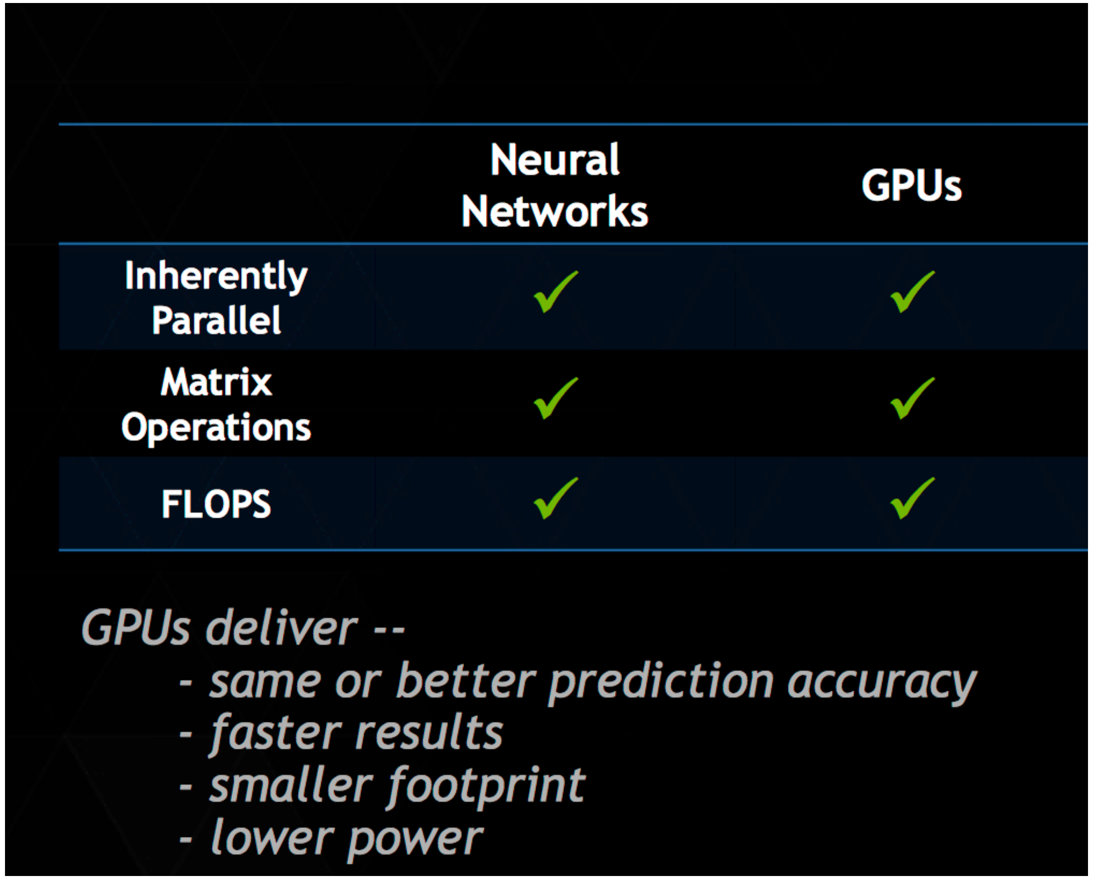
- Text: trillions of words of English + other languages
- Visual: billions of images and videos
- Audio: thousands of hours of speech per day
- User activity: queries, user page clicks, map requests, etc,
- Knowledge graph: billions of labeled relational triplets
- ....

Dr. Jeff Dean’s talk

Reason: Advanced Computer Architecture that fits DNNs



http://www.nvidia.com/content/events/geoInt2015/LBrown_DL.pdf



	Neural Networks	GPUs
Inherently Parallel	✓	✓
Matrix Operations	✓	✓
FLOPS	✓	✓

GPUs deliver --

- *same or better prediction accuracy*
- *faster results*
- *smaller footprint*
- *lower power*

Some Recent Trends

https://qdata.github.io/deep2Read/

- 1. Autoencoder / layer-wise training
- 2. CNN / Residual / Dynamic parameter
- 3. RNN / Attention / Seq2Seq, …
- 4. Neural Architecture with explicit Memory
- 5. NTM 4program induction / sequential decisions
- 6. Learning to optimize / Learning DNN architectures
- 7. Learning to learn / meta-learning/ few-shots
- 8. DNN on graphs / trees / sets
- 9. Deep Generative models, e.g., autoregressive
- 10. Generative Adversarial Networks (GAN)
- 11. Deep reinforcement learning
- 12. Validate / Evade / Test / Understand / Verify DNNs

Recap

https://qdata.github.io/deep2Read/

Inputs and Outputs

Architectures:

Losses

Learned Models

Adapt from From NIPS 2017 DL Trend Tutorial

Making Deep Learning Understandable for Analyzing Sequential Data about Gene Regulation

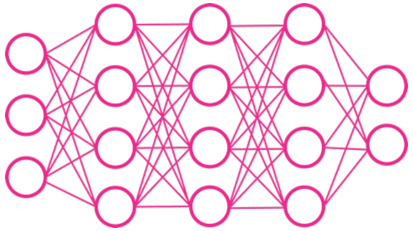
Dr. Yanjun Qi
Department of Computer Science
University of Virginia

Tutorial @ ACM BCB-2018

BREAK 5mins ->Second Half

State-of-the-art: Deep Neural Networks (DNNs)

→

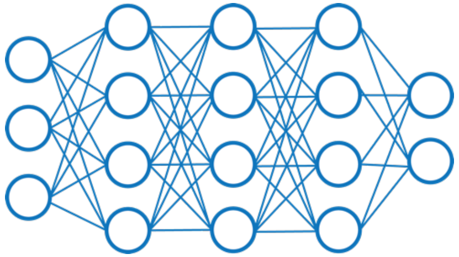


→ “Dog”

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.

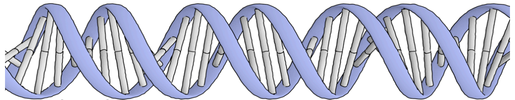
Full Review... | May 25, 2006

→

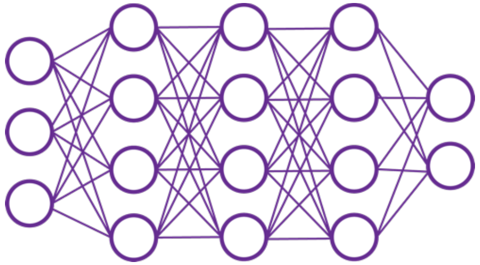


→ 👍

ATGCGATCAAGTCTG



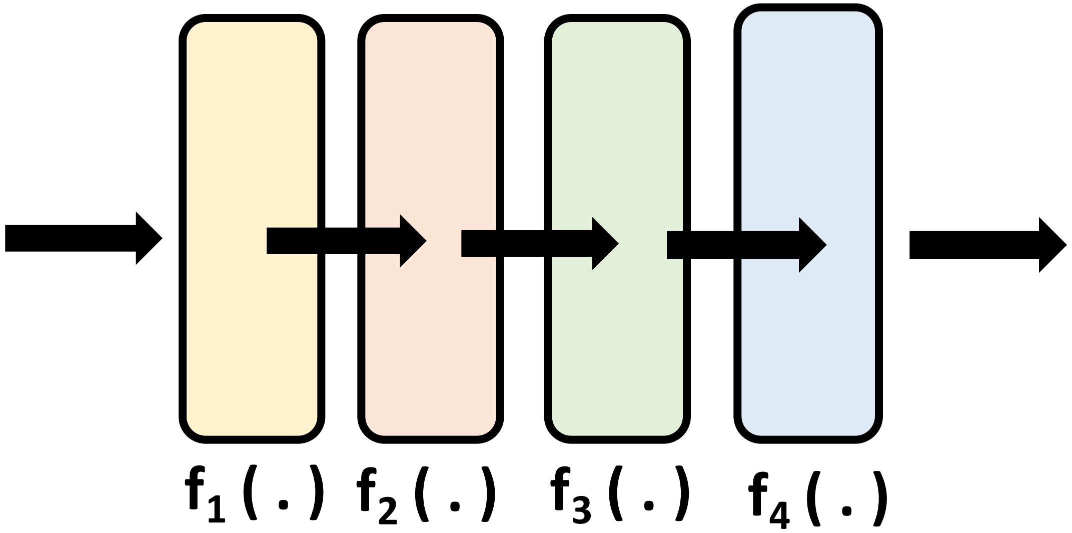
→



→ “Protein-binding Site”

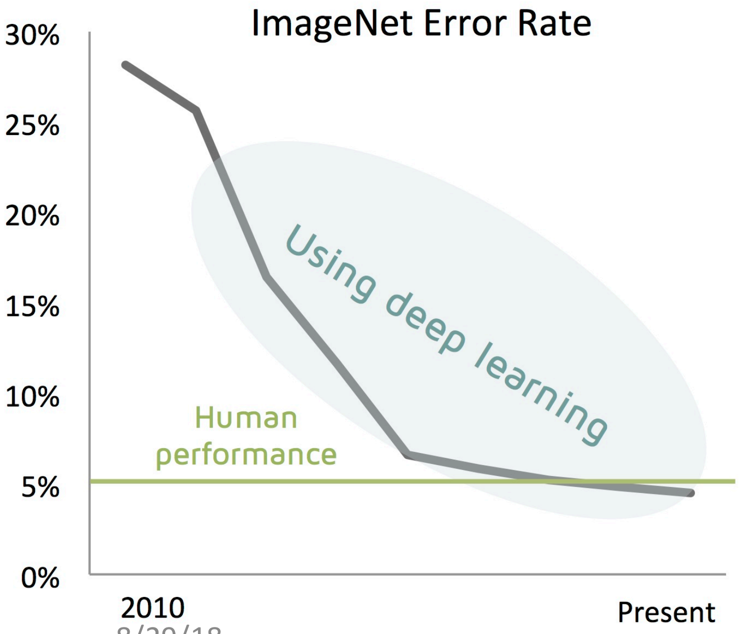
Challenge : DNNs are hard to Interpret

X

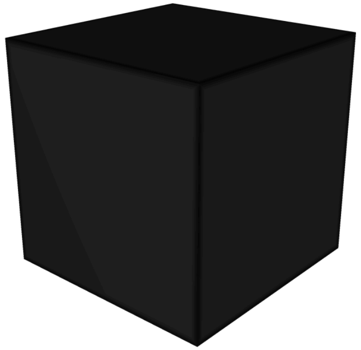


Y

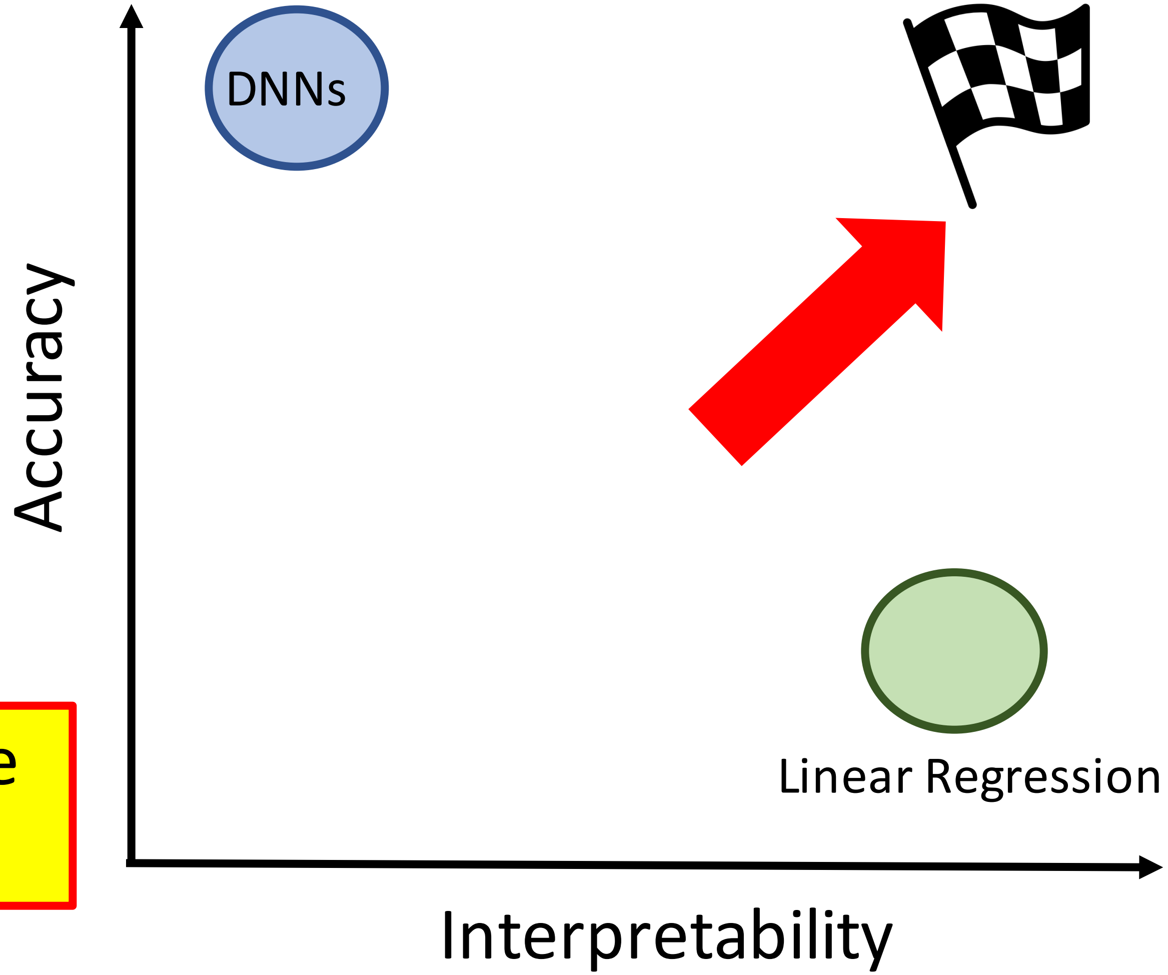
“Dog”


ImageNet Error Rate

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



Our Goal: Interpretable DNNs



Challenge : DNNs are hard to Interpret

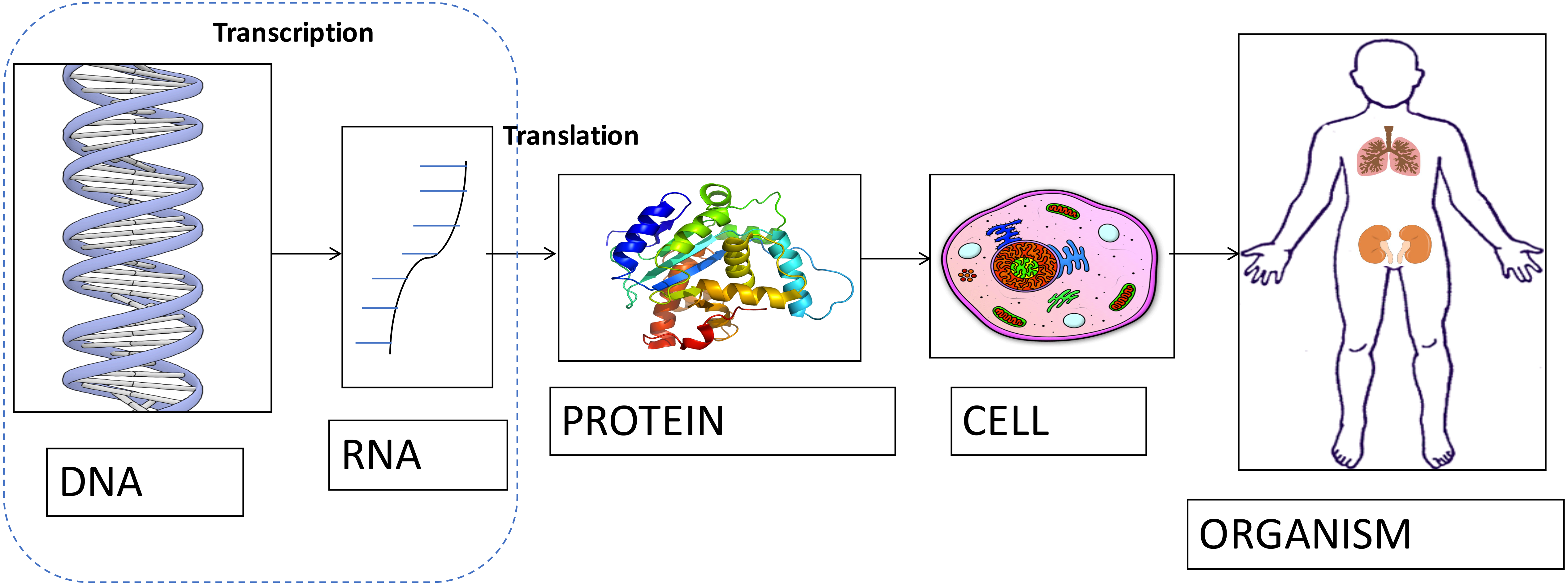
Today

- Machine Learning: a quick review
- Deep Learning: a quick review
- Background Biology: a quick review
- Deep Learning for analyzing Sequential Data about Regulation:
  - DeepChrome
  - AttentiveChrome
  - DeepMotif

https://qdata.github.io/deep2Read/

https://www.deepchrome.org

Biology in a Slide



Transcription

Translation

DNA

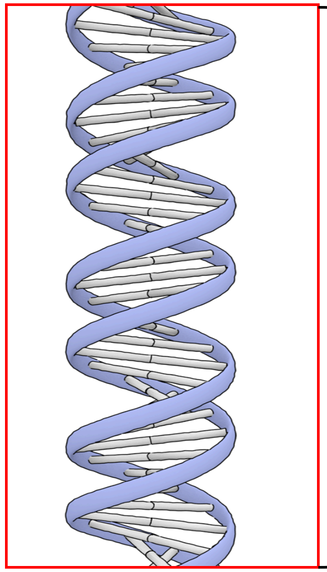
RNA

PROTEIN

CELL

ORGANISM

DNA and Diseases



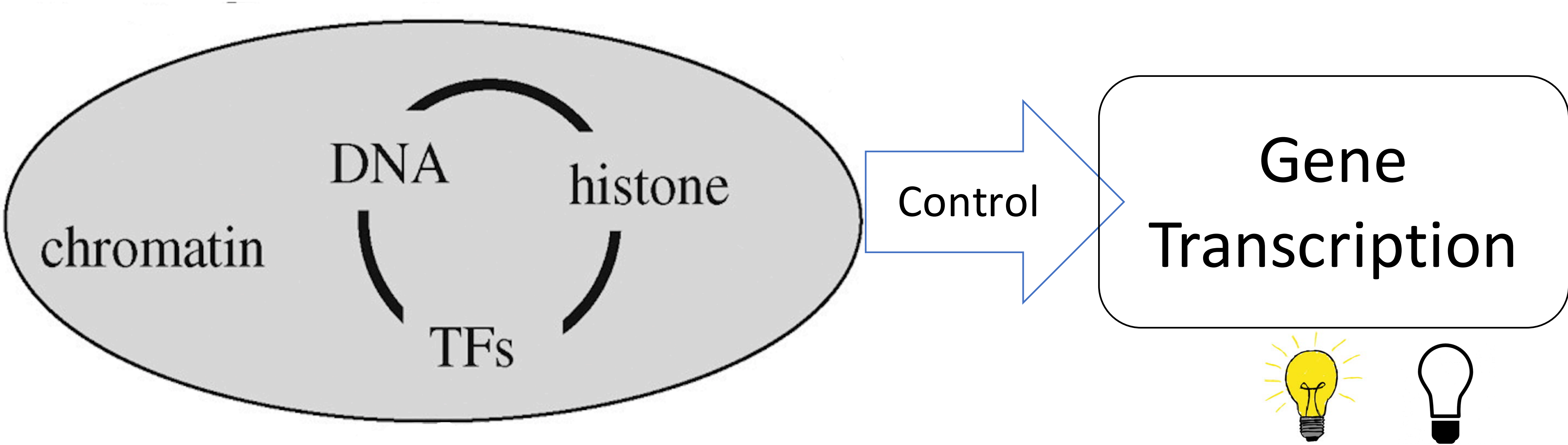
DNA

- Down Syndrome
- Parkinson’s Disease
- Autism
- Muscular Atrophy
- Sickle Cell Disease

……….

………..

Chromatin

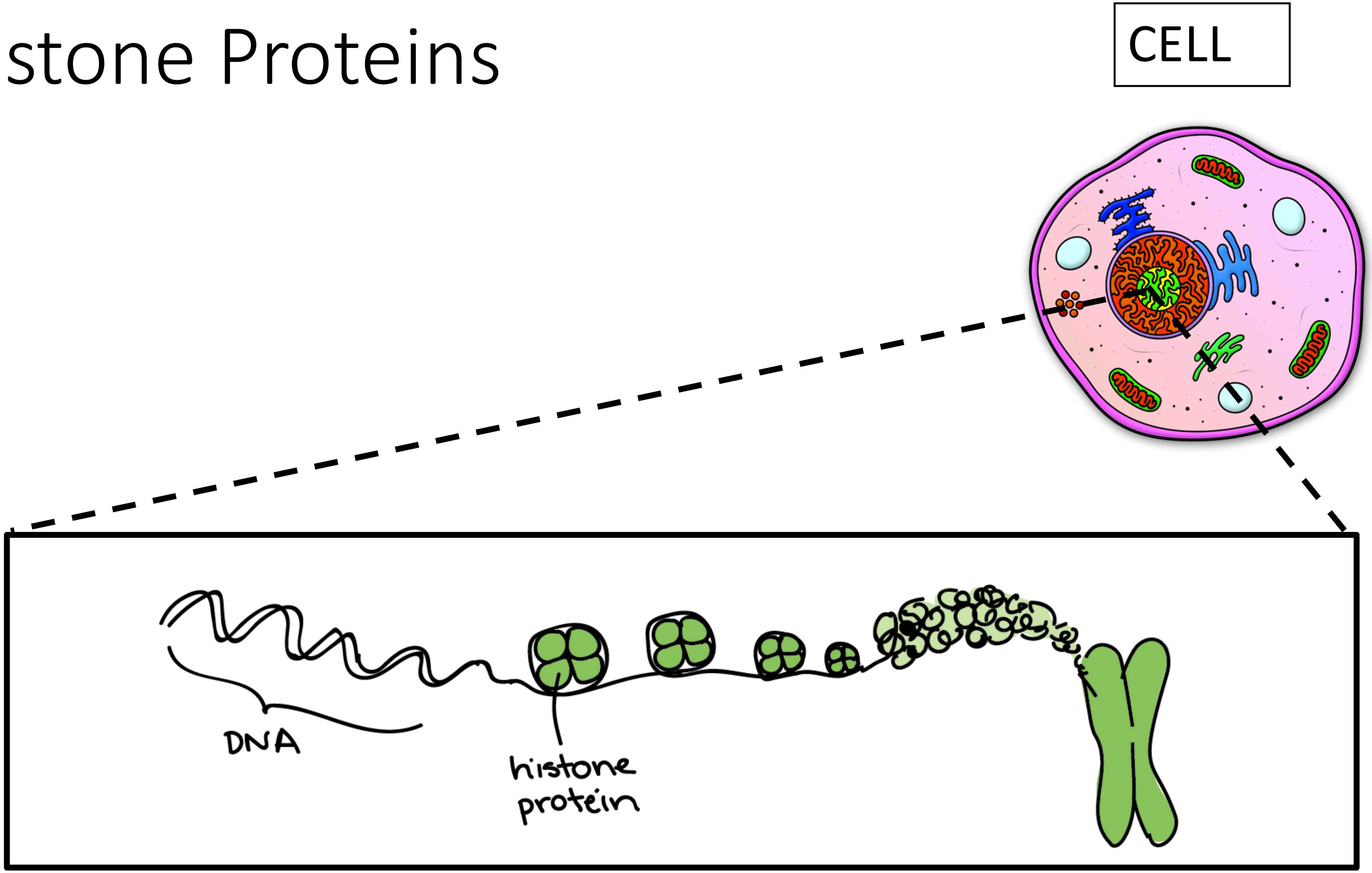


Control

Gene Transcription

Epigenetics
“Environment of the DNA”

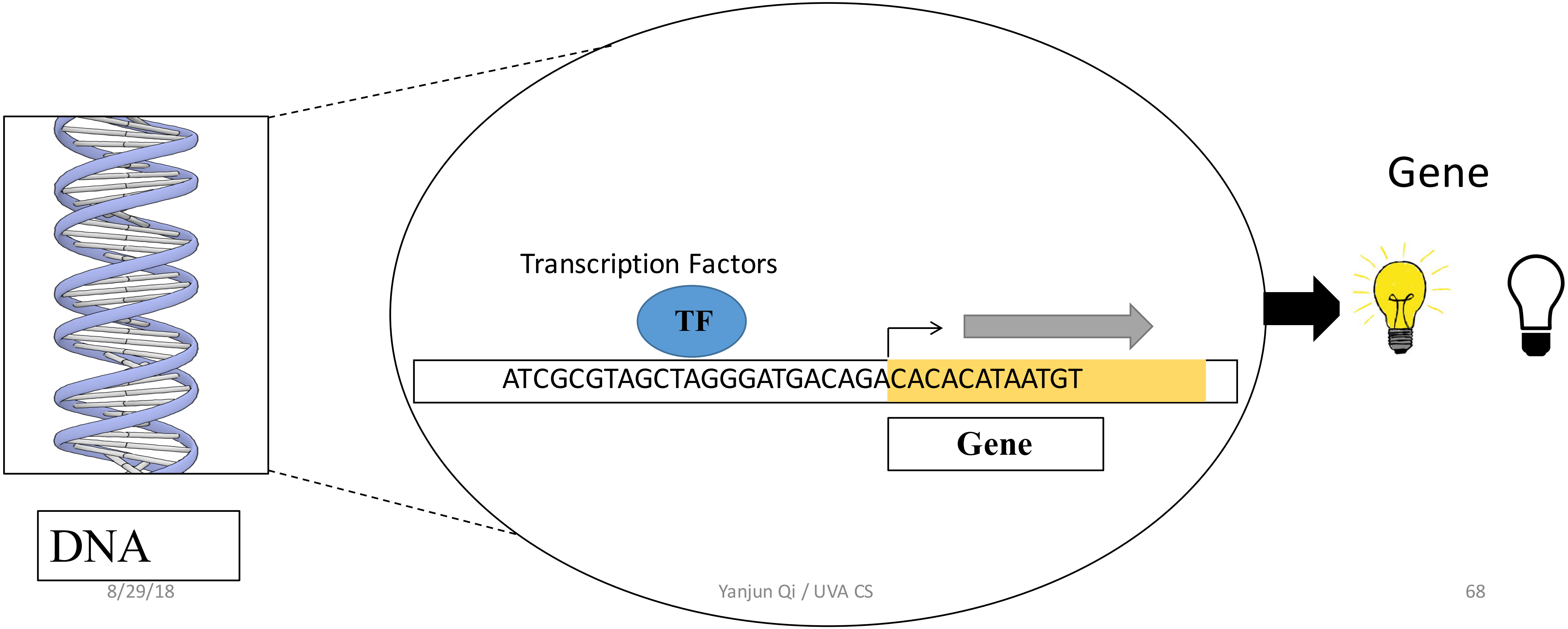
Histone Proteins



CELL

Image:https://www.khanacademy.org/science/biology/cellular-molecular-biology/intro-to-cell-division/a/dna-and-chromosomes-article

Transcription Factor Binding => Gene Transcription



Transcription Factors

TF

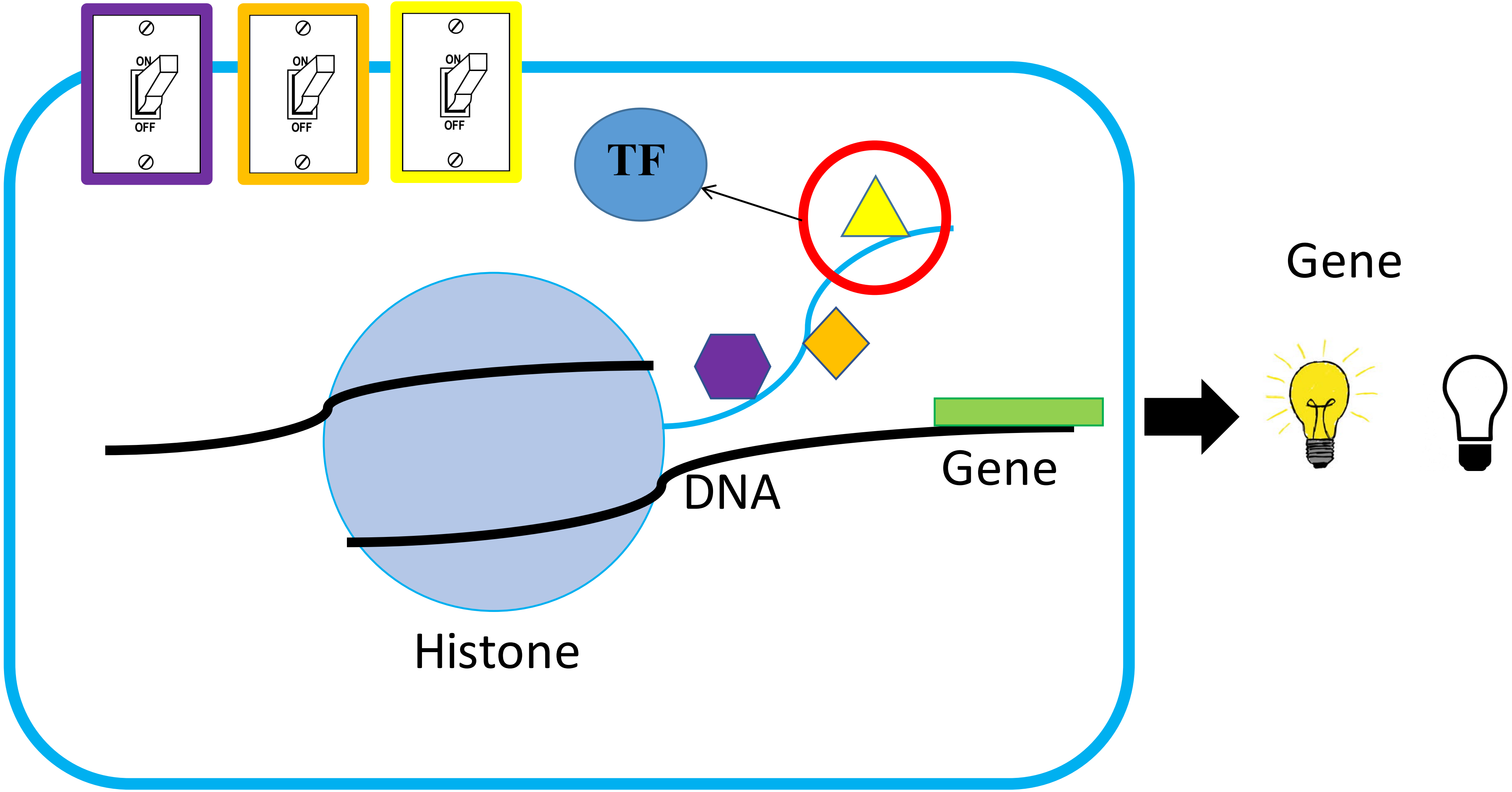
ATCGCGTAGCTAGGGATGACAGACACACATAATGT

Gene

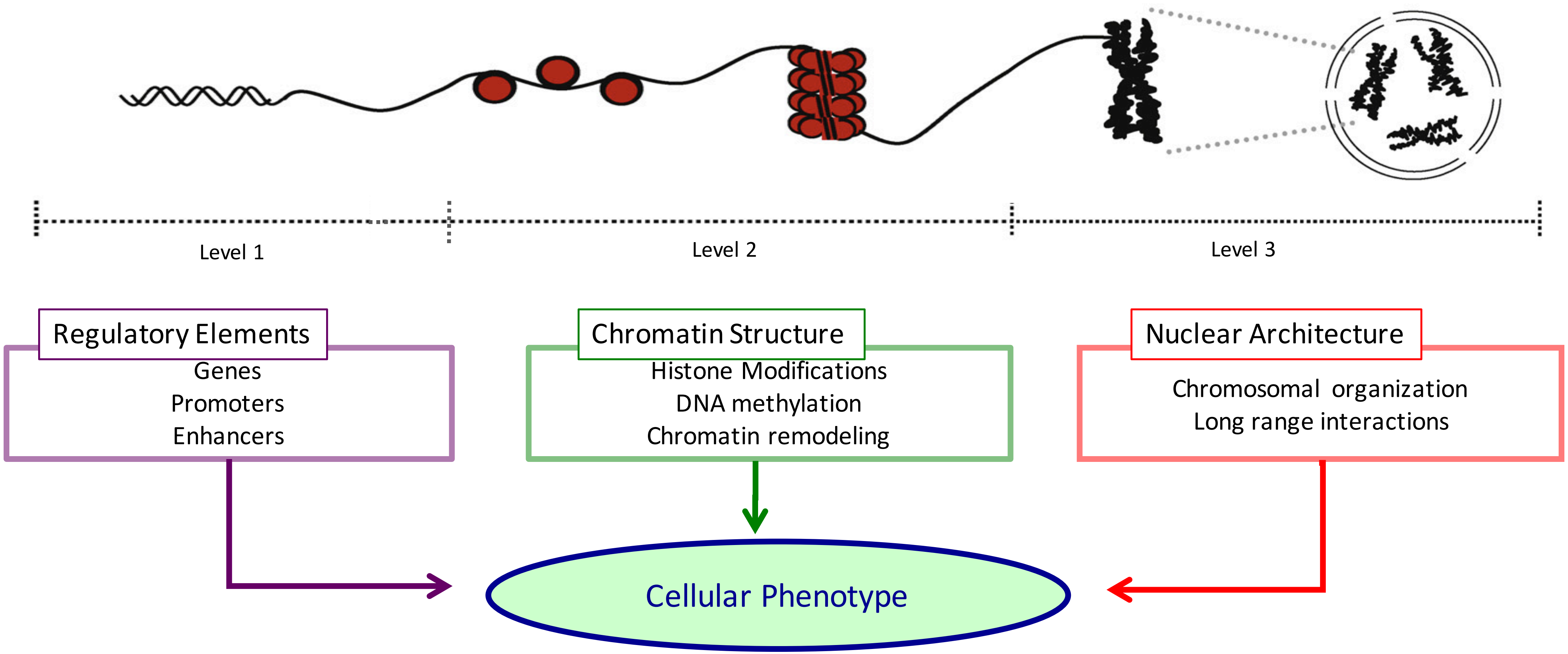
DNA

Gene

Histone Modifications (HM)



Genome Organization and Gene Regulation



Regulatory Elements

Genes
Promoters
Enhancers

Chromatin Structure

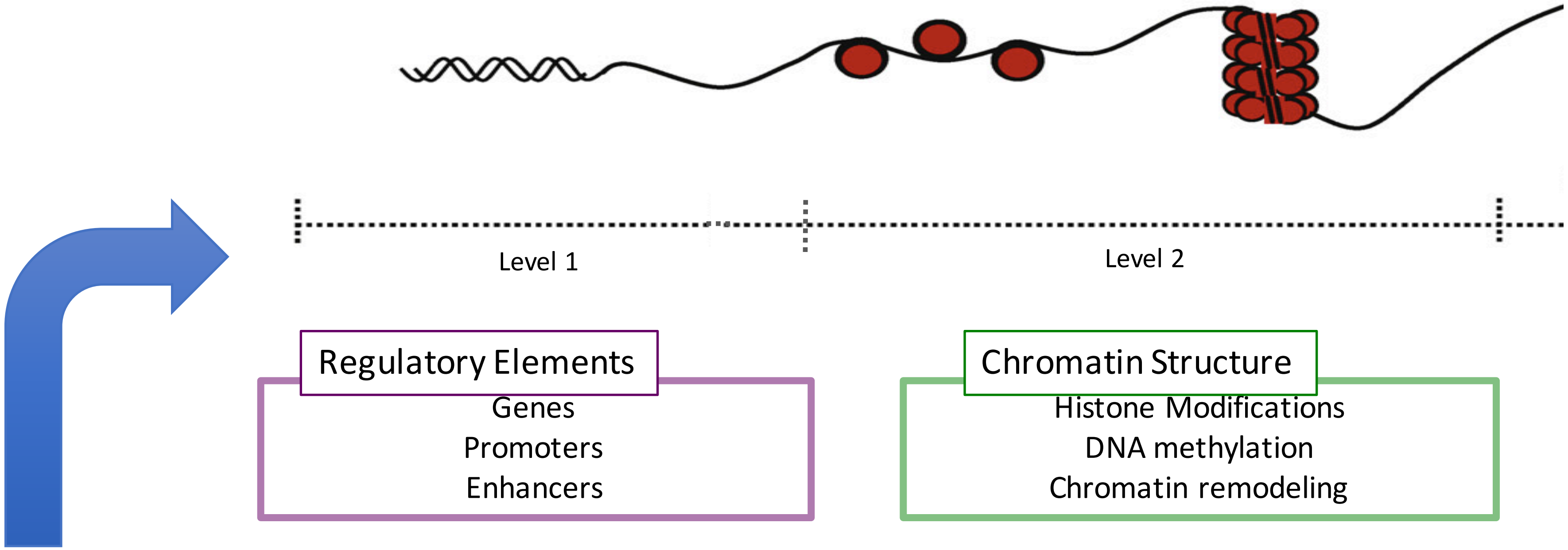
Histone Modifications
DNA methylation
Chromatin remodeling

Nuclear Architecture

Chromosomal organization
Long range interactions

Cellular Phenotype

(adapted from Babu et al., 2008)



Regulatory Elements

Genes
Promoters
Enhancers

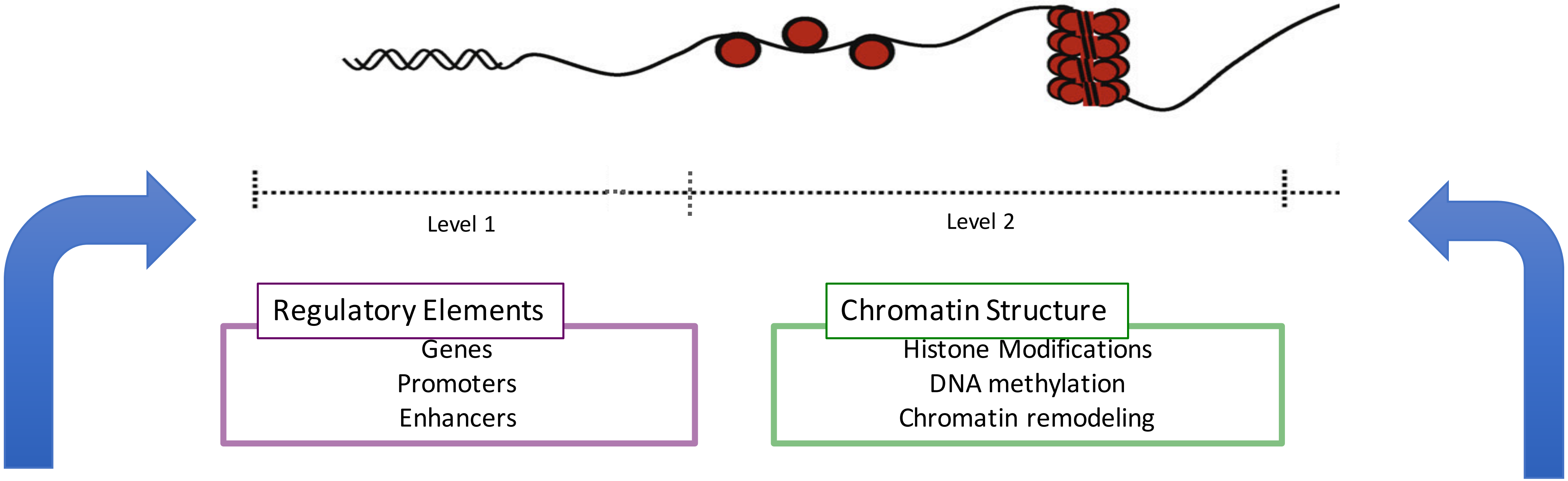
Chromatin Structure

Histone Modifications
DNA methylation
Chromatin remodeling

ENCODE Project (2003-Present)

Describe the functional elements encoded in human DNA

nature
ENCODE
GUIDEBOOK TO THE HUMAN GENOME
The ENCODE project in print and online
Science
GENES IN ACTION
AAAS
nature
MARS'S ANCIENT OCEAN
Polar wander solves an enigma
THE DEPTHS OF DISGUST
Understanding the ugliest emotion
MENTORING
How to be top
NATUREJOBS
Contract research
DECODING THE BLUEPRINT
The ENCODE pilot maps human genome function



Level 1

Level 2

Regulatory Elements

Genes

Promoters

Enhancers

Chromatin Structure

Histone Modifications

DNA methylation

Chromatin remodeling

ENCODE Project (2003-)

Describe the functional elements encoded in human DNA

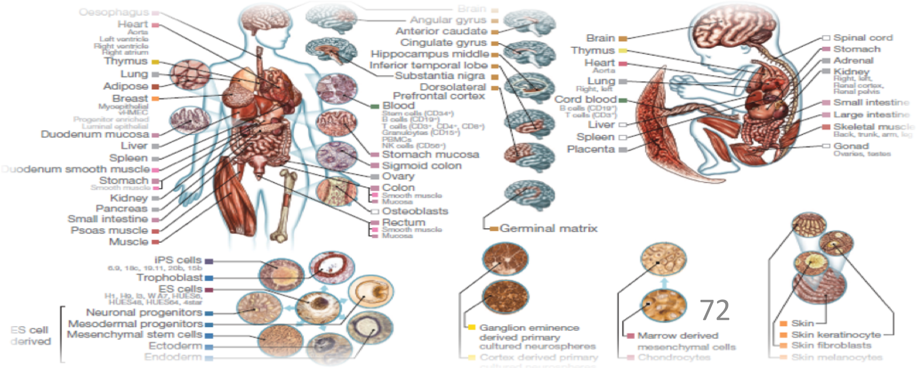
Roadmap Epigenetics Project (REMC, 2008-)

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.

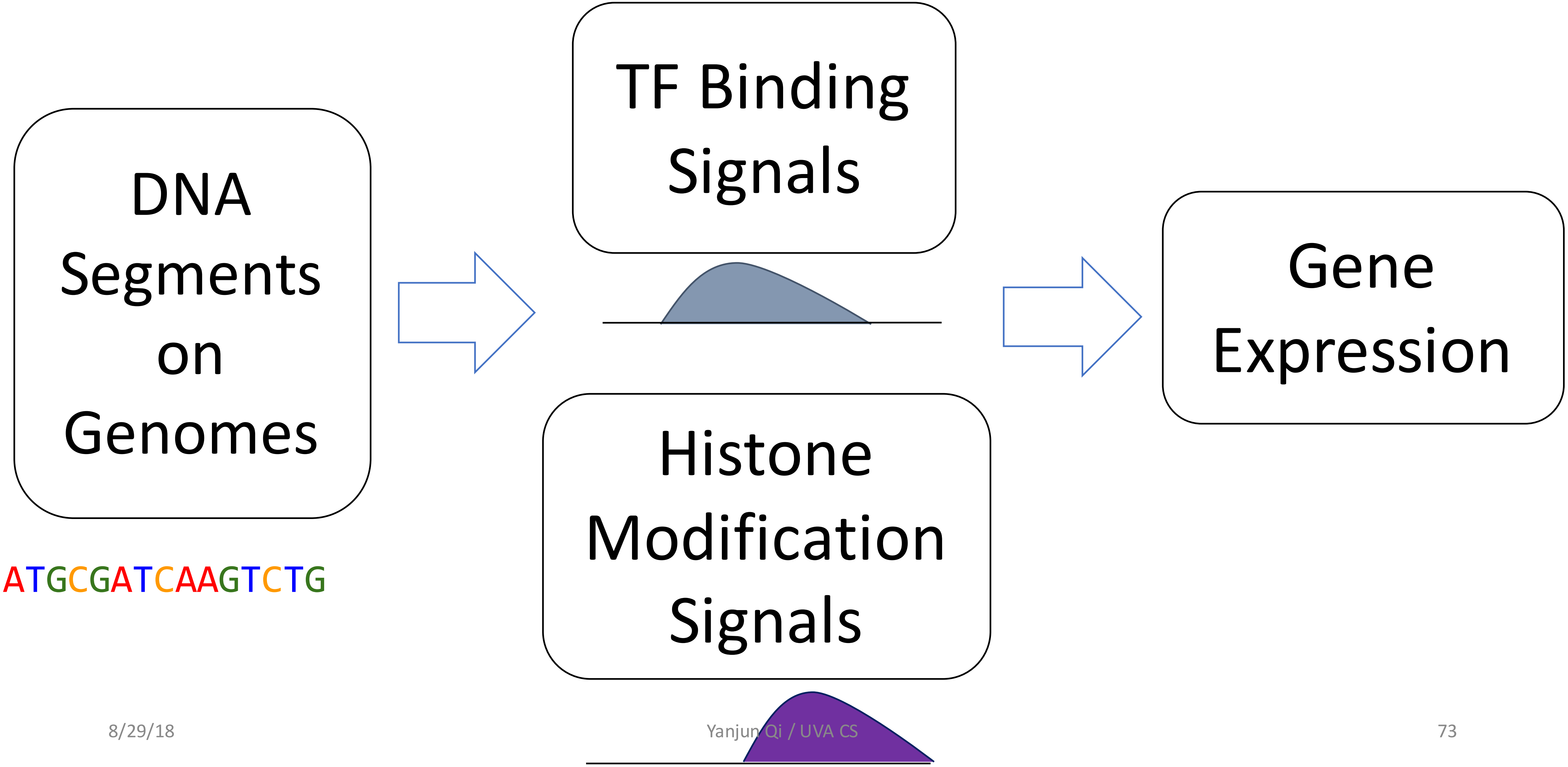
Nature

February 18, 2015

Integrative analysis of 111 reference human epigenomes (Abstract)



Many Important Data-Driven Computational Tasks



DNA Segments on Genomes

ATGCGATCAAGTCTG

TF Binding Signals

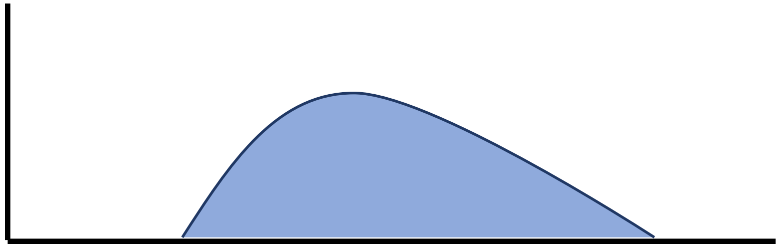
Histone Modification Signals

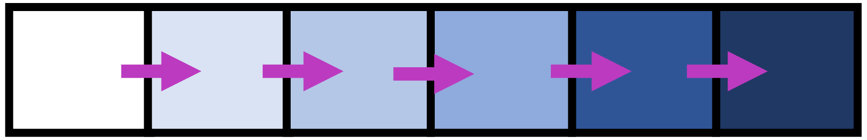
Gene Expression

Sequential Input (X)

Strings, signals etc.

ATCGATCTCTAGATCTCTG. .

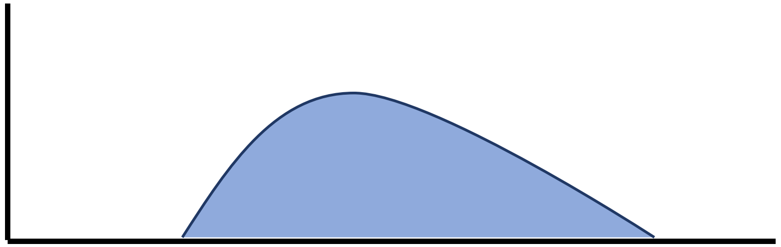


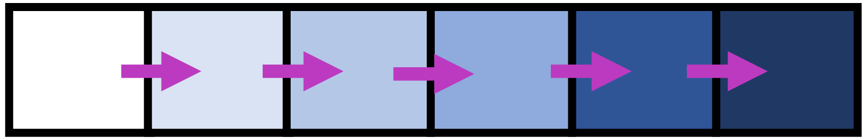


Sequential Input (X)

Strings, signals etc.

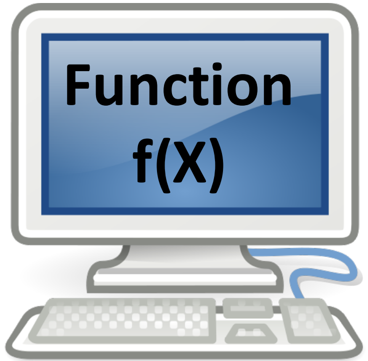
ATCGATCTCTAGATCTCTG..





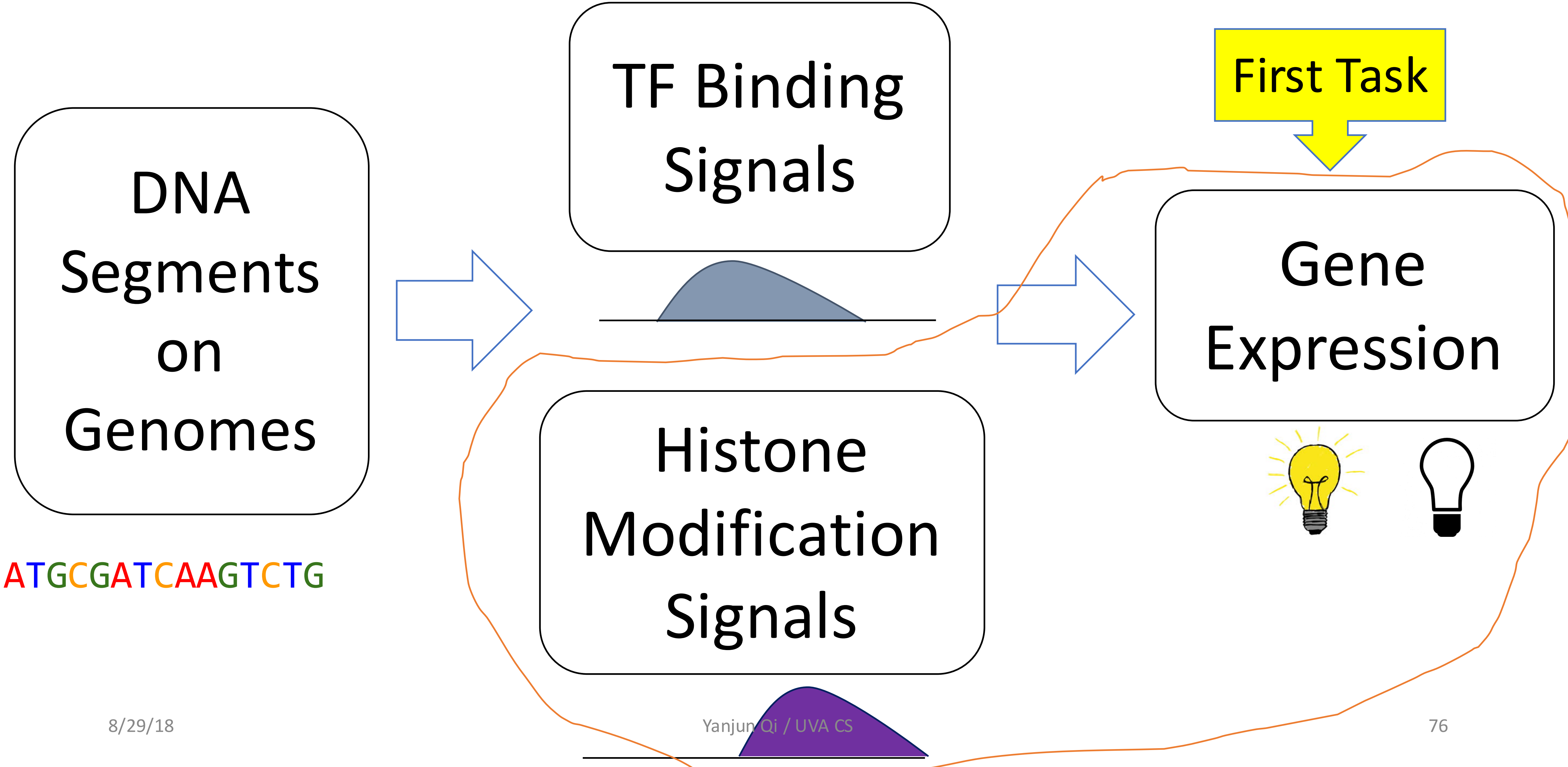
X

This Food is not good.



NO
(-1)

Many Important Data-Driven Computational Tasks



DNA Segments on Genomes

ATGCGATCAAGTCTG

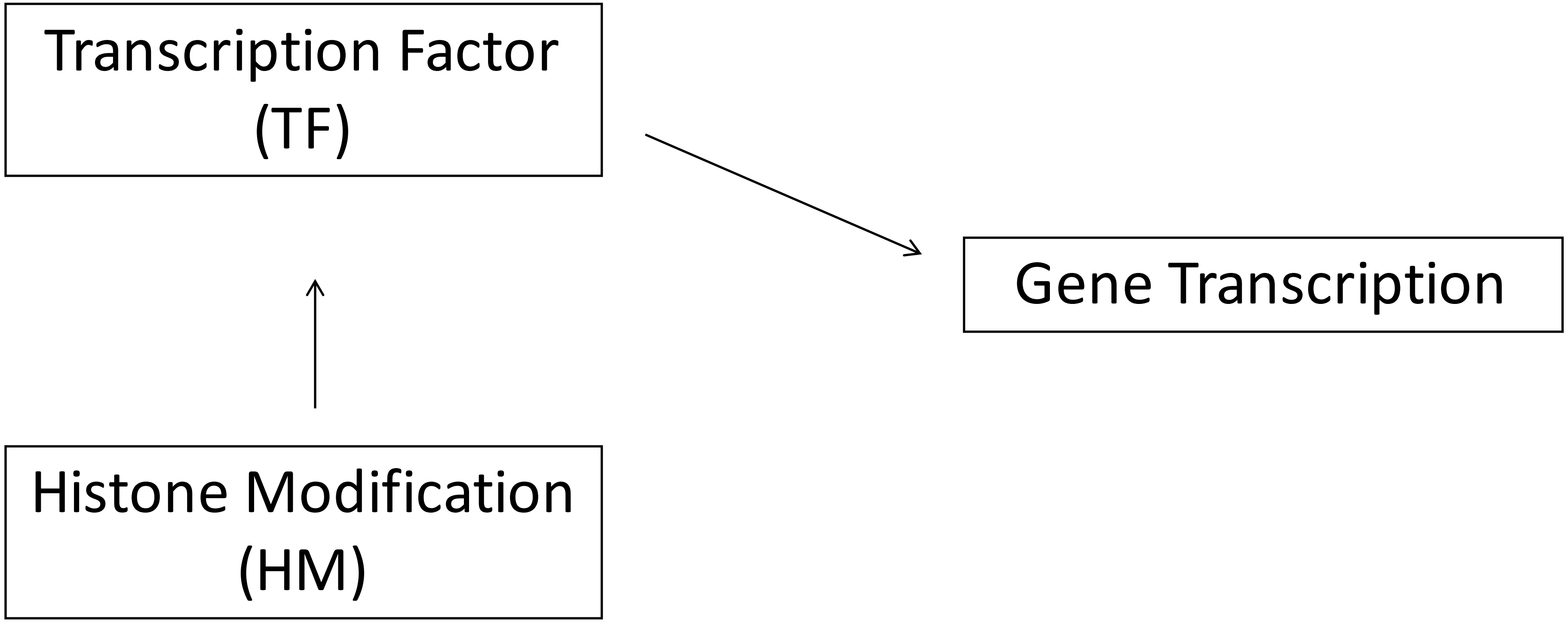
TF Binding Signals

Histone Modification Signals

First Task

Gene Expression

Histone Modification and Gene Transcription

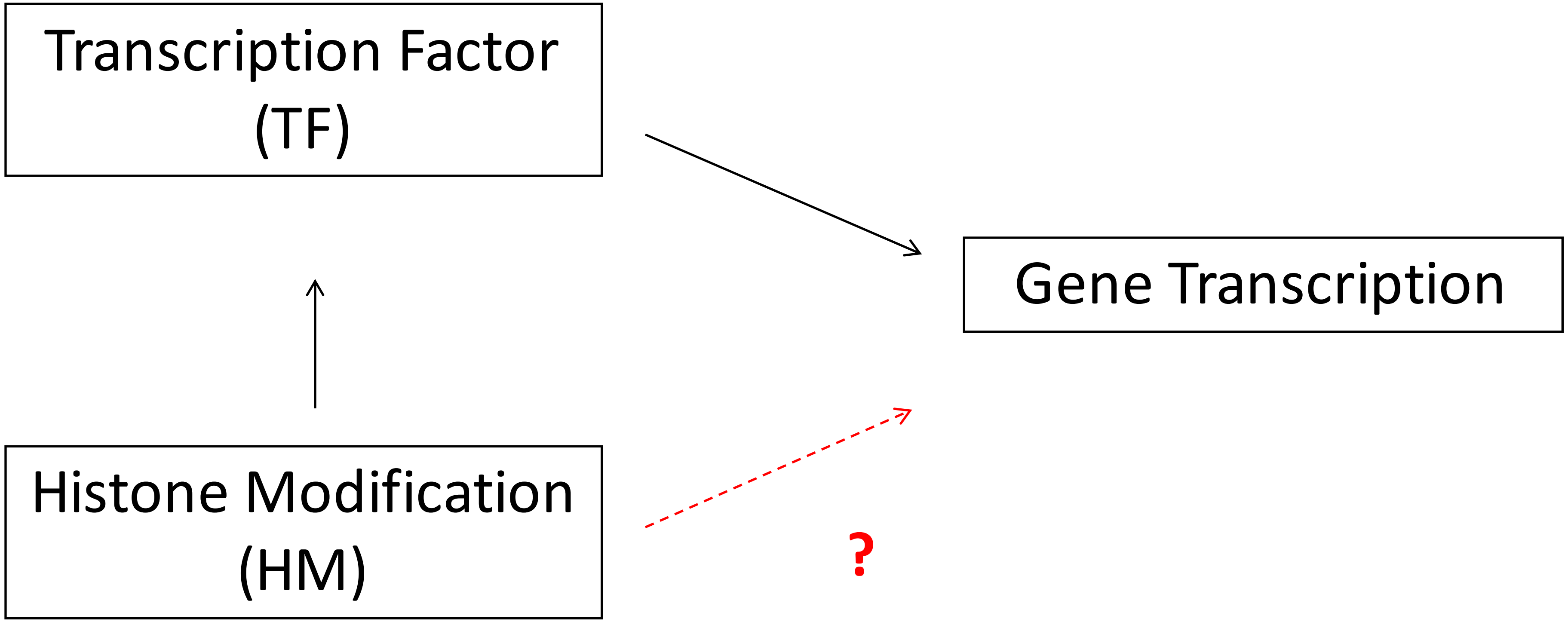


Transcription Factor (TF)

Gene Transcription

Histone Modification (HM)

Histone Modification and Gene Transcription



Transcription Factor (TF)

Gene Transcription

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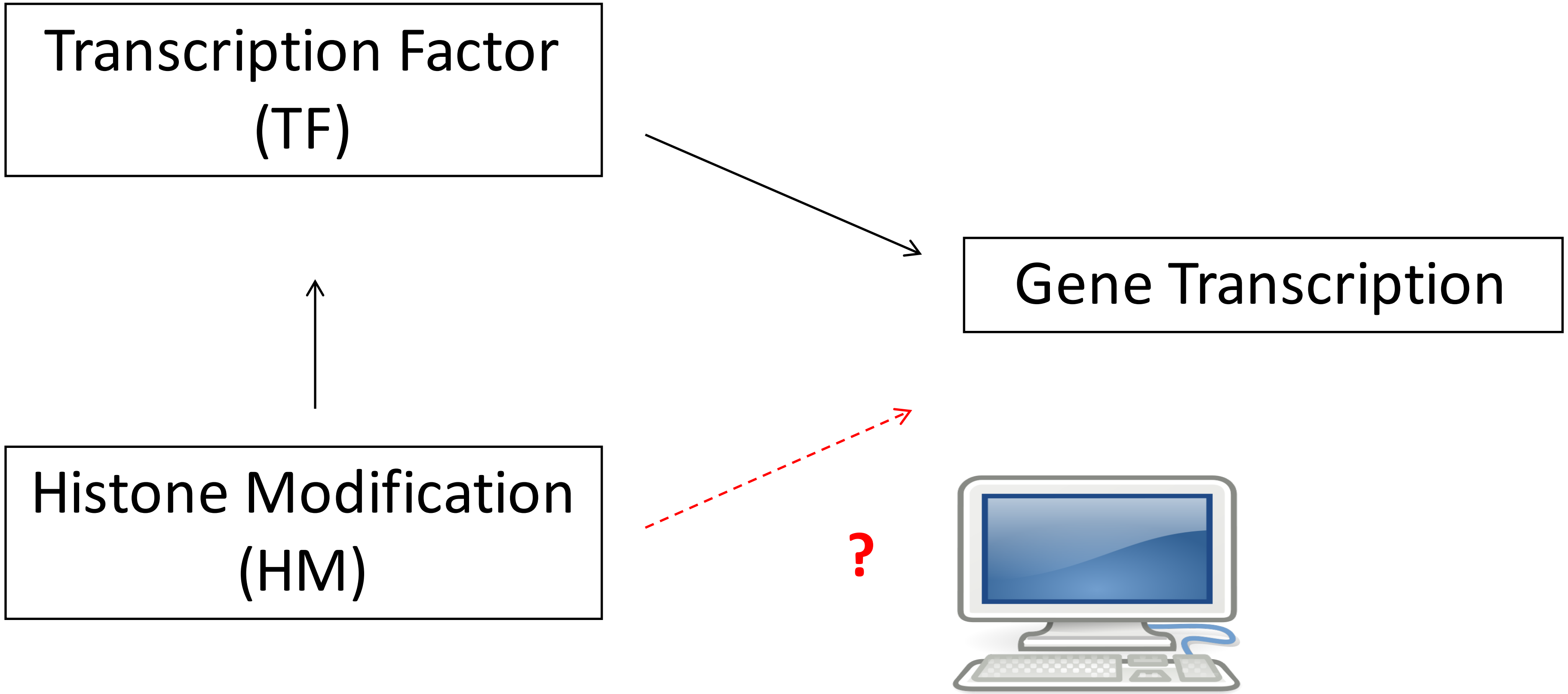
Histone Modification and Gene Transcription



Transcription Factor (TF)

Gene Transcription

Histone Modification (HM)

?

Why Studying [HM => Gene Expression] ?

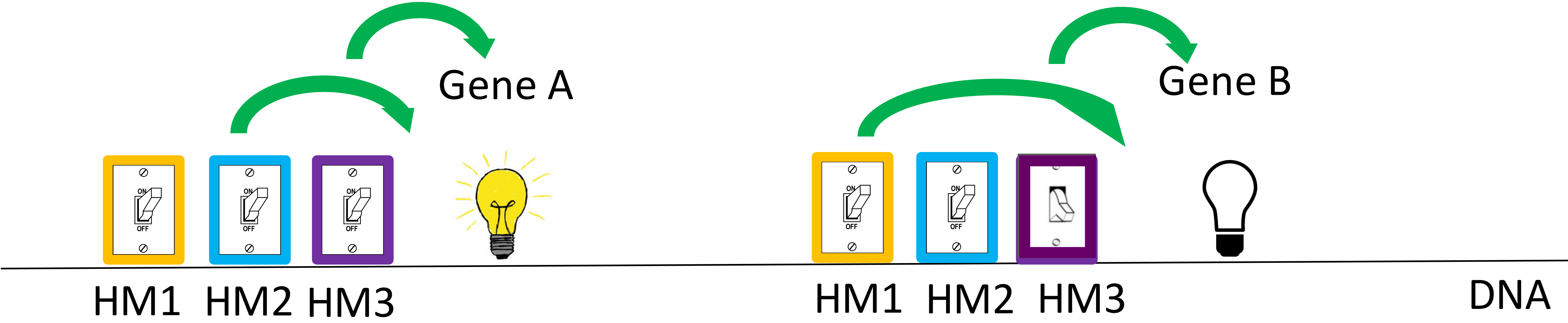
- Epigenomics:
  - Study of chemical changes in DNA and histones (without altering DNA sequence)
  - Inheritable and involved in regulating gene expression, development, tissue differentiation and suppression …

- 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 how HMs influence genes?

~56 Cell Types



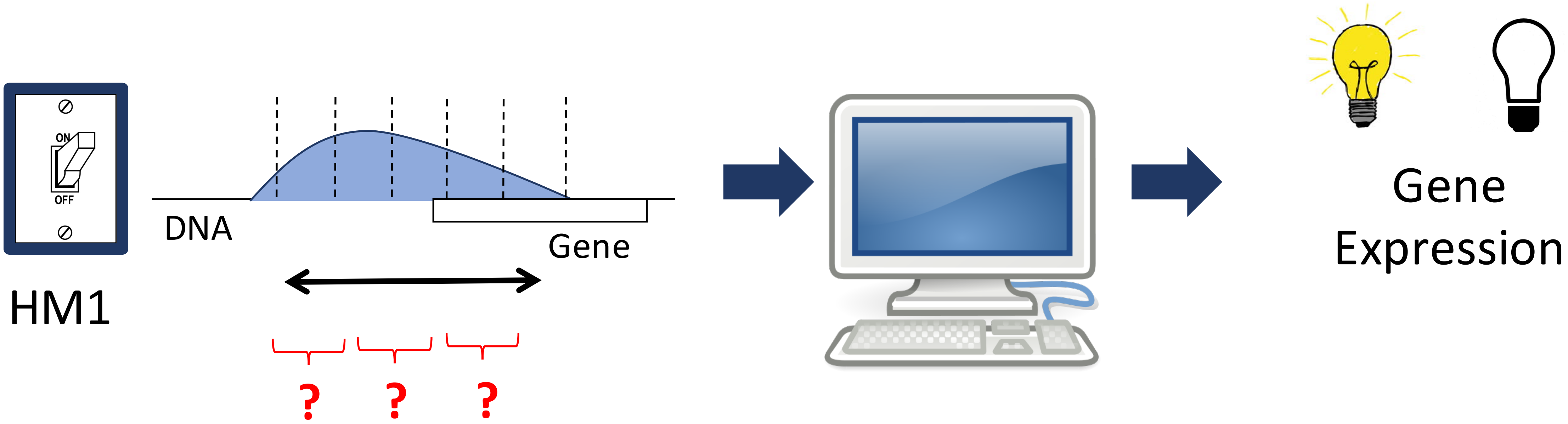
K~20 HMs

G~30,000 Genes

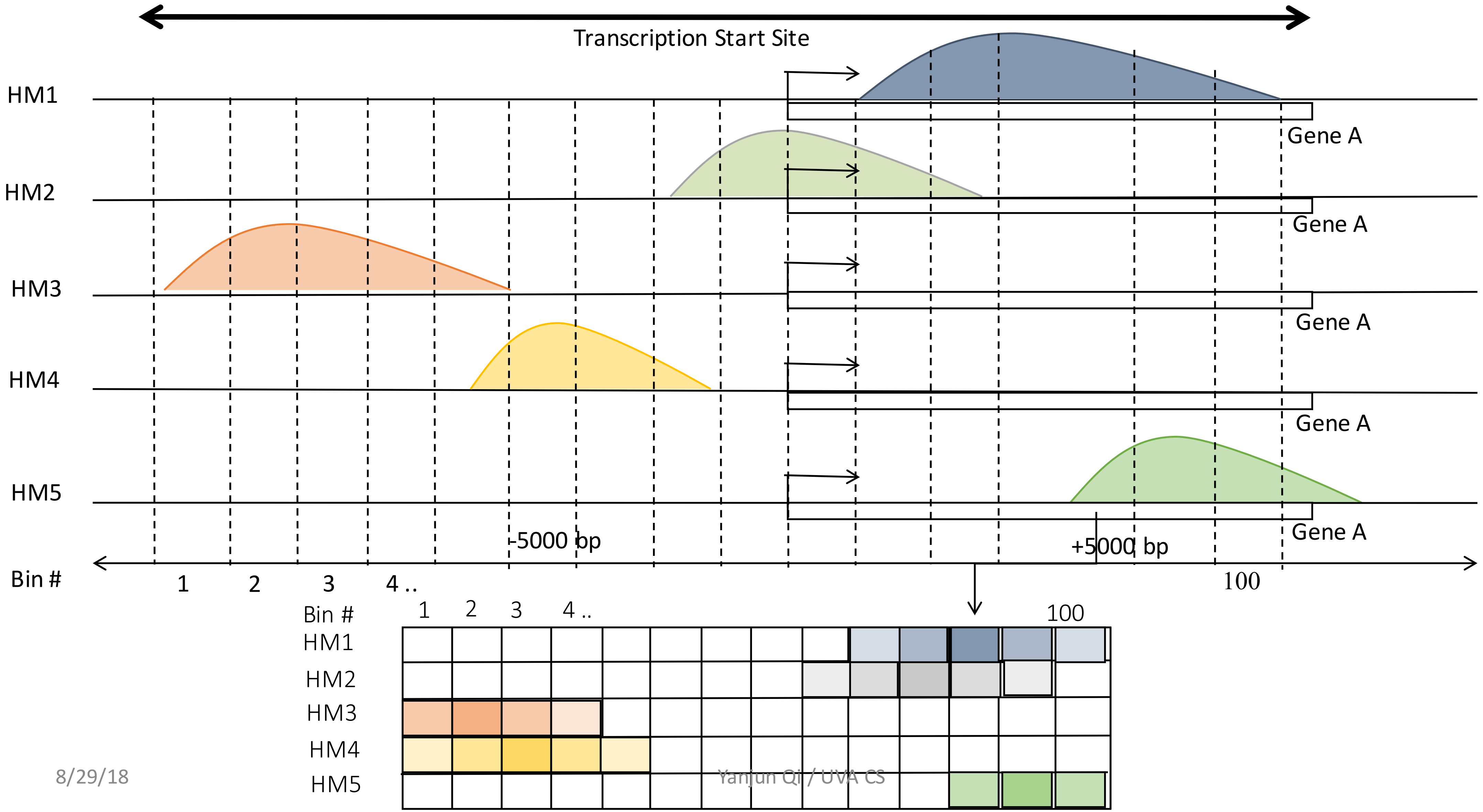
Task Formulation

Input:

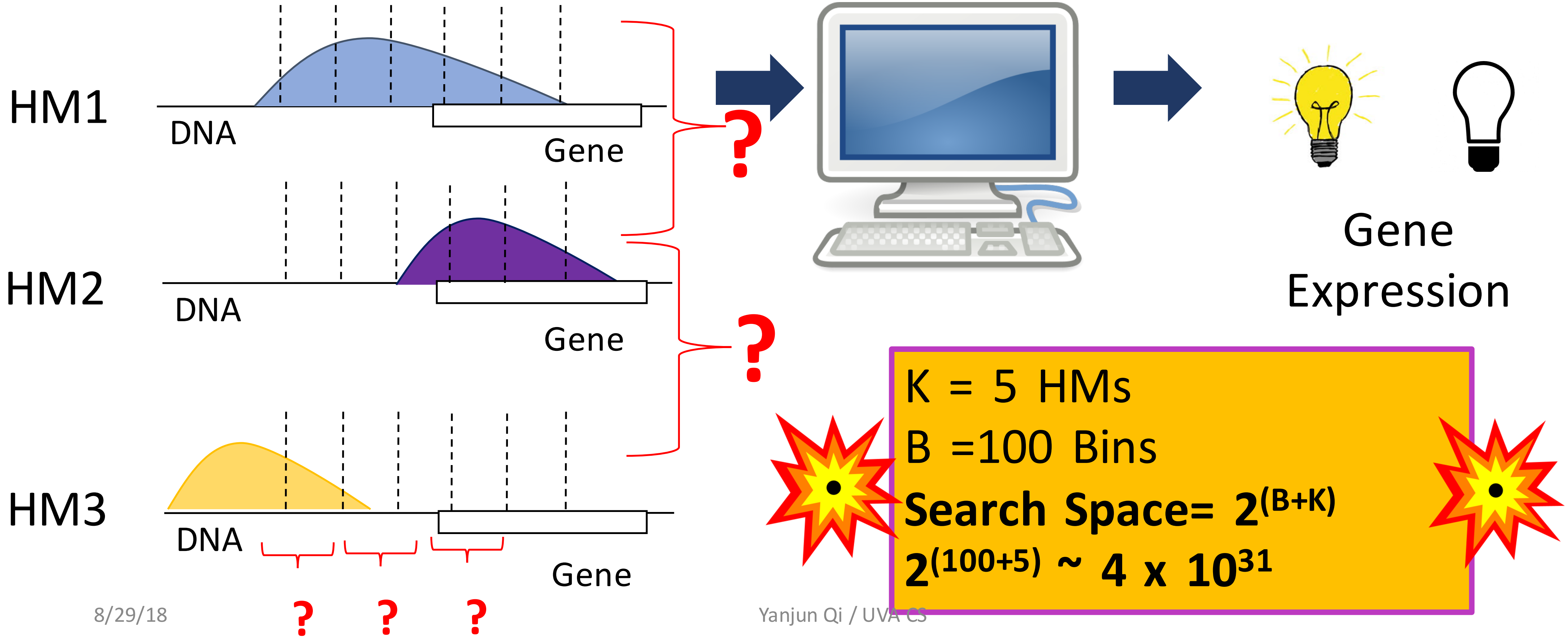
Output:



Input


Transcription Start Site
HM1
HM2
HM3
HM4
HM5
Gene A
Gene A
Gene A
Gene A
Gene A
-5000 bp
+5000 bp
Bin #
1
2
3
4 ..
100
Bin #
1
2
3
4 ..
100
HM1
HM2
HM3
HM4
HM5

Computational Challenge



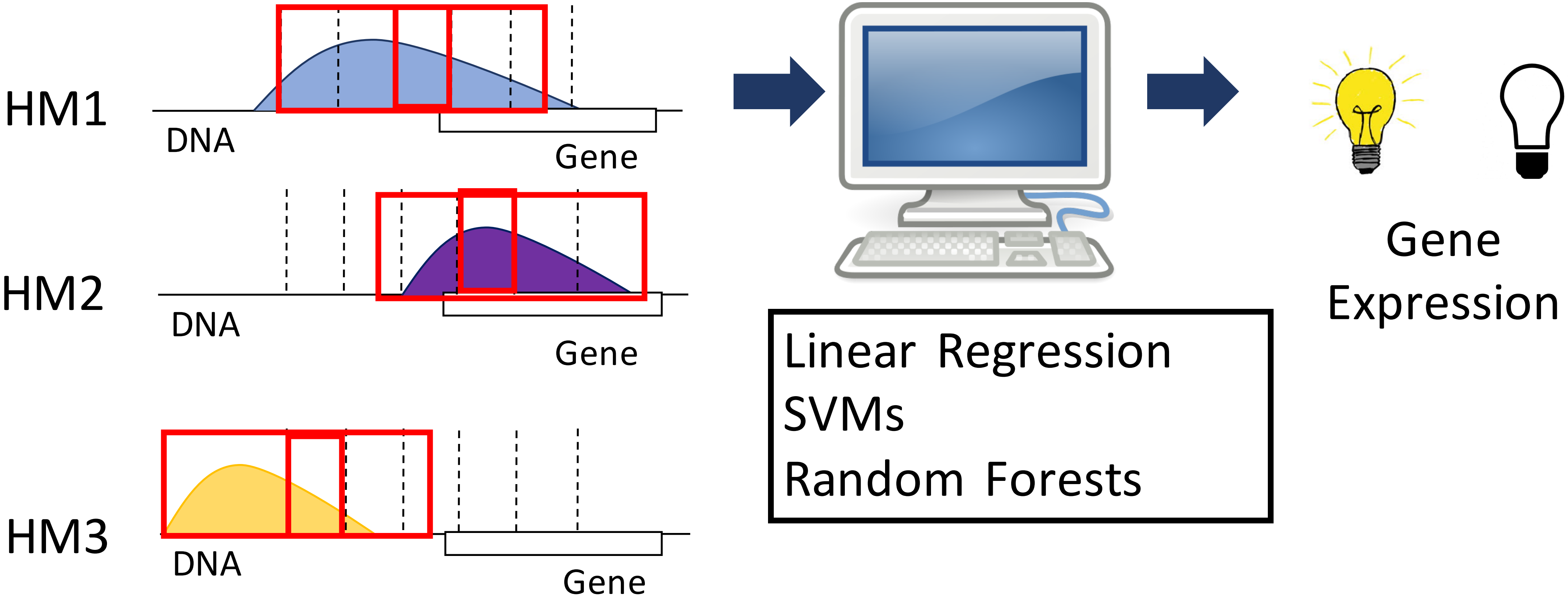
K = 5 HMs

B =100 Bins

Search Space= $2^{(B+K)}$

$2^{(100+5)} \sim 4 \times 10^{31}$

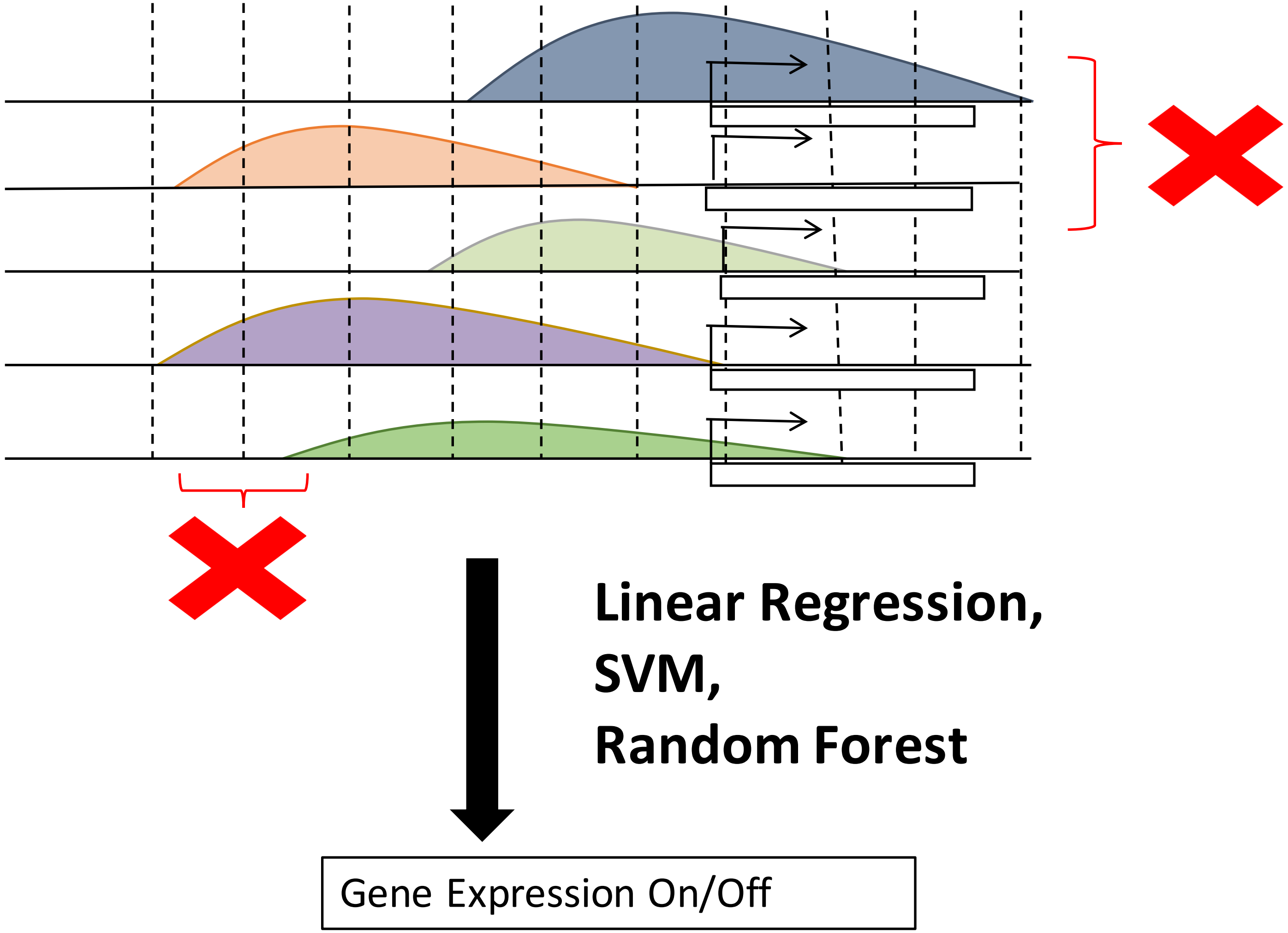
Related Work



Linear Regression
SVMs
Random Forests

[1] Karli´c, R. et al, Histone modification levels are predictive for gene expression. Proceedings of the National Academy of Sciences (2010)
[2] Cheng, C. et al, A statistical framework for modeling gene expression using chromatin features and application to modENCODE datasets. Genome Biology (2011)
[3] Dong, X. et al, Modeling gene expression using chromatin features in various cellular contexts. Genome Biology (2012)

Drawback of Related Works



Linear Regression,
SVM,
Random Forest

Gene Expression On/Off

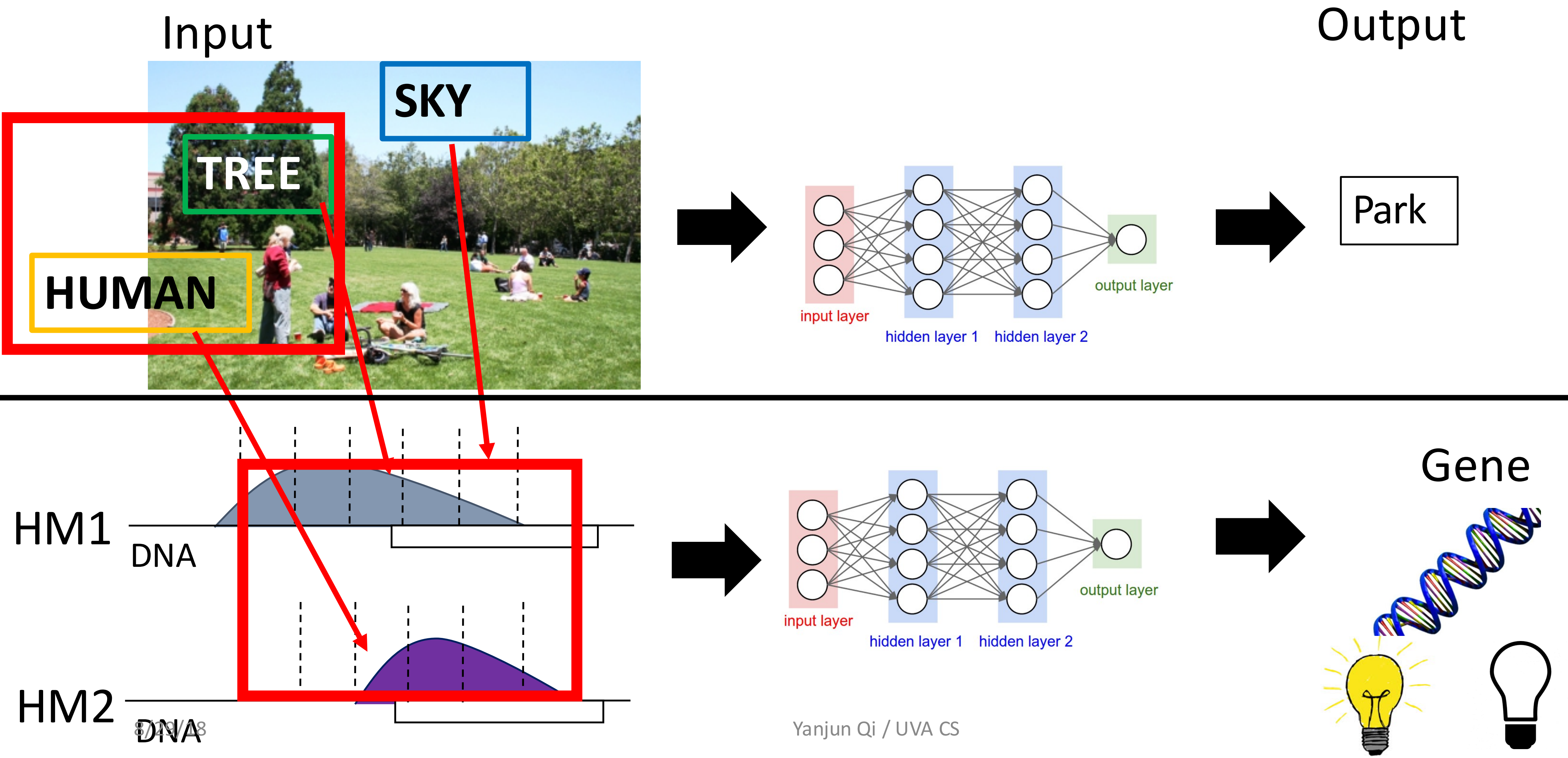
[1] Karli´c, R. et al, Histone modification levels are predictive for gene expression. Proceedings of the National Academy of Sciences (2010)

[2] Cheng, C. et al, A statistical framework for modeling gene expression using chromatin features and application to modENCODE datasets. Genome Biology (2011)

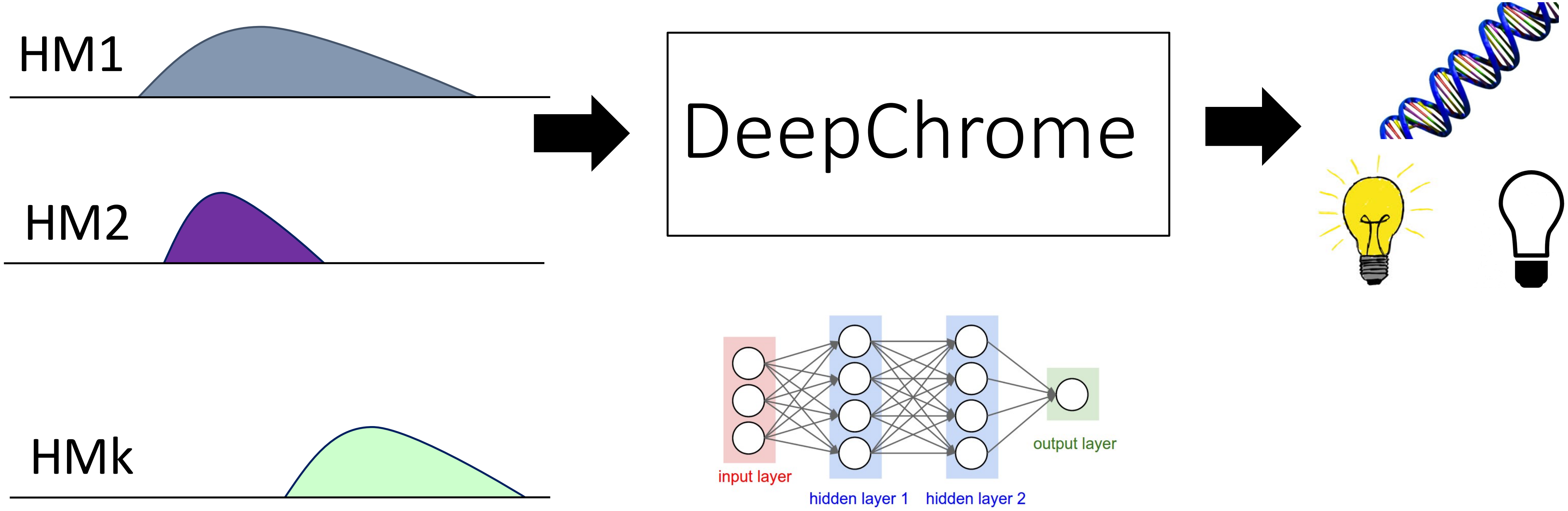
[3] Dong, X. et al, Modeling gene expression using chromatin features in various cellular contexts. Genome Biology (2012)

First Solution : CNN

HM signals occupy a local region and look similar in different parts?



First Solution: DeepChrome : CNN



HM1

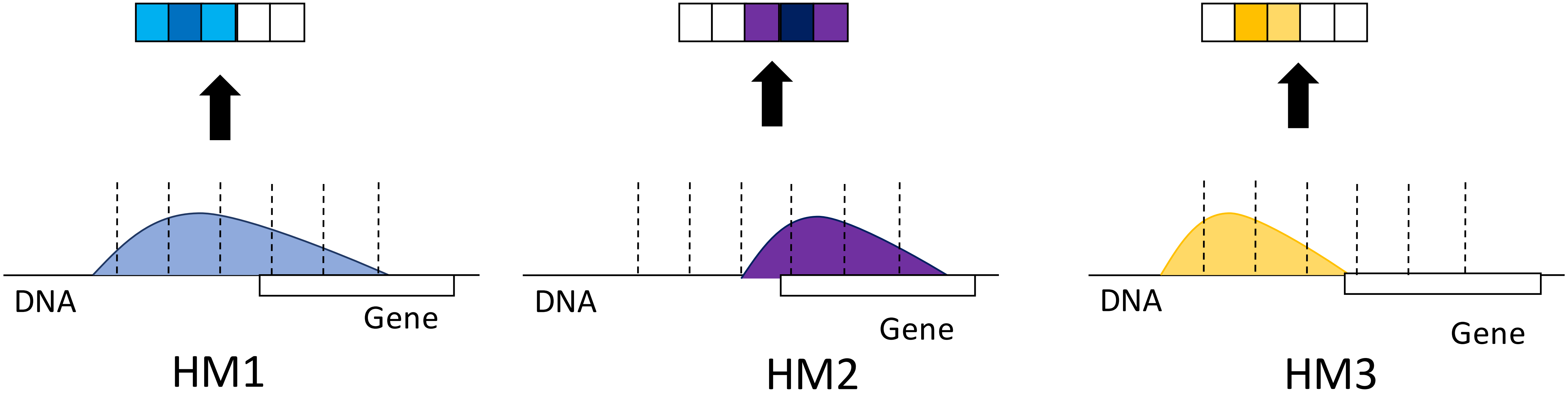
HM2

HMk

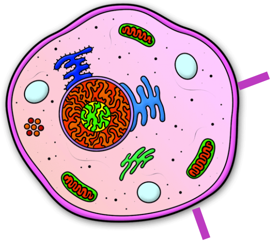
DeepChrome

R. Singh, et al. ”Deep-learning for predicting gene expression from histone modifications”. *Bioinformatics.* (ECCB) (2016)

Input (X)



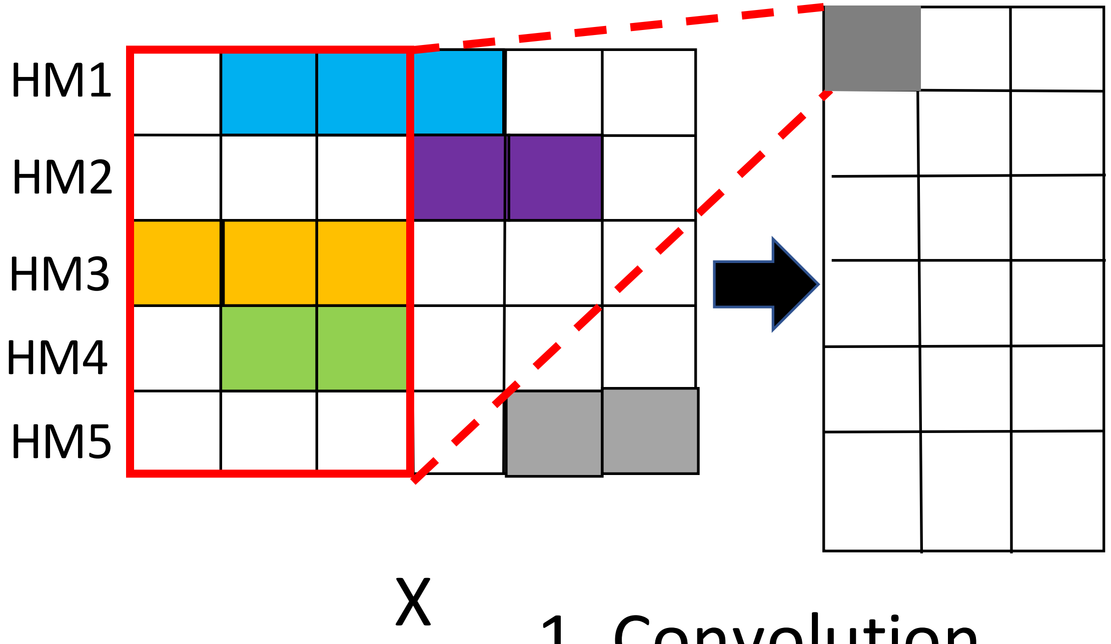
Output (Y) Labels



Genes	Gene Expression (RPKM)	Y Labels
RUNX1	1.296	0
SMAD2	14.902	1
MYC	3.805	0
PAX5	15.066	1
……	…….	……

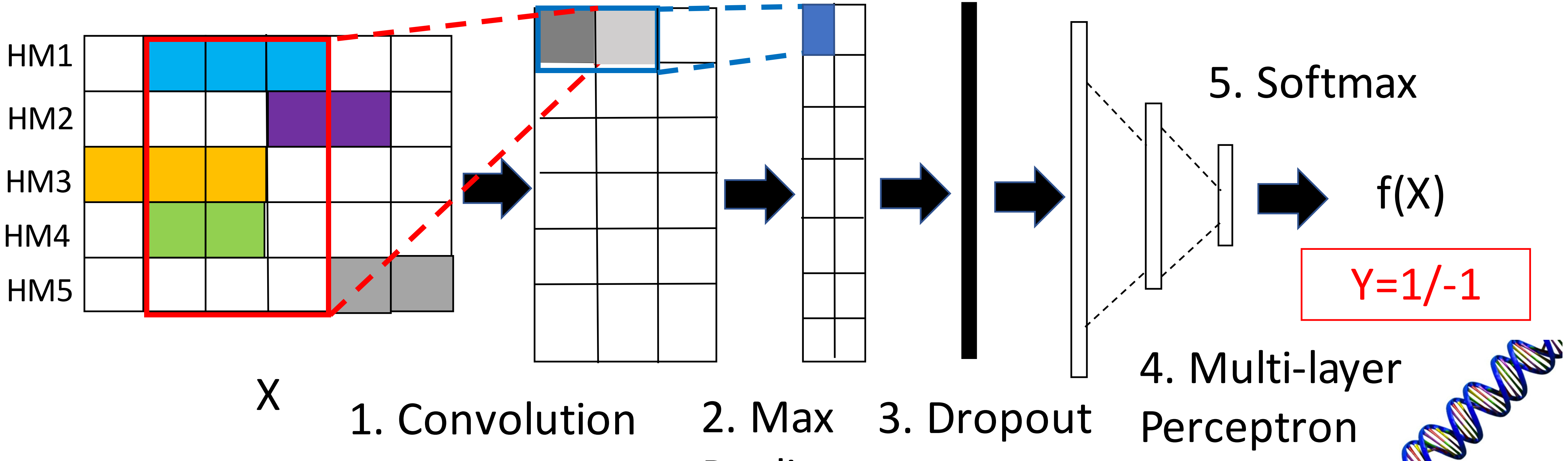
Threshold = 10.245 (Median)

DeepChrome: Convolutional Neural Network (CNN)



1. Convolution

DeepChrome: Convolutional Neural Network (CNN)



1. Convolution

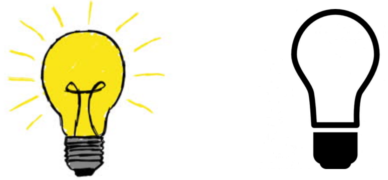
2. Max Pooling

3. Dropout

4. Multi-layer Perceptron

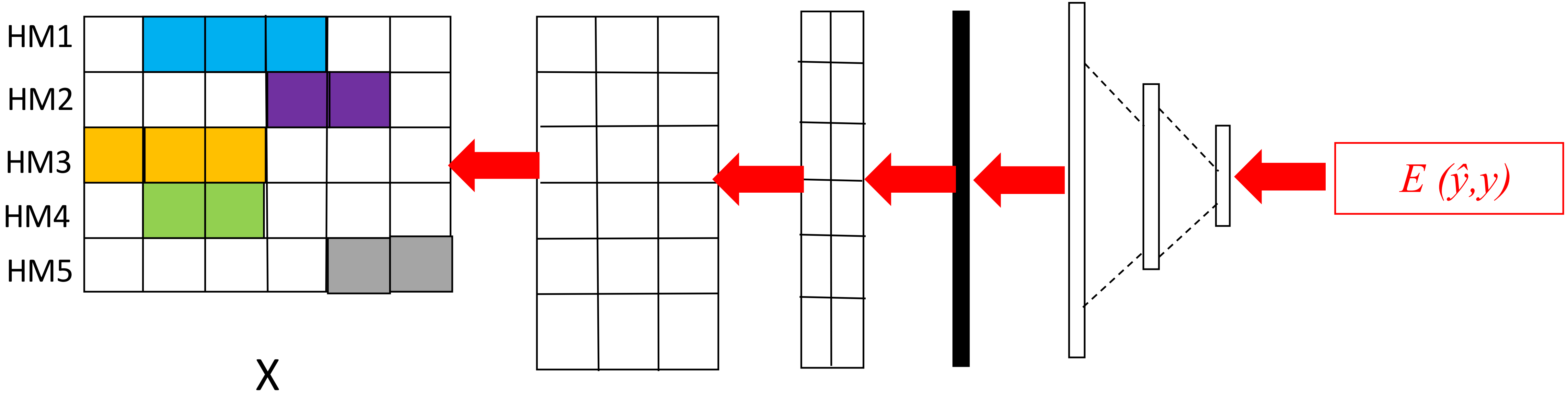
5. Softmax

Y=1/-1



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

DeepChrome: Convolutional Neural Network (CNN)



Back-propagation: $\Theta \leftarrow \Theta - \eta \frac{\partial E}{\partial \Theta}$

Experimental Setup

- Roadmap Epigenetics Project (REMC)
- **Cell-types:** 56
- **Input (HM):** ChIP-Seq Maps / 5 Tier-1 HMs

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

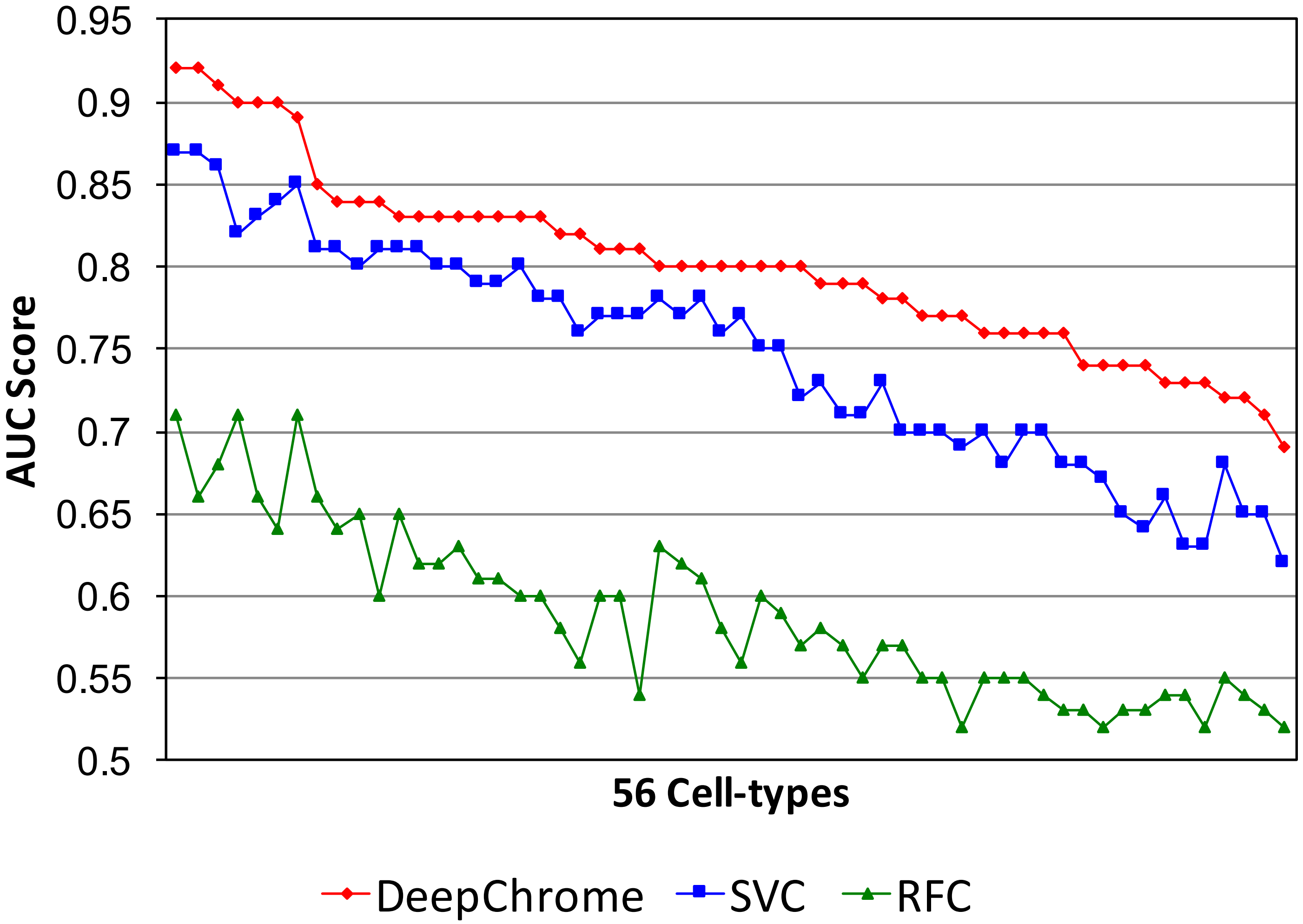
- **Output (Gene Expression):** Discretized RNA-Seq
- **Baselines:** Support Vector Classifier (SVC) and Random Forest Classifier (RFC)

Training Set
6601 Genes

Validation Set
6601 Genes

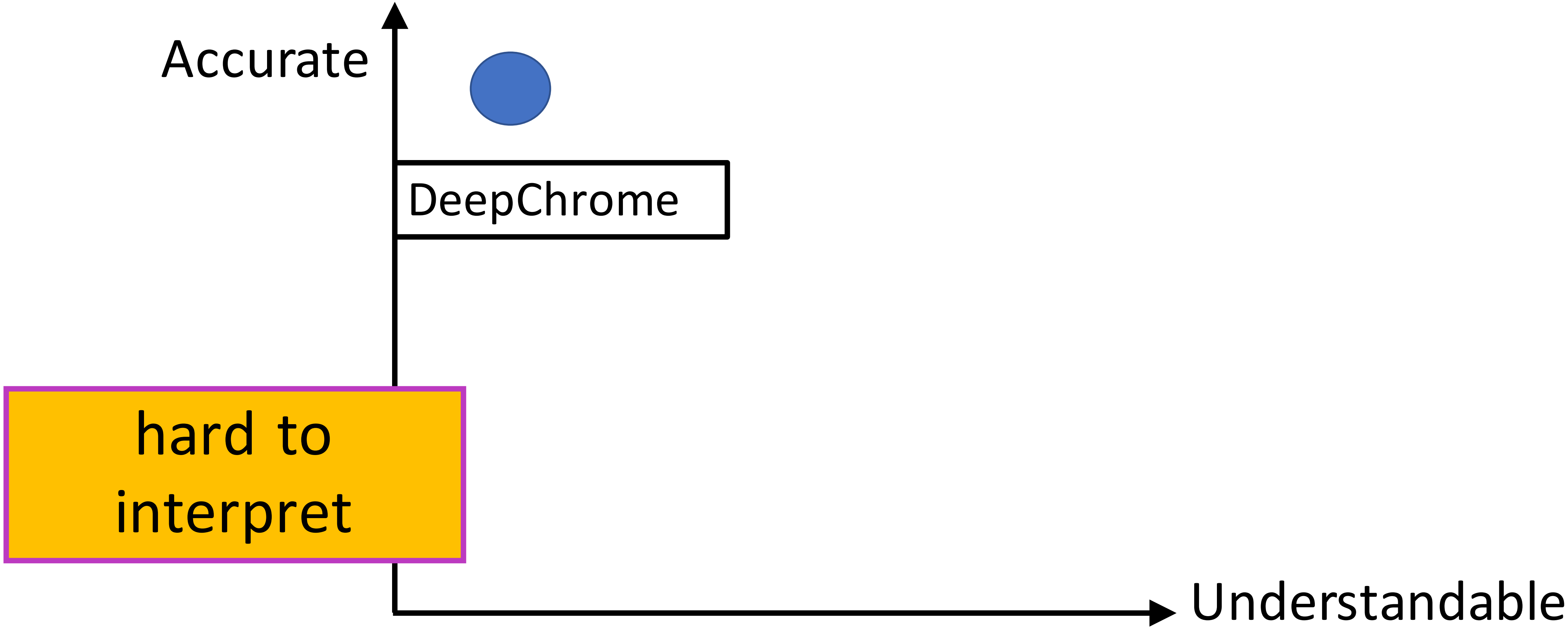
Test Set
6600 Genes

Results: Accuracy



https://www.deepchrome.org

Summary of tools


Accurate

DeepChrome

hard to interpret

Understandable

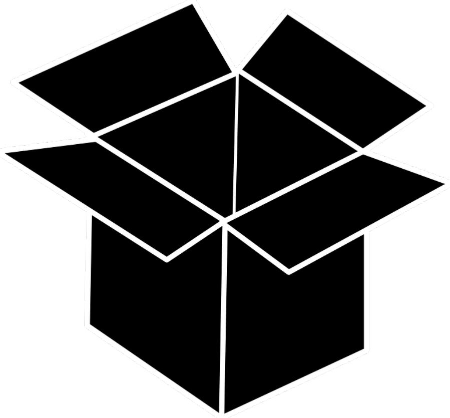
R. Singh, et al. Deep-learning for predicting gene expression from histone modifications”. *Bioinformatics.* (2016)

Solution: Interpretability by Hierarchical Attention

Input

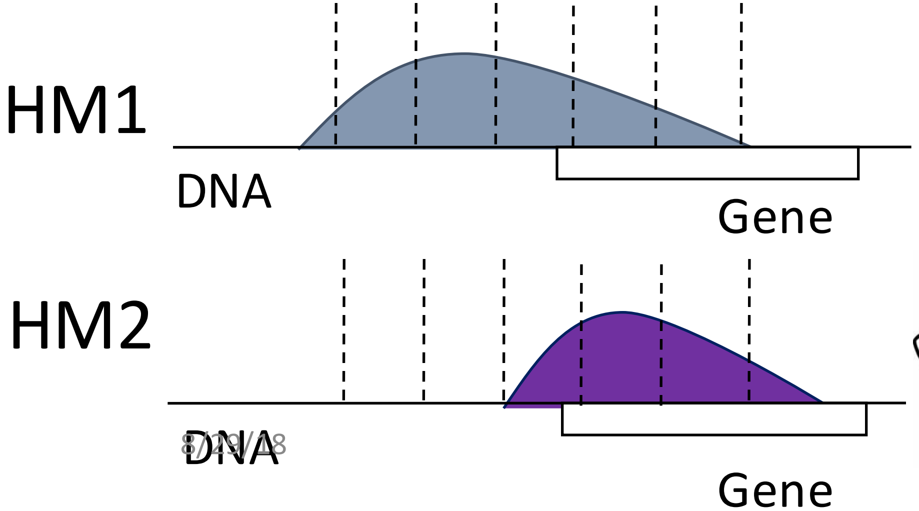
Output

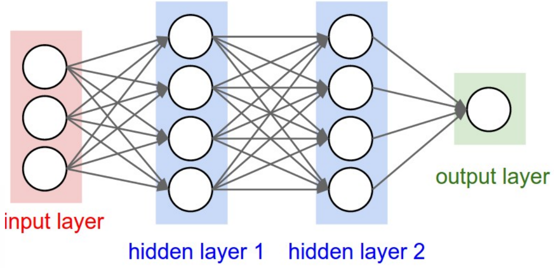
Attention Mechanism

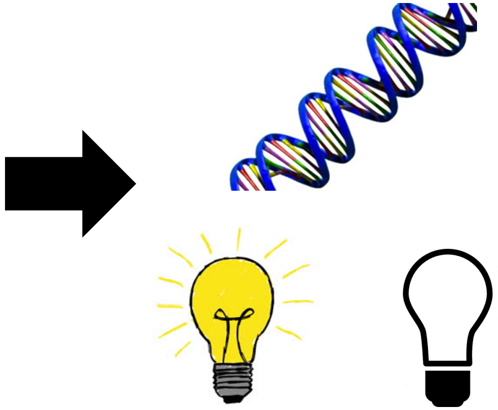


Park

Gene







Solution: Interpretability by Hierarchical Attention

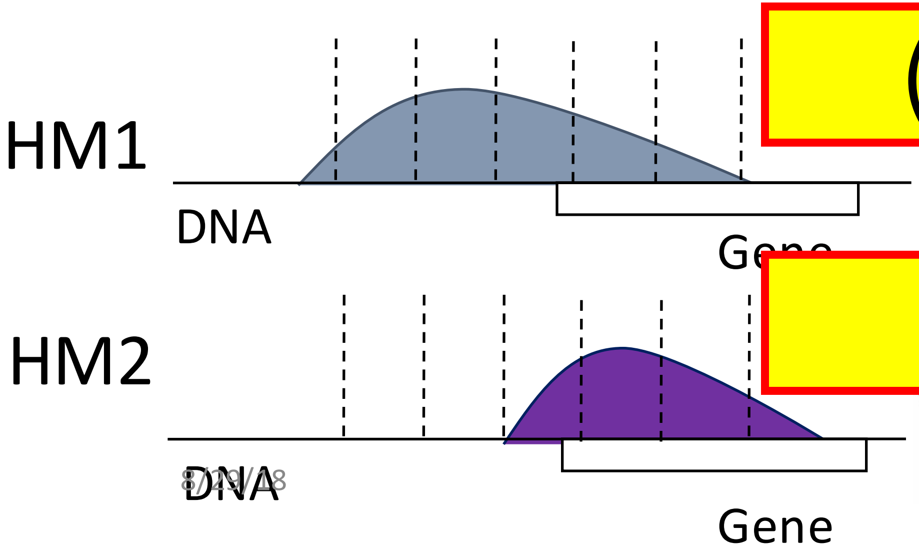
Input

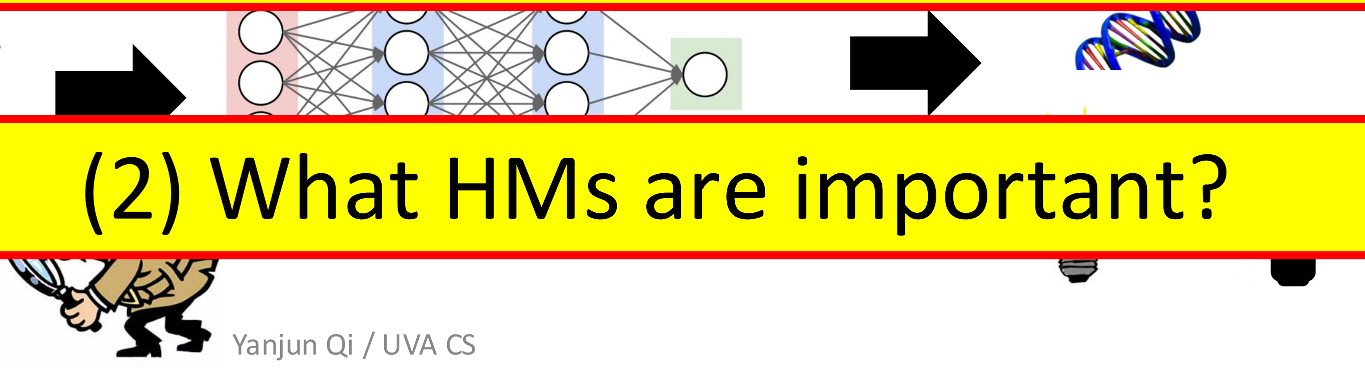
Attention Mechanism

Output

Park

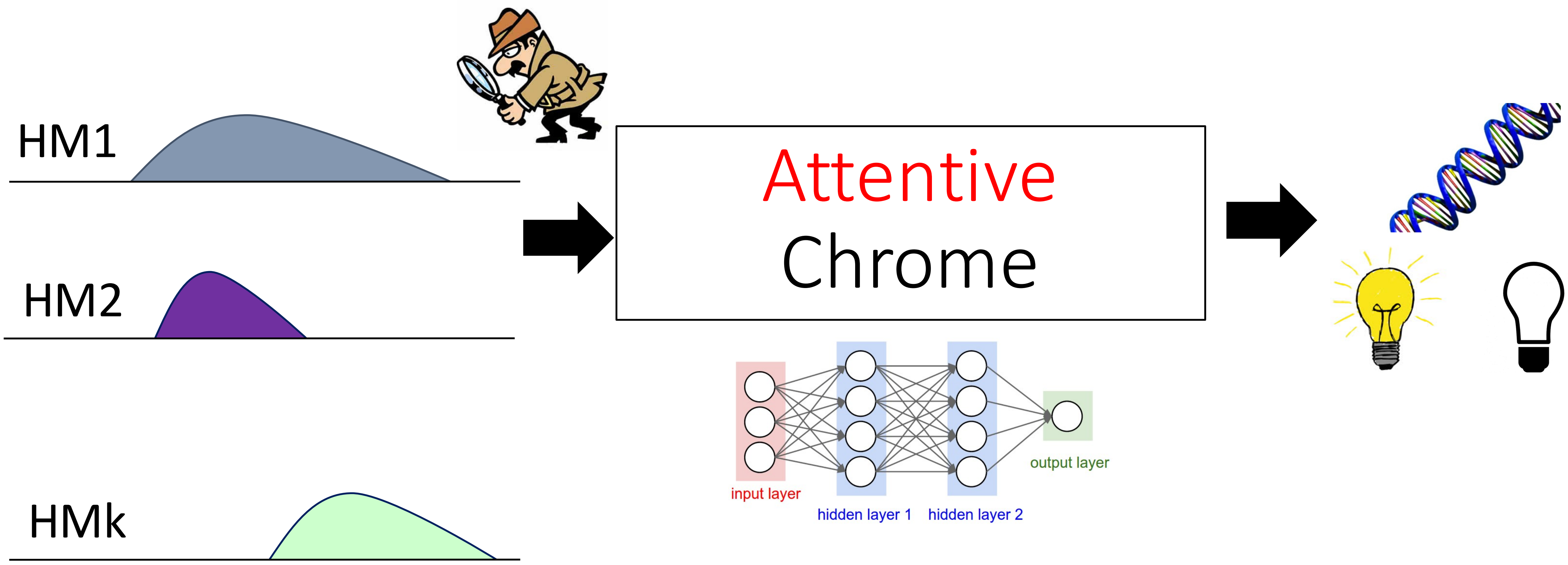
Gene





(1) What positions are important?

(2) What HMs are important?

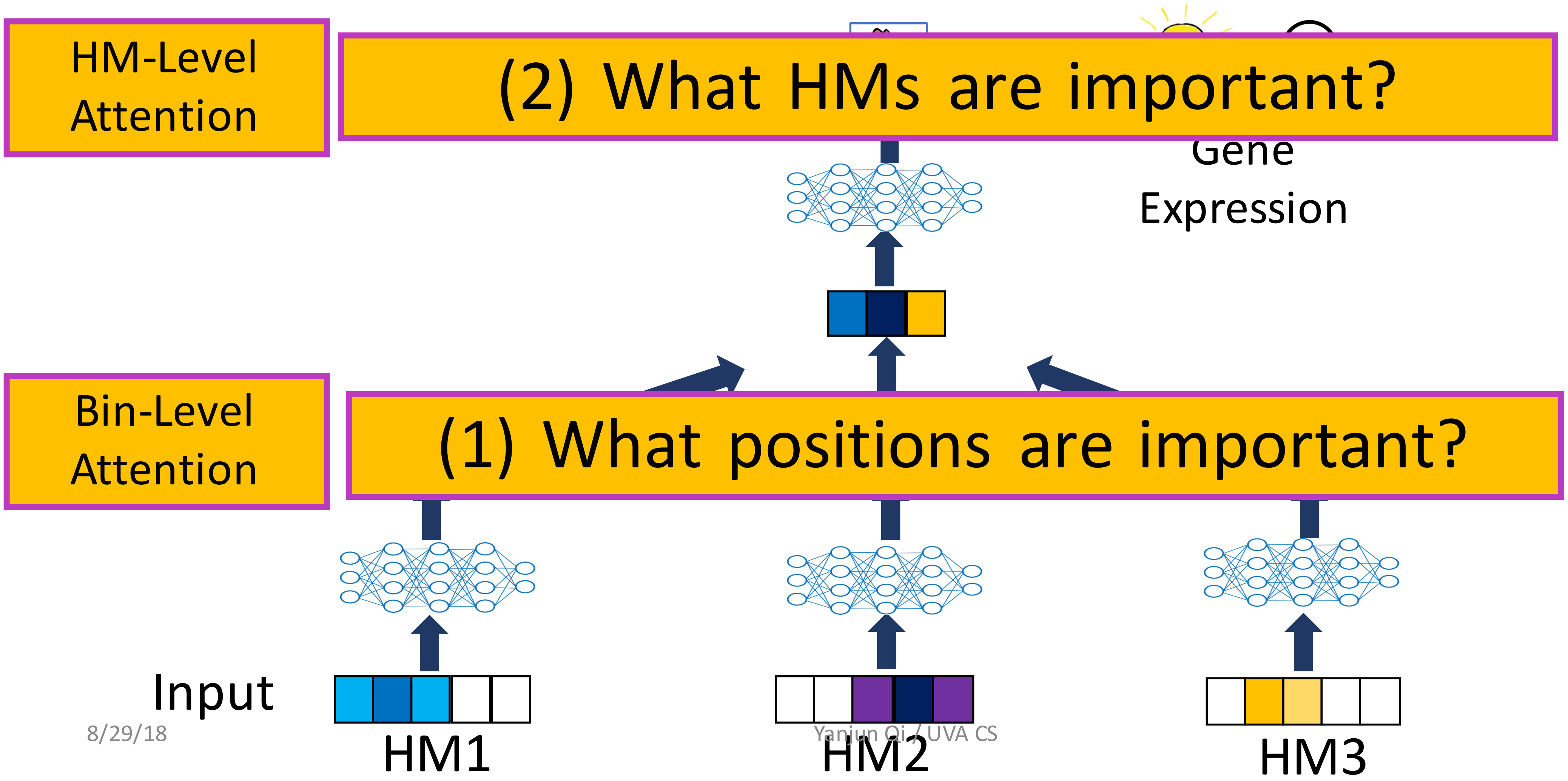


Attentive
Chrome

R. Singh, et al. ”Attend and Predict: Understanding Gene Regulation by Selective Attention on Chromatin”. *NIPS (2017)*

AttentiveChrome

[NIPS 2017]



HM-Level Attention

(2) What HMs are important?

Gene Expression

Bin-Level Attention

(1) What positions are important?

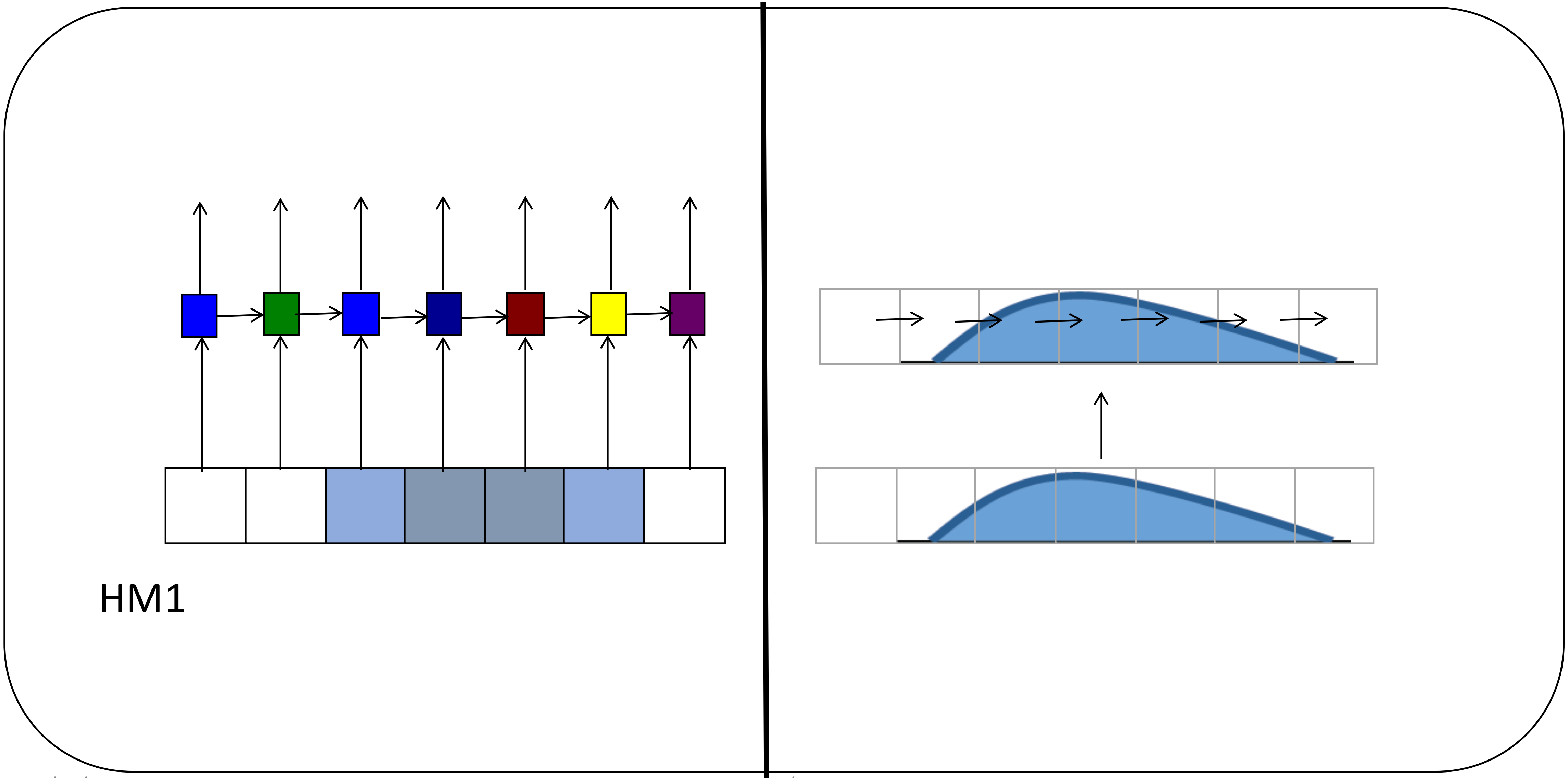
Input

HM1

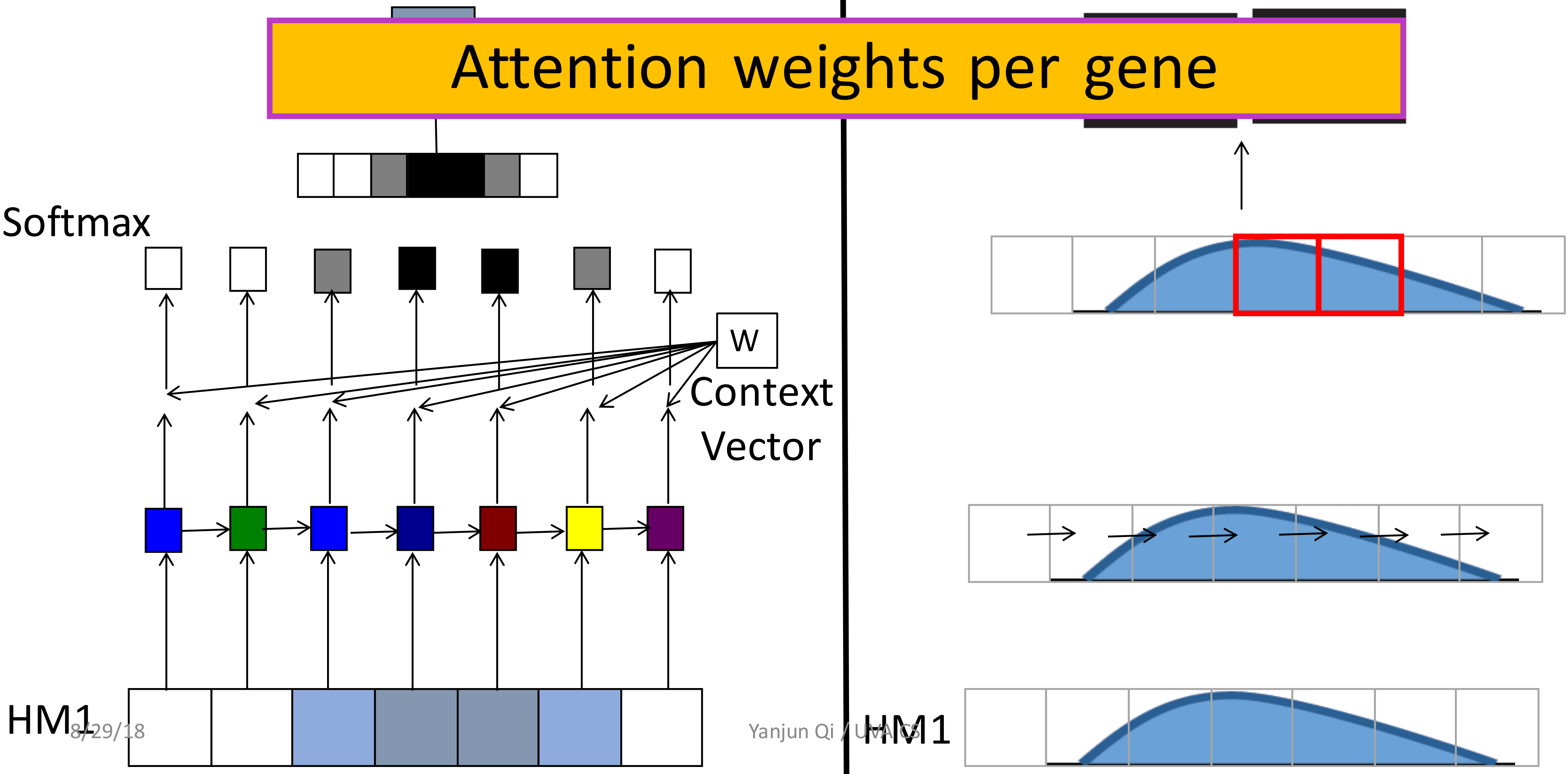
HM2

HM3

Multiple Recurrent Neural Networks (Hierarchical RNNs) to model each HM and the Combination of all HMs : for example on HM1

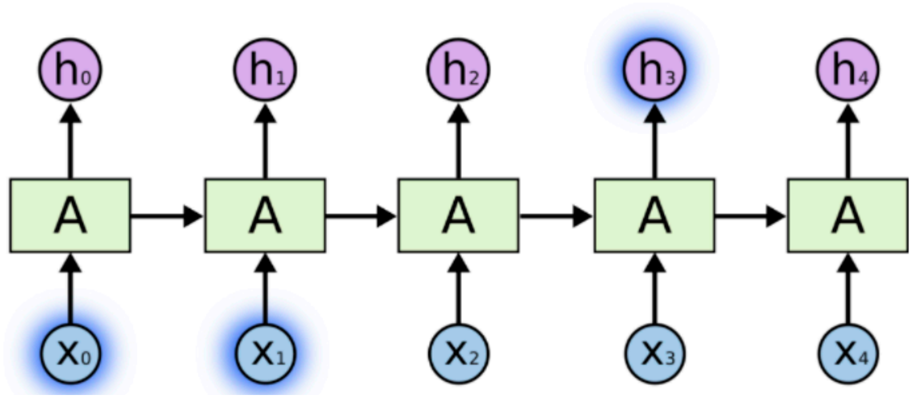


Attention Mechanism



Attention weights per gene

Using Attention to Select RNN per-unit outputs



$$\boxed{h_t} = \boxed{f_W}(\boxed{h_{t-1}}, \boxed{x_t})$$

new state

some function
with parameters W

old state

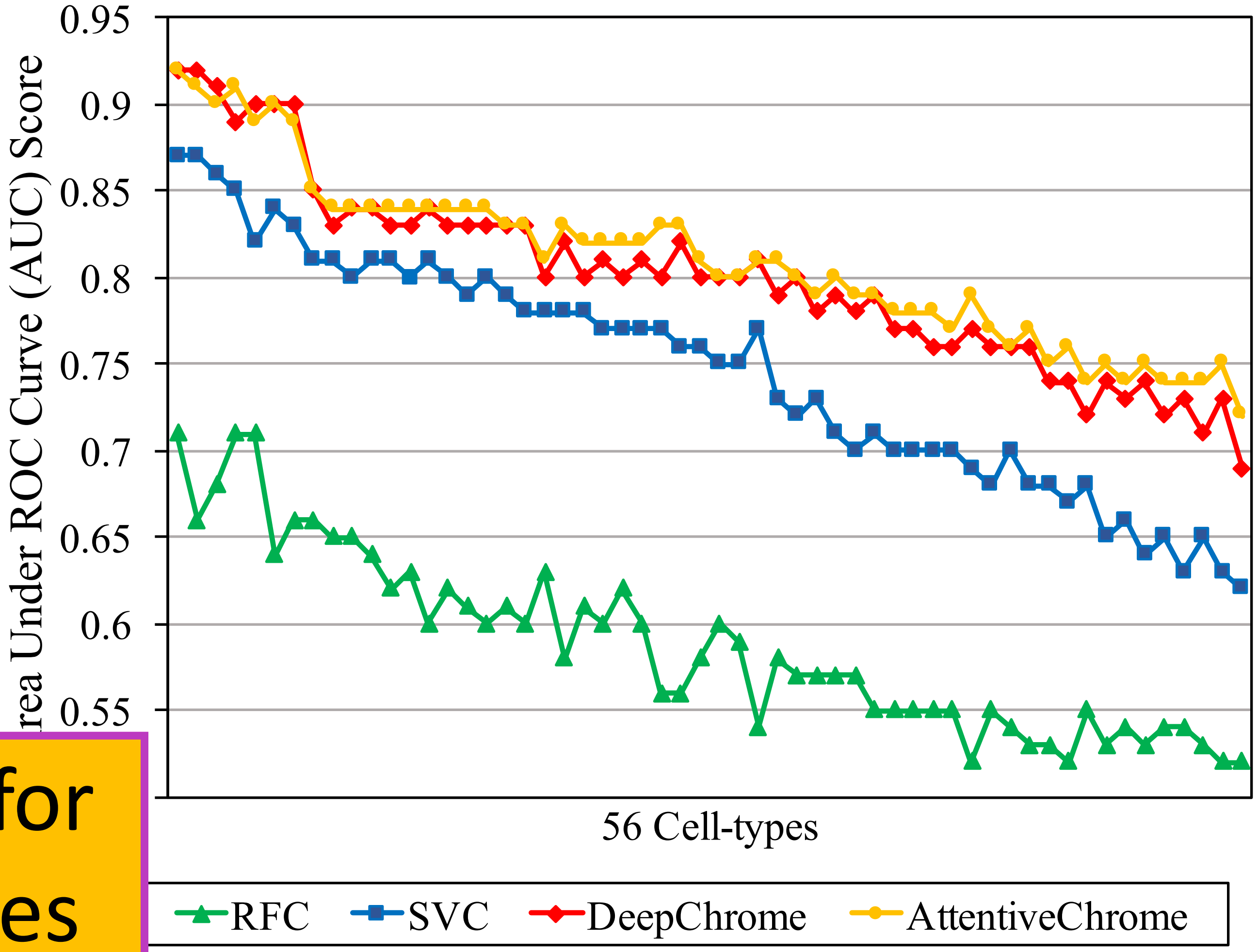
input vector at
some time step

$$\boldsymbol{\alpha}_t^j = \frac{exp(\mathbf{W}_b \mathbf{h}_t^j)}{\sum_{i=1}^{T} exp(\mathbf{W}_b \mathbf{h}_i^j)}$$

W_b is learned

Image Credits from Christopher Olah

Prediction



Improvement for 49/56 Cell-types

Bin-Level Visualization

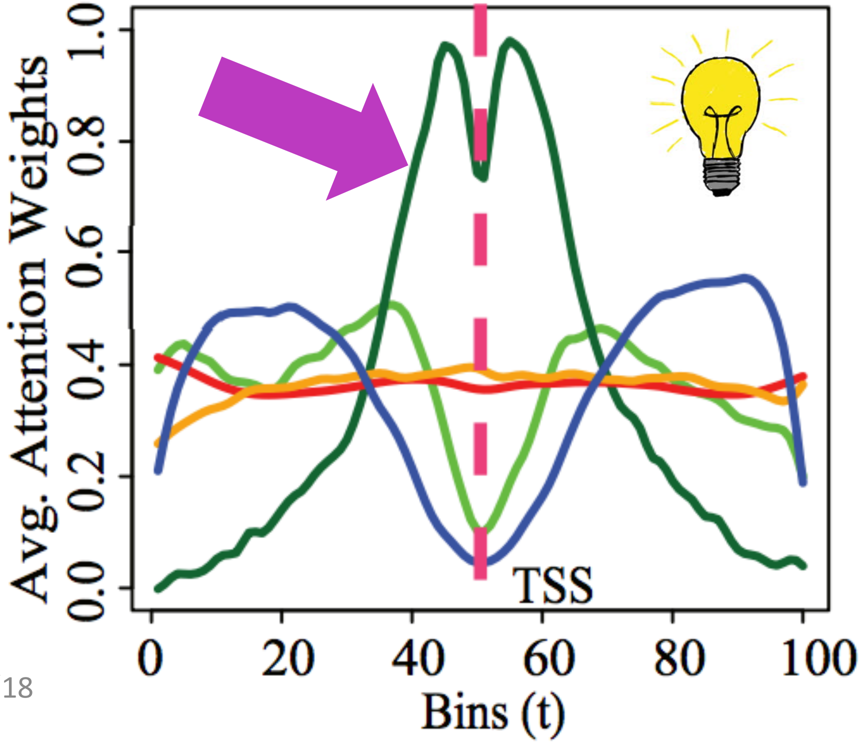
(1) What positions are important?

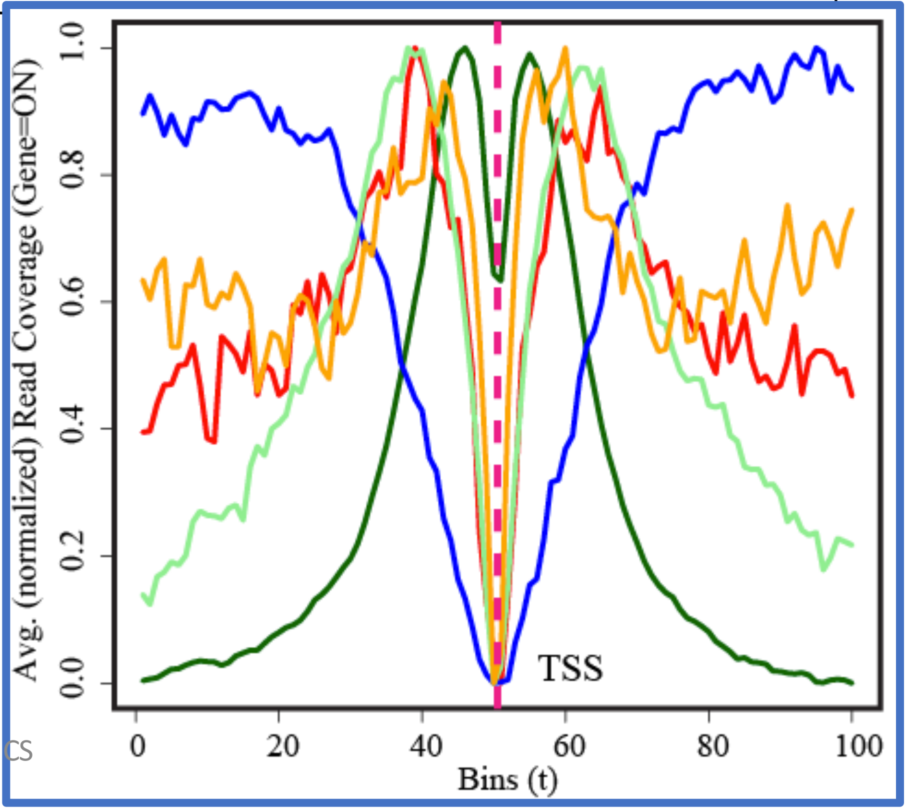
CELL TYPE: GM1

Repressors

Promoters

🟥 H3K27me3 🟨 H3K9me3 🟩 H3K4me1 🟩 H3K4me3 🟦 H3K36me3

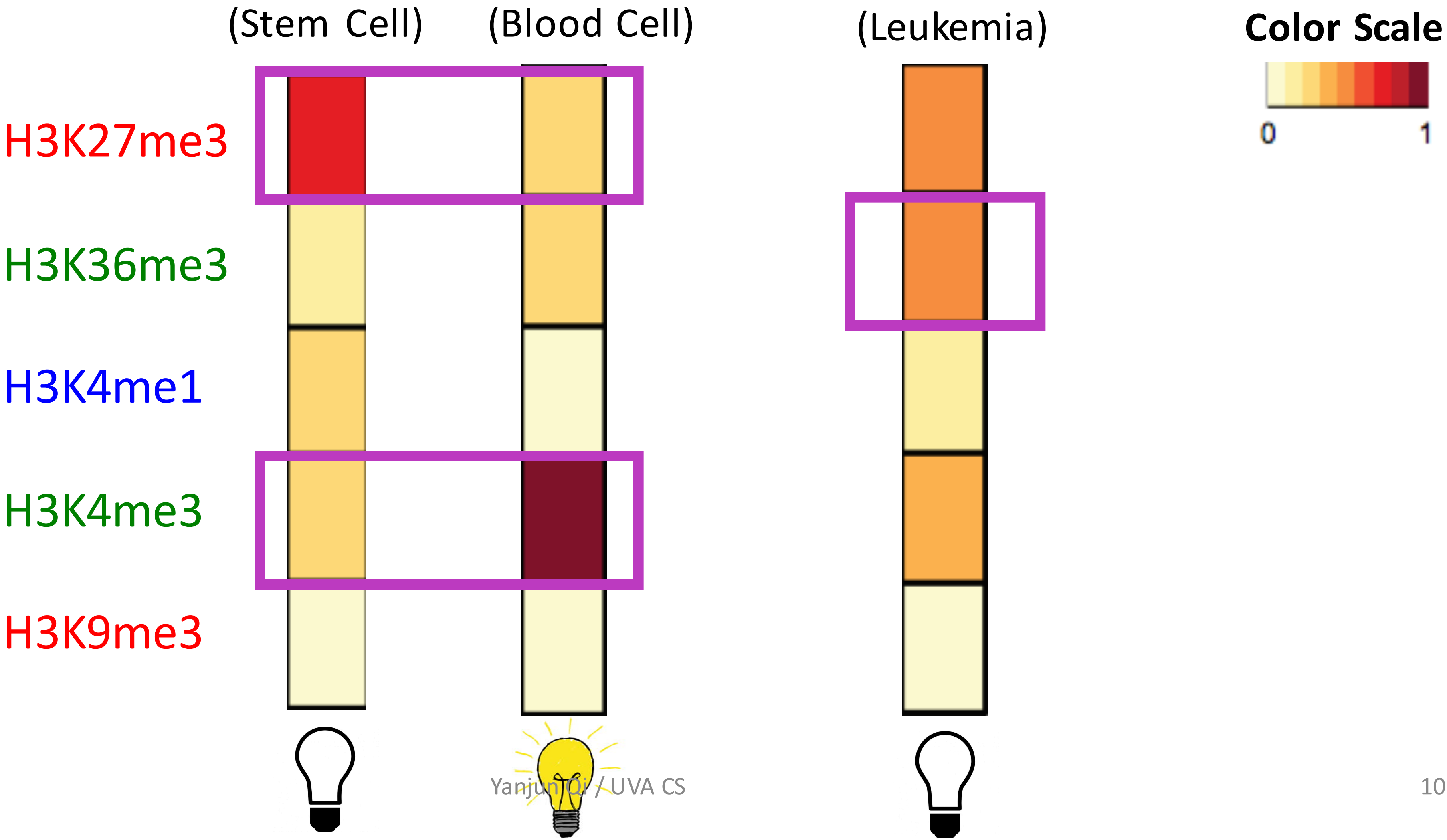




HM-Level Visualization

(2) What HMs are important?

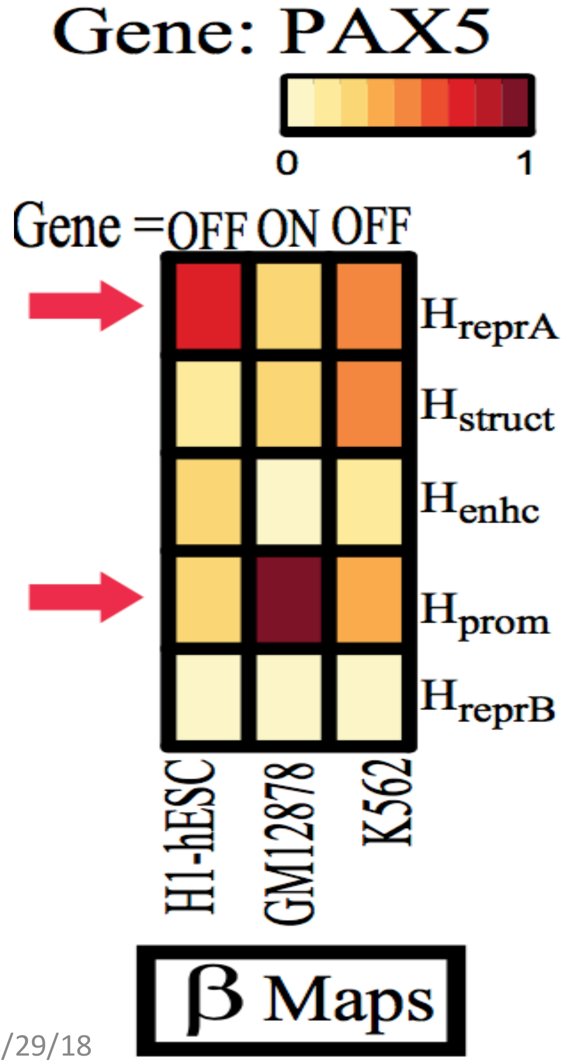
Cell Types:



PROMOTER
DISTAL PROMOTER
REPRESSOR

Gene: PAX5

Results: HM level attention



- 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.

(2) What HMs are important?

Validation of Attention Weights (using one extra HM signals)

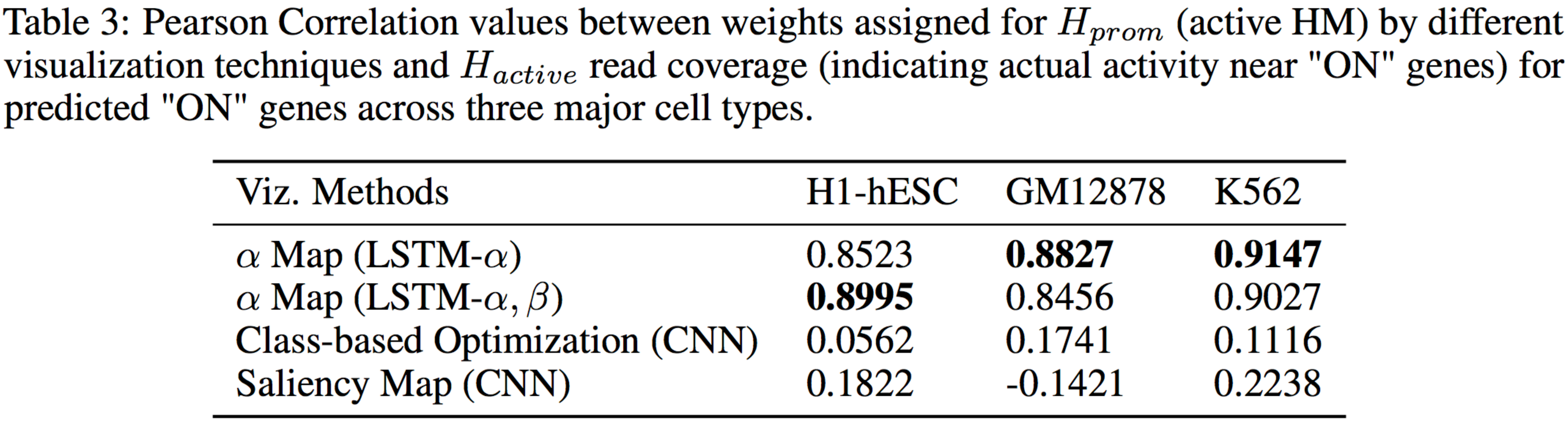


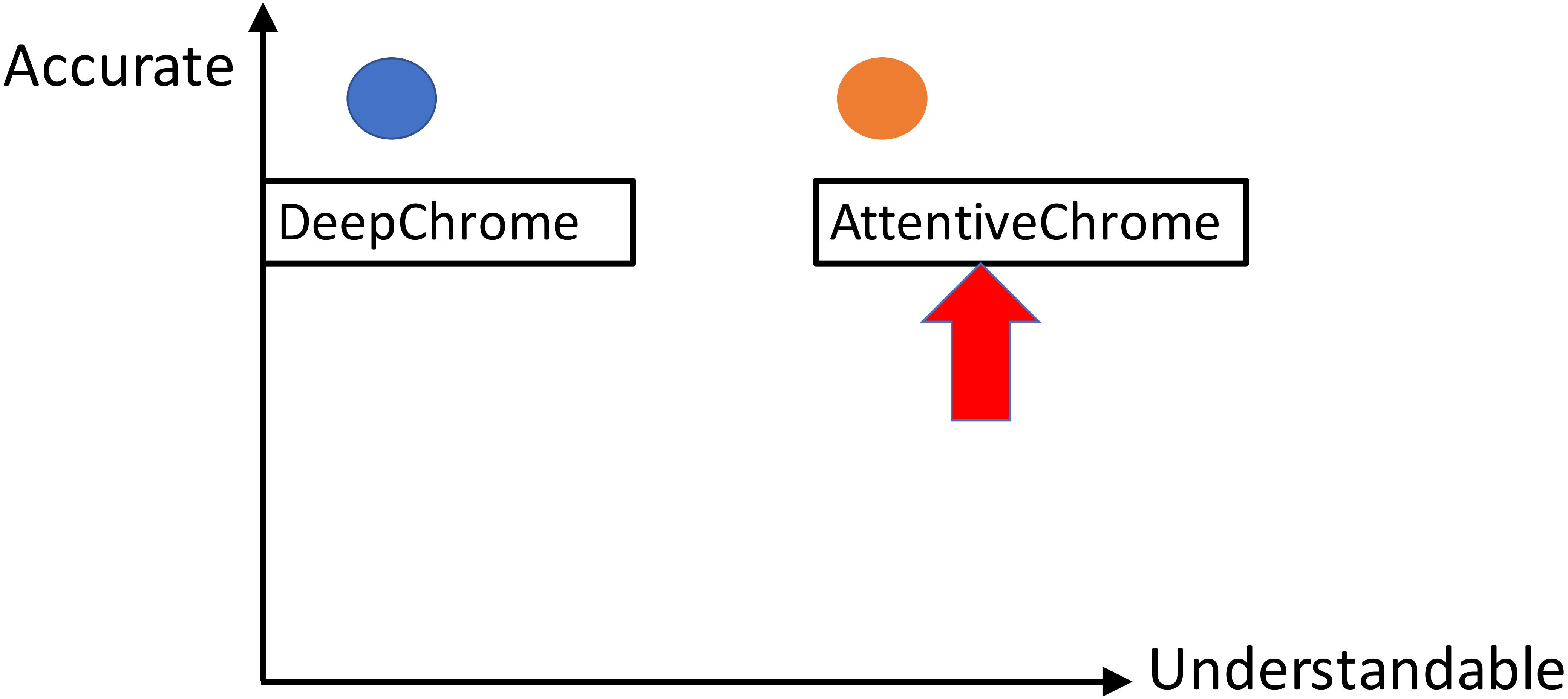
Table 3: Pearson Correlation values between weights assigned for H_{prom} (active HM) by different visualization techniques and H_{active} read coverage (indicating actual activity near "ON" genes) for predicted "ON" genes across three major cell types.

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

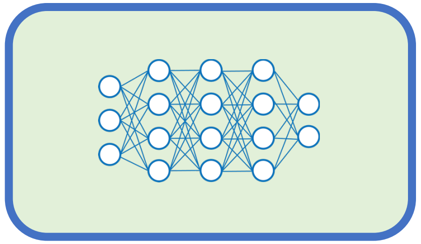
- Additional signal - H3K27ac (H-Active) from REMC
- Average local attention weights of gene=ON correspond well with H-active
- Indicating AttentiveChrome is focusing on the correct bin positions

https://www.deepchrome.org

Summary of tools

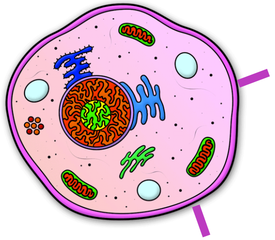


R. Singh, et al. ”Attend and Predict: Understanding Gene Regulation by Selective Attention on Chromatin”. *NIPS (2017)*



Where are we heading?

Changing Task : Classification →Regression



1.770

Gene Expression

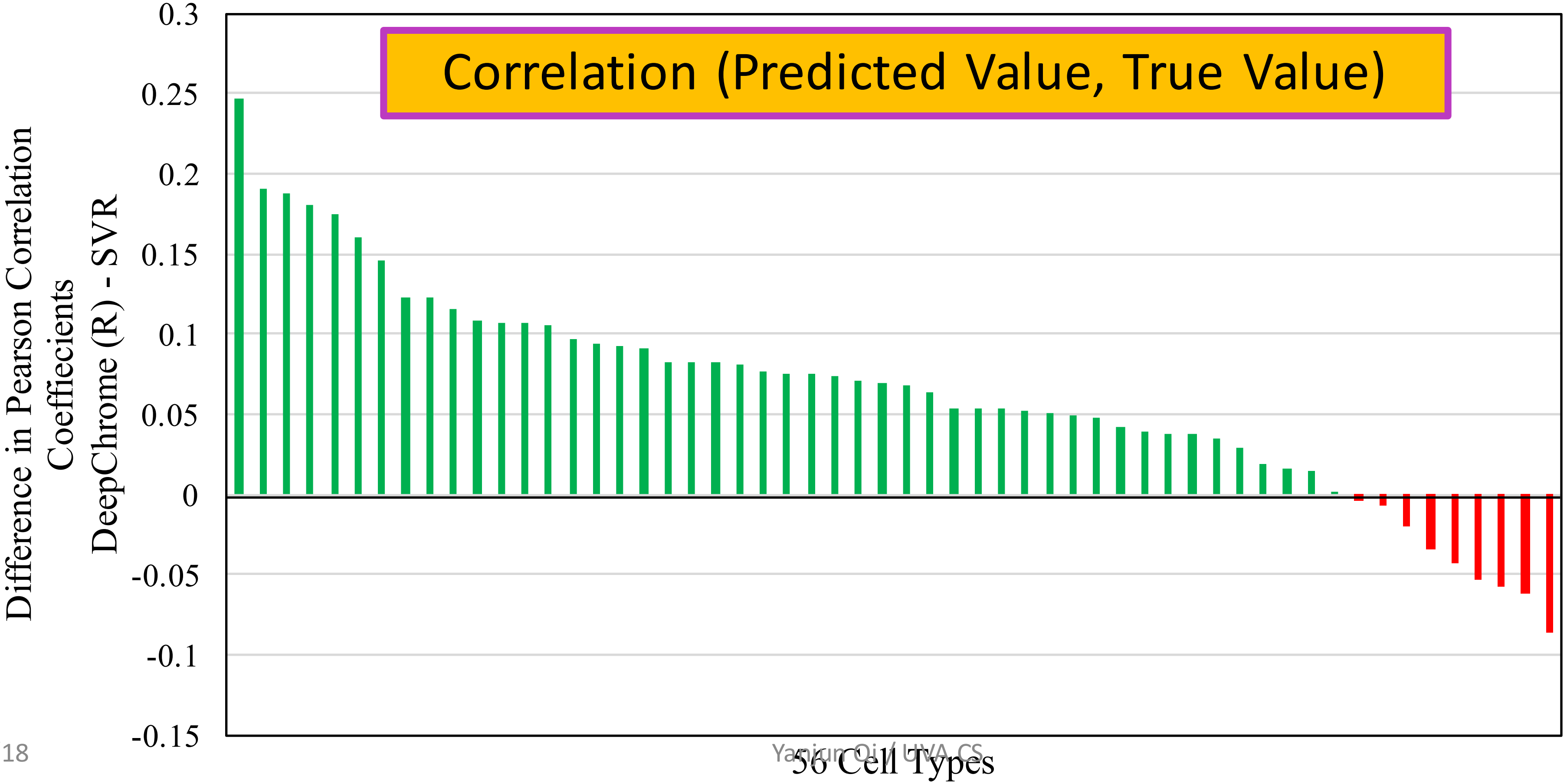
Genes	Gene Expression (RPKM)	Y log(RPKM)
RUNX1	1.296	01126
SMAD2	14.902	1.1737
MYC	3.805	0.5803
PAX5	15.066	1.779
……	…….	……

Mean Square Error Loss

$(Y - f(X))^2$

Where are we heading?

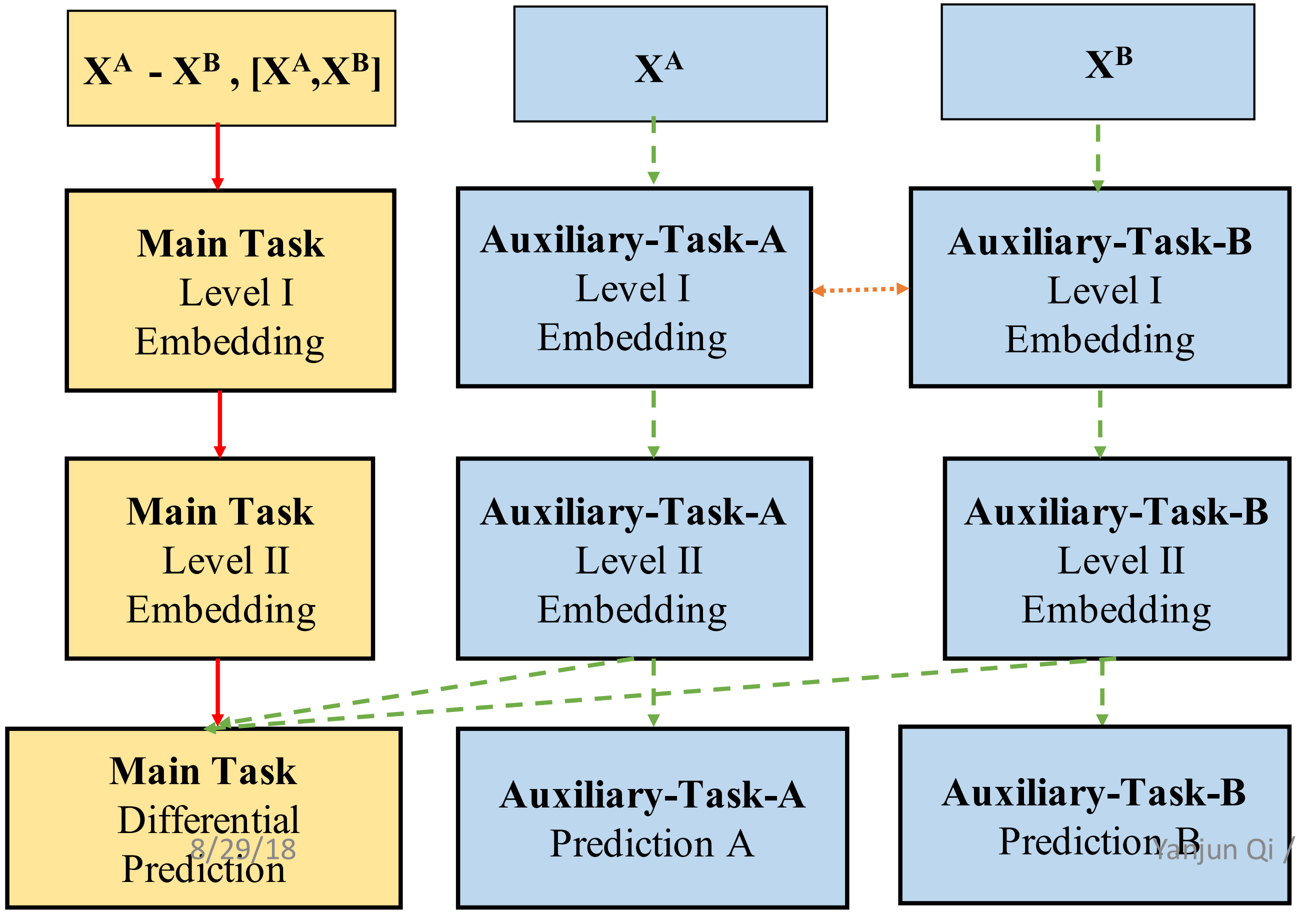
Changing Task : Classification →Regression



Where are we heading?

DeepDiff: Deep-learning for predicting Differential gene expression from histone modifications

Changing Task : Cell-Specific → Cross Cell


X^A - X^B , [X^A,X^B]
X^A
X^B
Main Task Level I Embedding
Auxiliary-Task-A Level I Embedding
Auxiliary-Task-B Level I Embedding
Main Task Level II Embedding
Auxiliary-Task-A Level II Embedding
Auxiliary-Task-B Level II Embedding
Main Task Differential Prediction
Auxiliary-Task-A Prediction A
Auxiliary-Task-B Prediction B

① **Main Task**: Differential gene expression prediction

② **Cell-Specific Auxiliary**: Auxiliary-Task-A and Auxiliary-Task-B cell type specific prediction

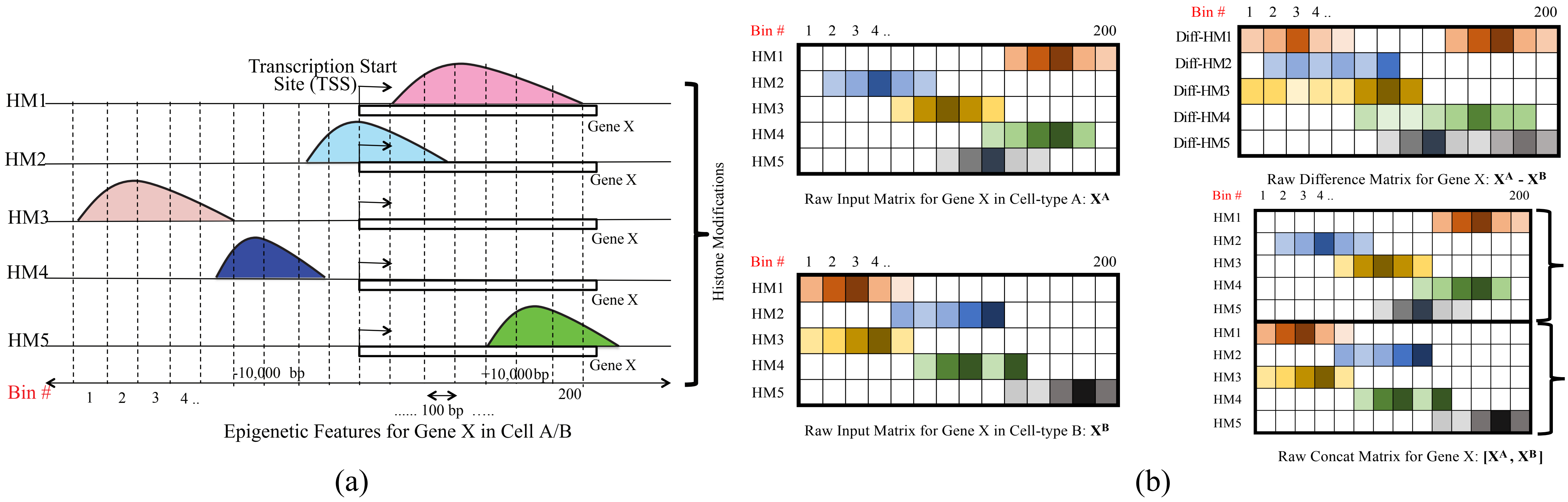
③ **Siamese Auxiliary**: Siamese contrastive loss

DeepDiff Variations	Objective Loss
① Raw:d, Raw:c, Raw	ℓ_{Diff}
② Aux	$\ell_{Diff}+\ell_{CellAux}$
① + ② Raw+Aux	$\ell_{Diff}+\ell_{CellAux}$
② + ③ Aux+Siamese	$\ell_{Diff}+\ell_{CellAux}+\ell_{Siamese}$
① + ② + ③ Raw+Aux+Siamese	$\ell_{Diff}+\ell_{CellAux}+\ell_{Siamese}$

Where are we heading?

DeepDiff: Deep-learning for predicting Differential gene expression from histone modifications

Changing Task : Cell-Specific → Cross Cell



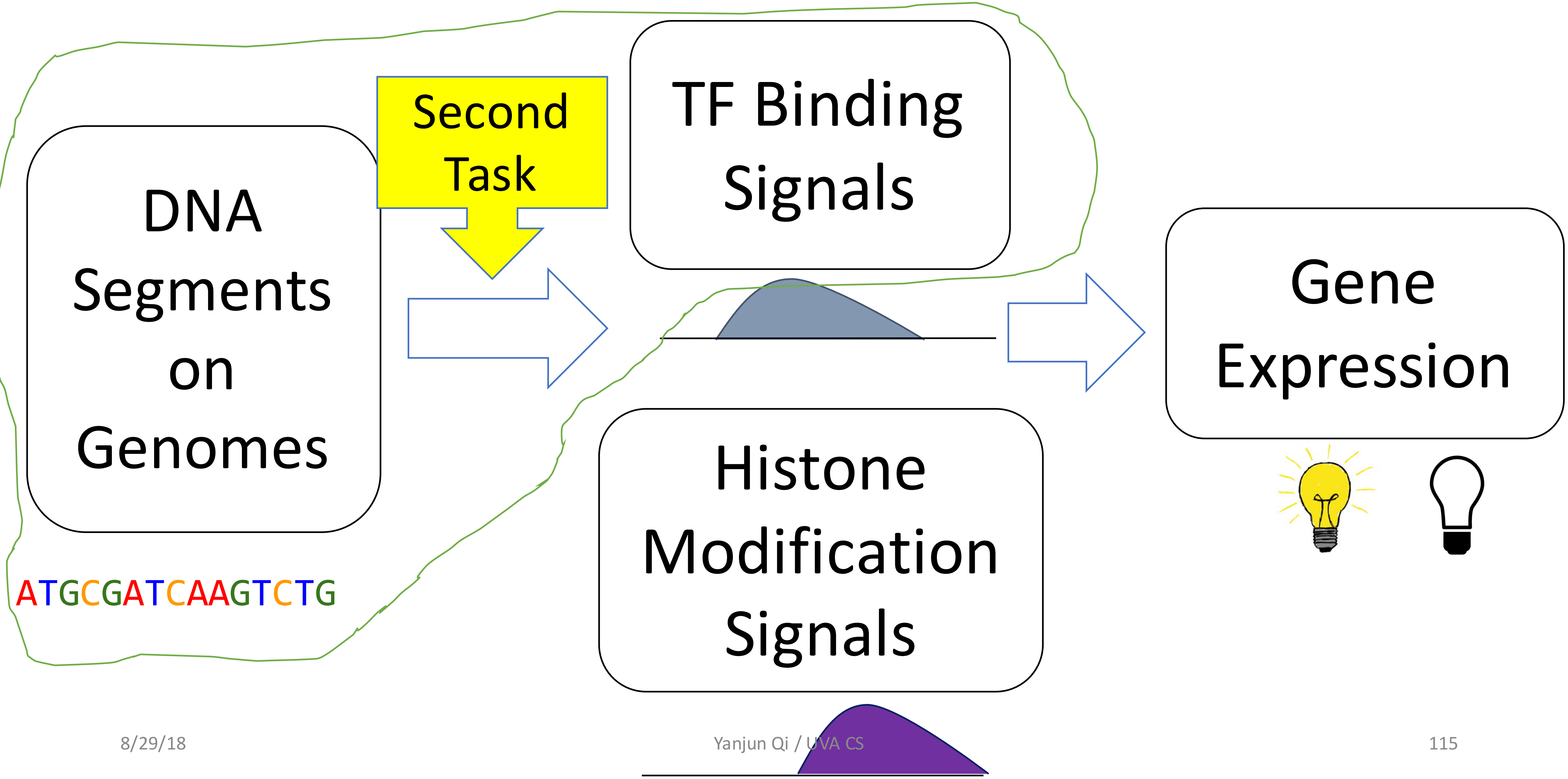
Today

- Machine Learning: a quick review
- Deep Learning: a quick review
- Background Biology: a quick review
- Deep Learning for analyzing Sequential Data about Regulation:
  - DeepChrome
  - AttentiveChrome
  - DeepMotif

https://qdata.github.io/deep2Read/

https://www.deepchrome.org

Many Important Data-Driven Computational Tasks



DNA Segments on Genomes

ATGCGATCAAGTCTG

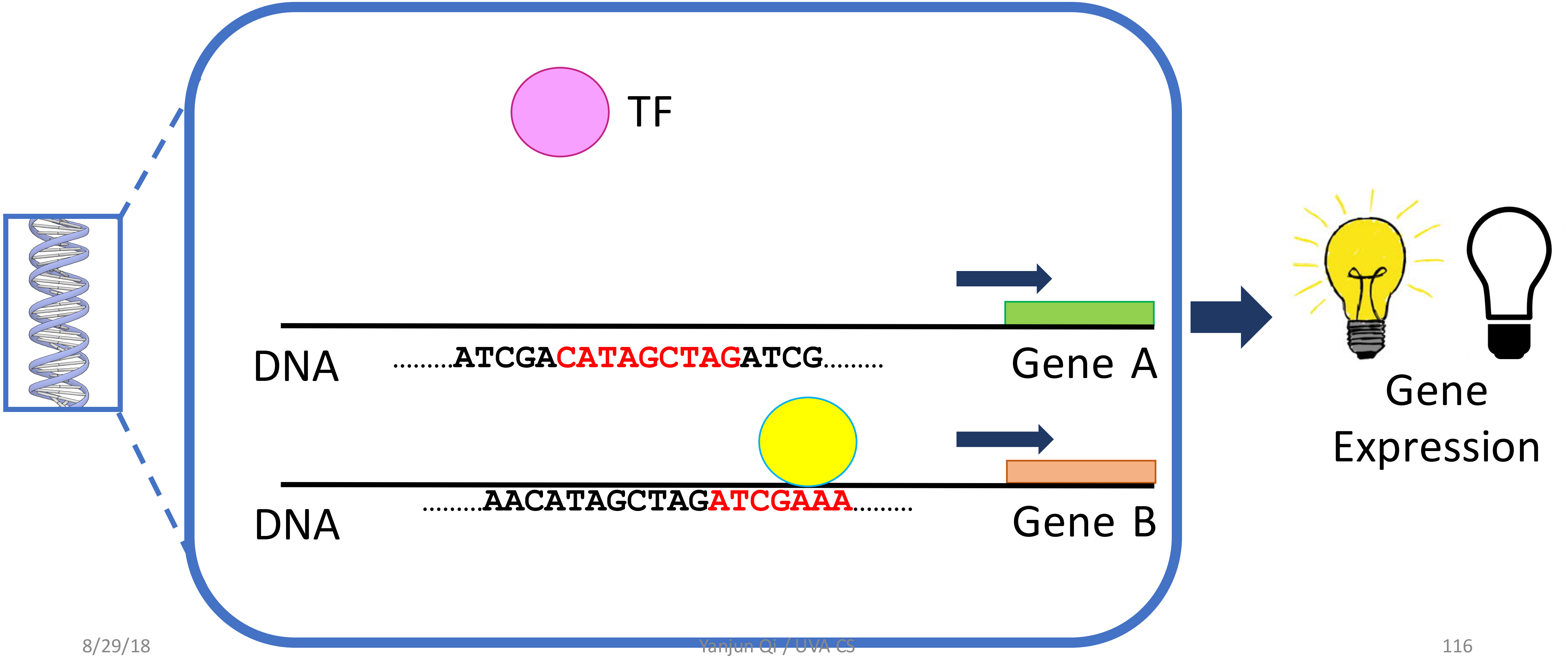
Second Task

TF Binding Signals

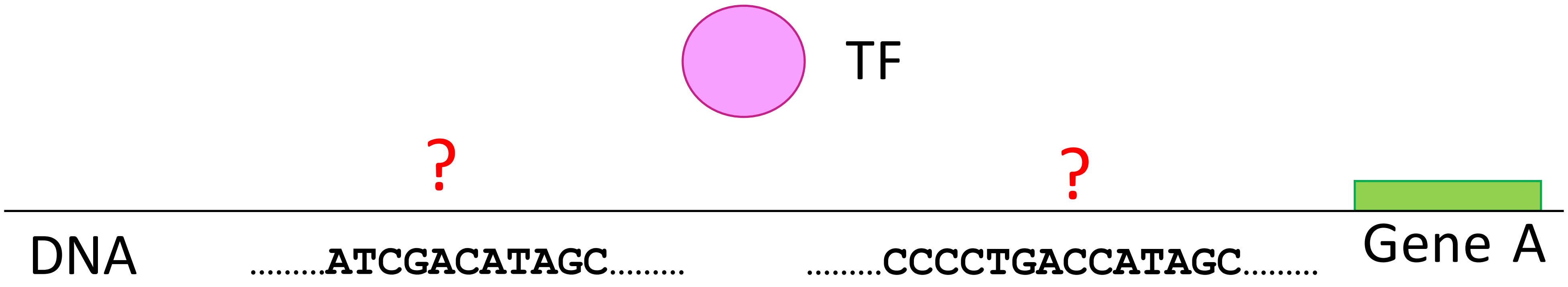
Histone Modification Signals

Gene Expression

Transcription Factors


TF
DNA
.........ATCGACATAGCTAGATCG.........
Gene A
DNA
.........AACATAGCTAGATCGAAA.........
Gene B
Gene Expression

TF-Binding Site?

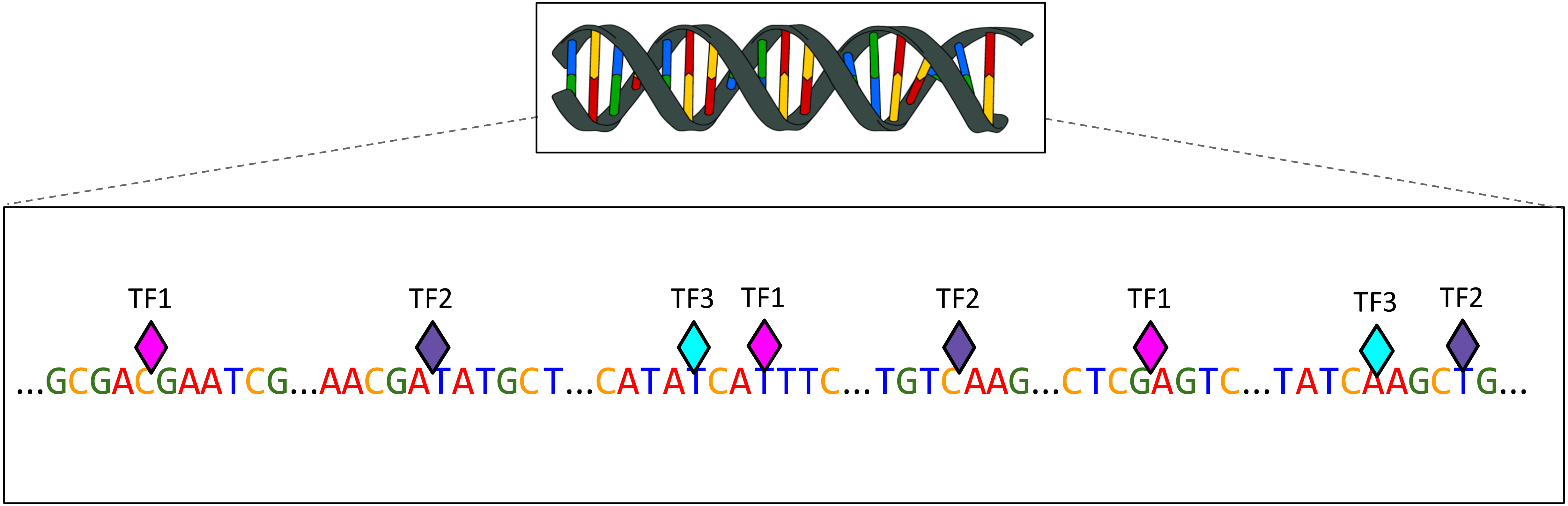

TF
?
?
DNA
.........ATCGACATAGC.........
.........CCCCTGACCATAGC.........
Gene A

“TF-Binding Site?”

ATCGAATCCG ✓

CCCTCTATCG ✗

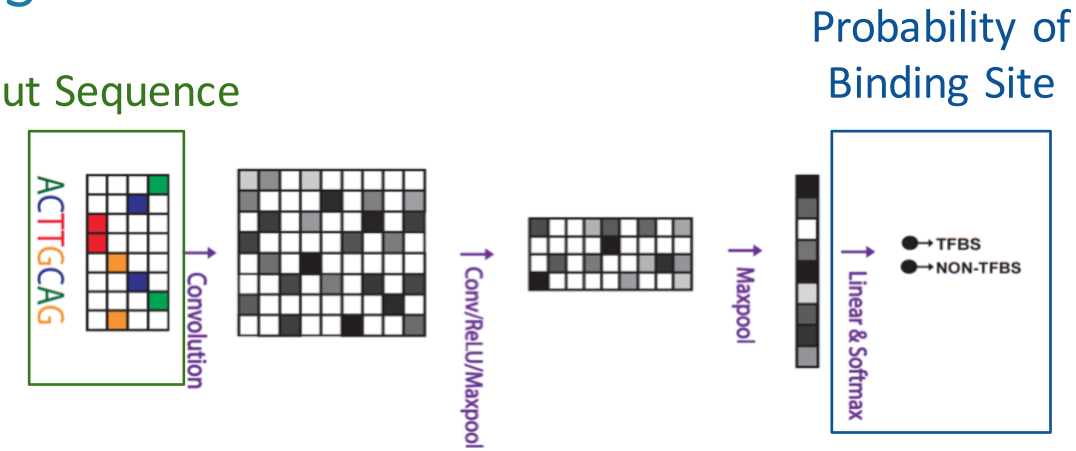
Task: Sequence Based Functional Annotation Tasks



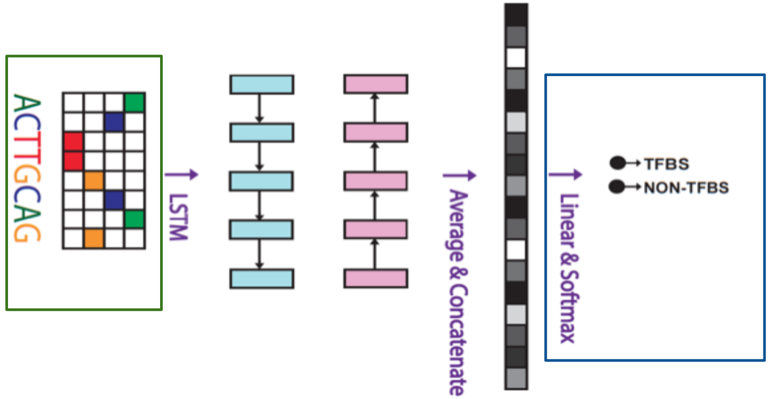
...GCGACGAATCG...AACGATATGCT...CATATCATTTC...TGTCAAG...CTCGAGTC...TATCAAGCTG...

Literature: Various DNN Tools

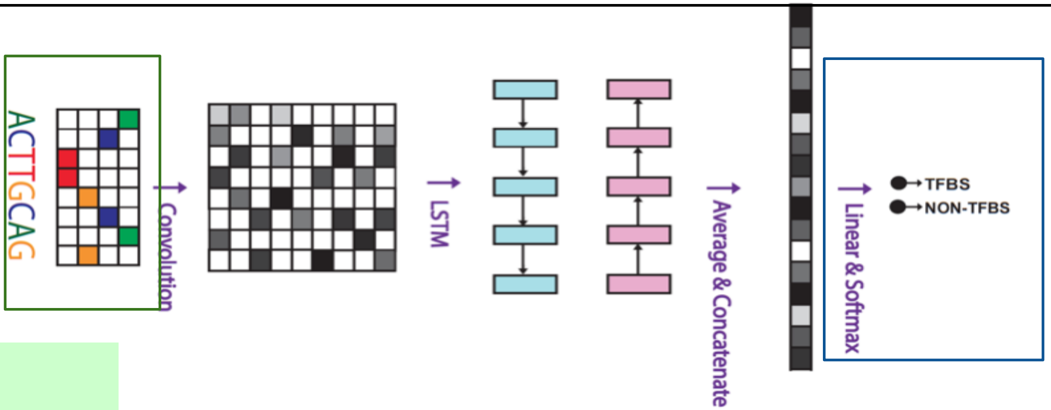
1. **Convolutional (CNN)**



2. **Recurrent (RNN)**



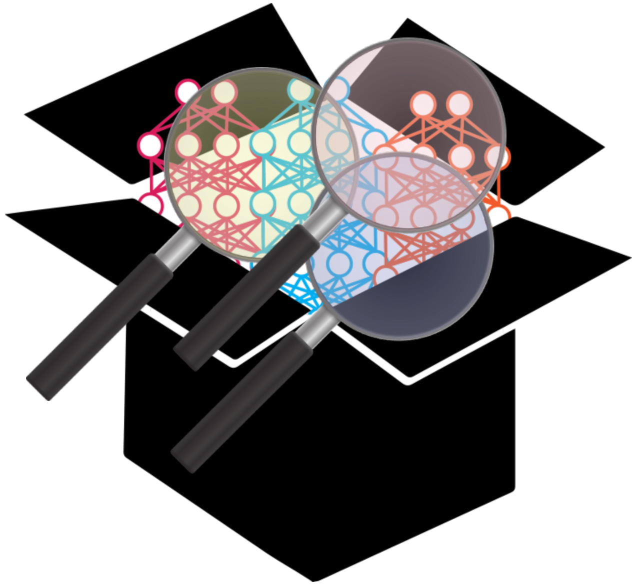
3. **Convolutional-Recurrent (CNN-RNN)**

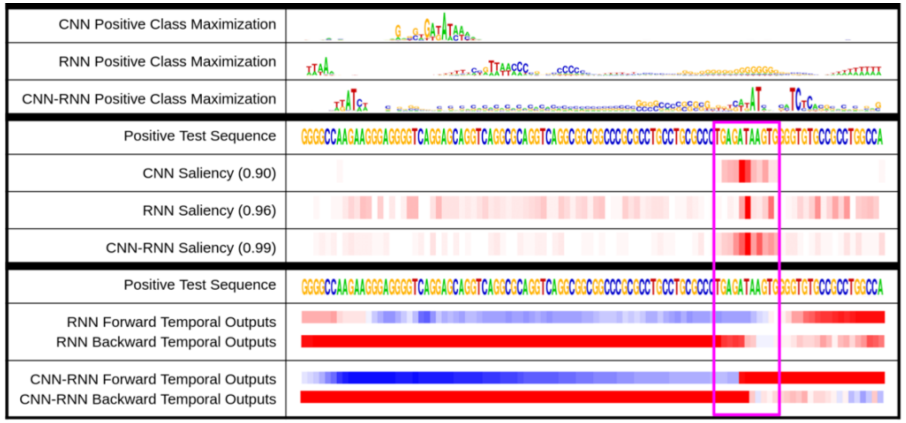


DeepSEA, DeepBind, BASSET, DanQ, ….

Deep Motif Dashboard: Understand DNNs by Post Analysis

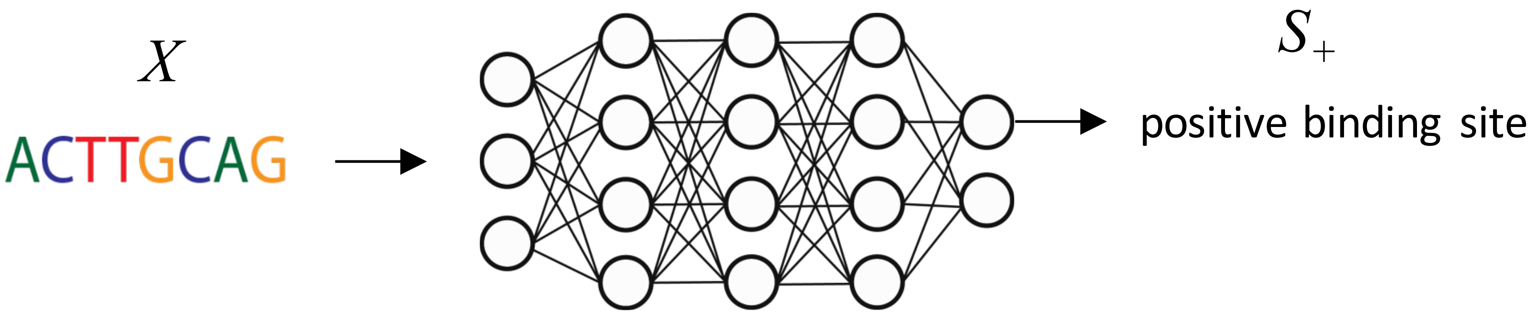
Lanchantin, Singh, Wang & Qi - Pacific Symposium on Biocomputing, 2017




CNN Positive Class Maximization
RNN Positive Class Maximization
CNN-RNN Positive Class Maximization
Positive Test Sequence
GGGGCCAAGAAGGGAGGGGTCAGGAGCAGGTCAGGCGCAGGTCAGGCGGCGGCCCGCGCCTGCCTGCGCCCTGAGATAAGTGGGGTGTGCCGCCTGGCCA
CNN Saliency (0.90)
RNN Saliency (0.96)
CNN-RNN Saliency (0.99)
Positive Test Sequence
GGGGCCAAGAAGGGAGGGGTCAGGAGCAGGTCAGGCGCAGGTCAGGCGGCGGCCCGCGCCTGCCTGCGCCCTGAGATAAGTGGGGTGTGCCGCCTGGCCA
RNN Forward Temporal Outputs
RNN Backward Temporal Outputs
CNN-RNN Forward Temporal Outputs
CNN-RNN Backward Temporal Outputs

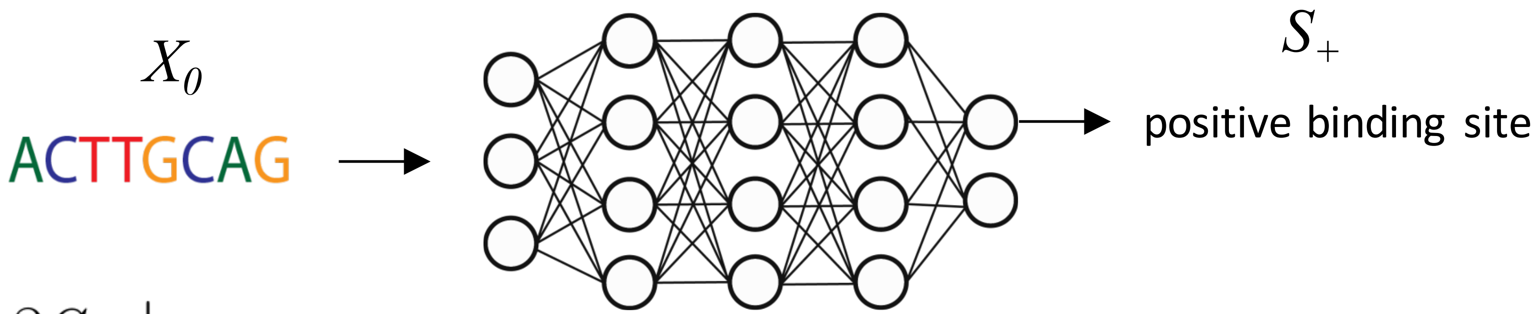
1. Saliency Maps - recommending on CNN kind
2. Temporal Output Values - recommending on RNN kind
3. Class Optimization - recommending on CNN kind

1. Saliency Map



Which nucleotides are most important for my current-sample classification?

1. Saliency Map



X_0

ACTTGCAG

S_+

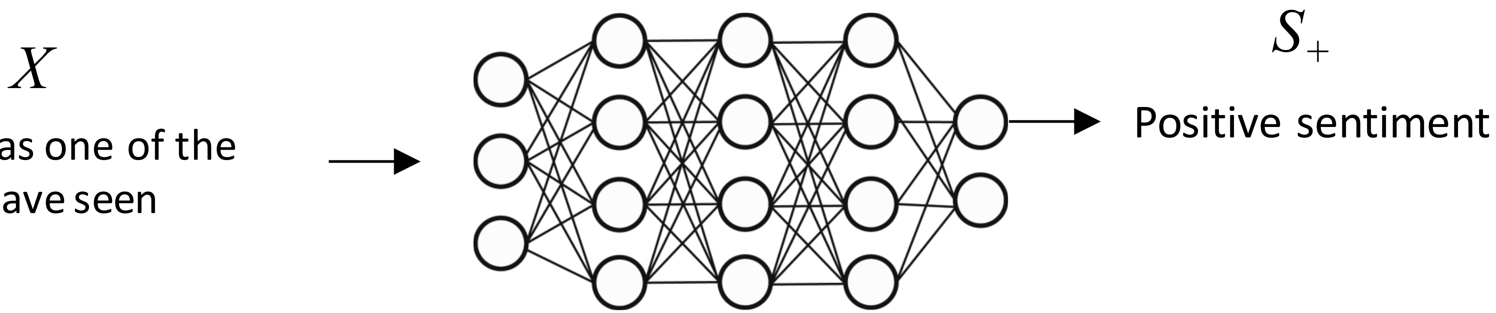
positive binding site

$$w = \left.\frac{\partial S_+}{\partial X}\right|_{X_0} = \text{“}\textit{saliency map}\text{”}$$

Quiz: What is gradient?

Deep Inside Convolutional Networks: Visualising Image Classification Models and Saliency Maps, ICLR 2013

1. Saliency Map

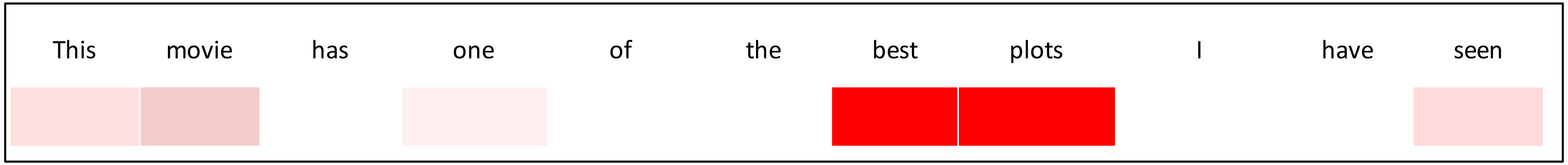


X

This movie has one of the best plots I have seen

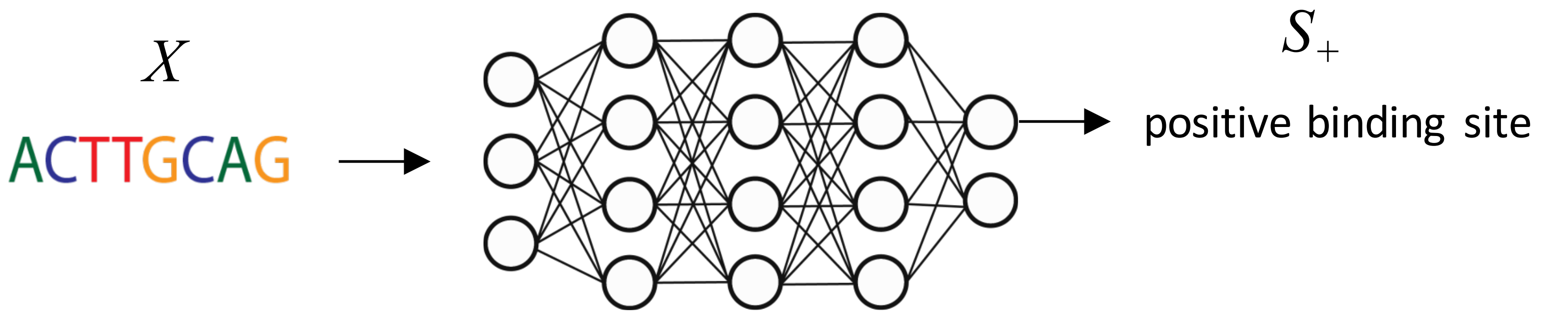
S_+

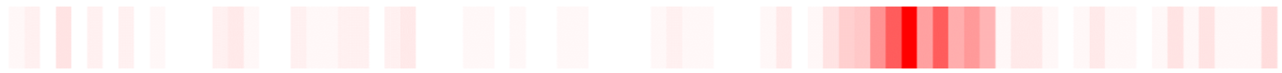
Positive sentiment



🟥 = important for classification

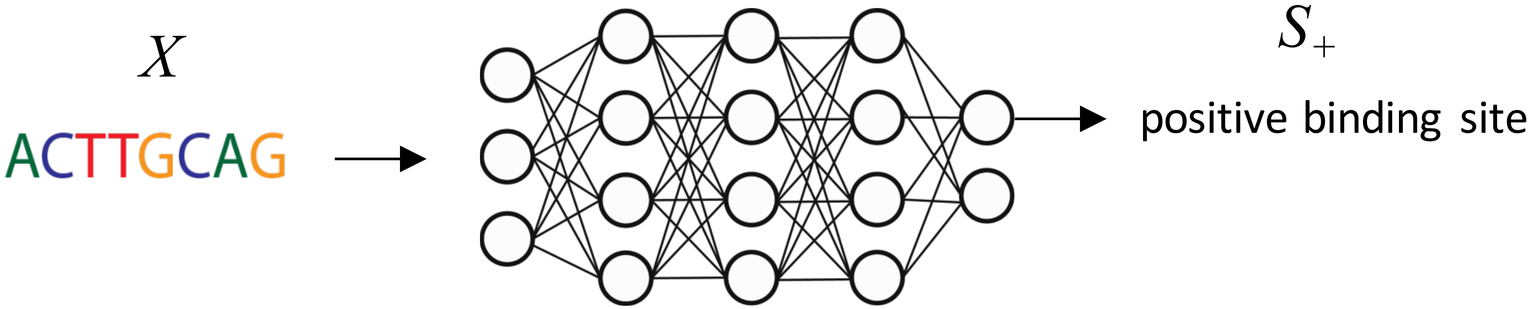
1. Saliency Map



Positive Test Sequence	TGCTCGCATCCTATTGGCCACGTTAGTCACATGGCCCCACCTGGCTGCAAAGCACGCTGGGAAACGTAGTCTTTCTT
Saliency Map	

🟥 = important nucleotide for prediction

2. Temporal Output Values



X

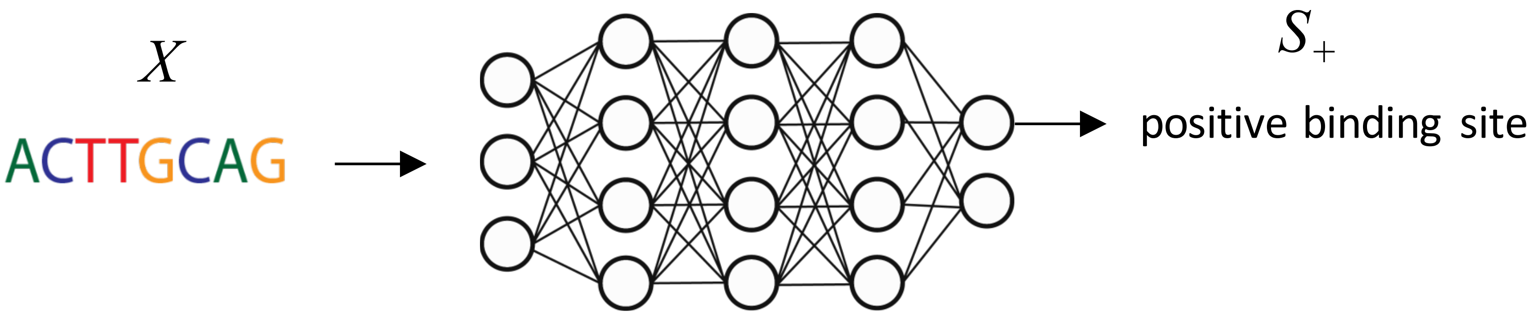
ACTTGCAG

S_+

positive binding site

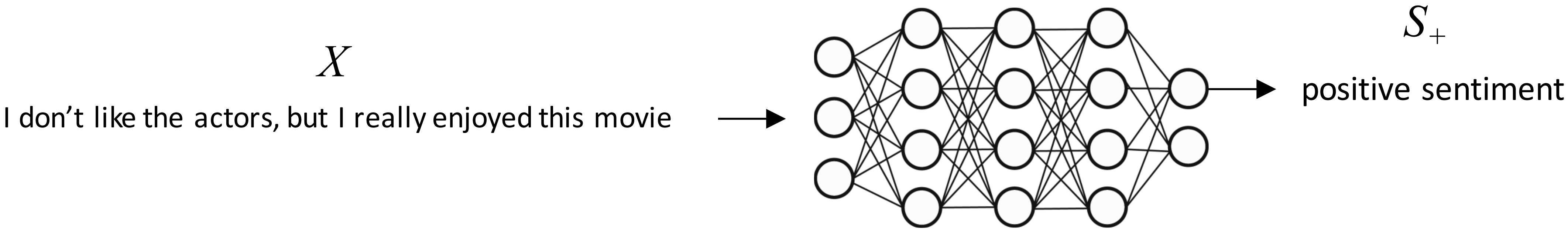
What are the model’s predictions at each timestep of the DNA sequence?

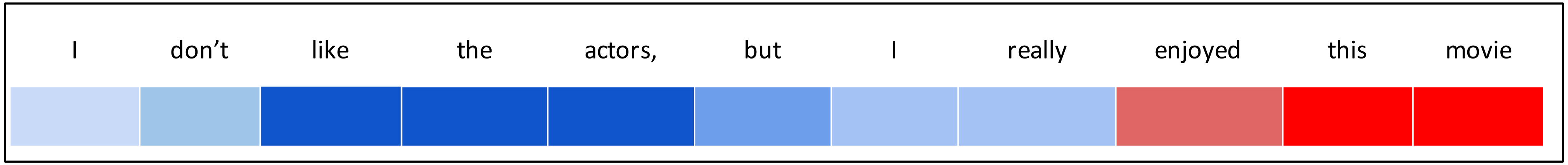
2. Temporal Output Values



Check the RNN's prediction scores when we vary the input of the RNN starting from the beginning to the end of a sequence.

2. Temporal Output Values

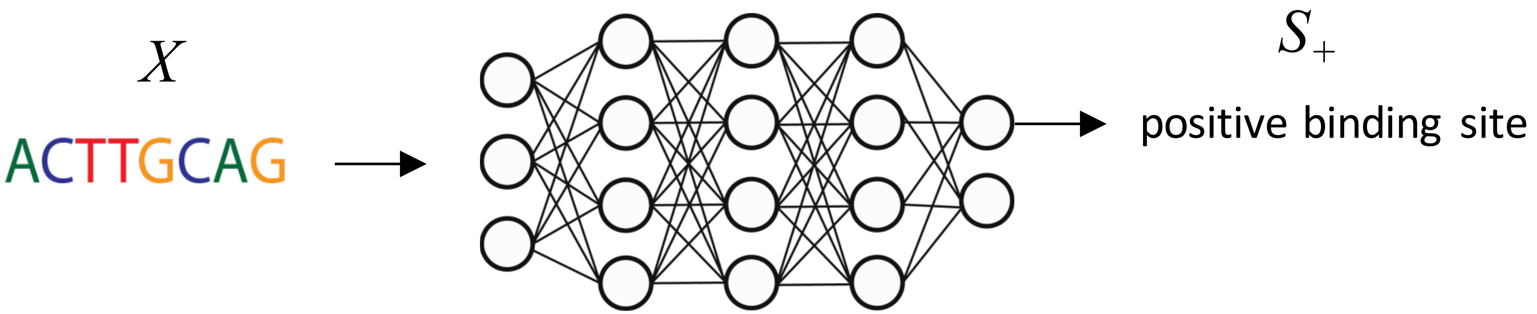




🟦 = negative sentiment

🟥 = positive sentiment

2. Temporal Output Values

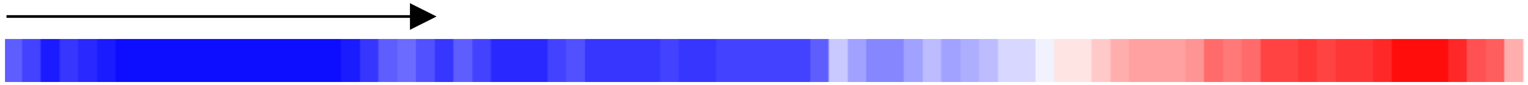
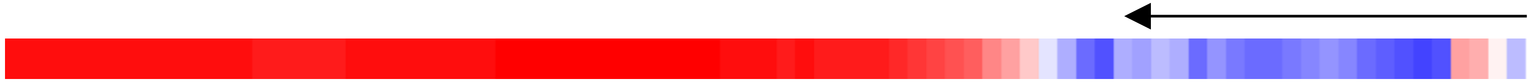


X

ACTTGCAG

S_+

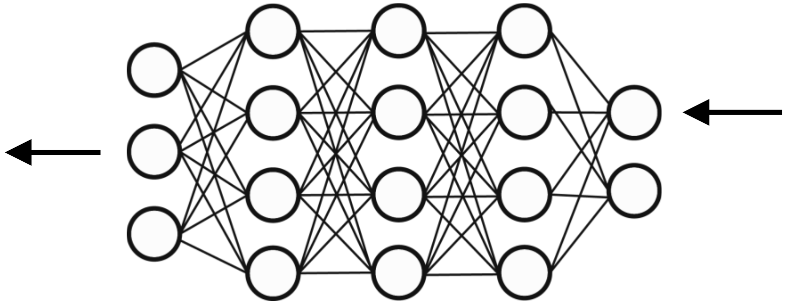
positive binding site

Positive Test Sequence	CTTCTGCTCGCATCCTATTGGCCACGTTAGTCACATGGCCCCACCTGGCTGCAAAGCACGCTGGGAAACGTAGTCTTTCTT
RNN Forward Output	
RNN Backward Output	

🟦 = negative binding site prediction 🟥 = positive binding site prediction

3. Class Optimization

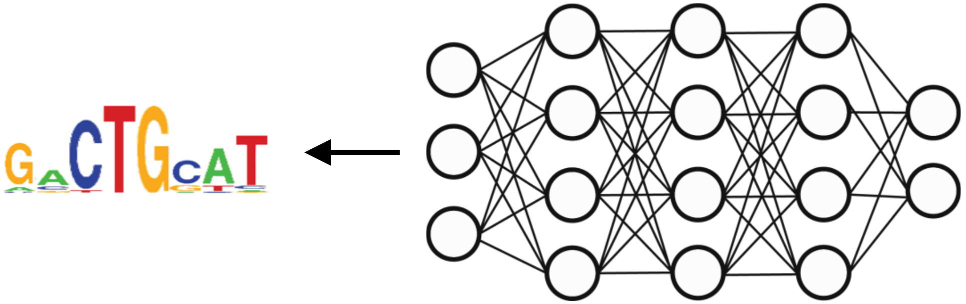
?



positive binding site for TF “CBX3”

For a particular TF, what does the optimal binding site sequence look like?

3. Class Optimization



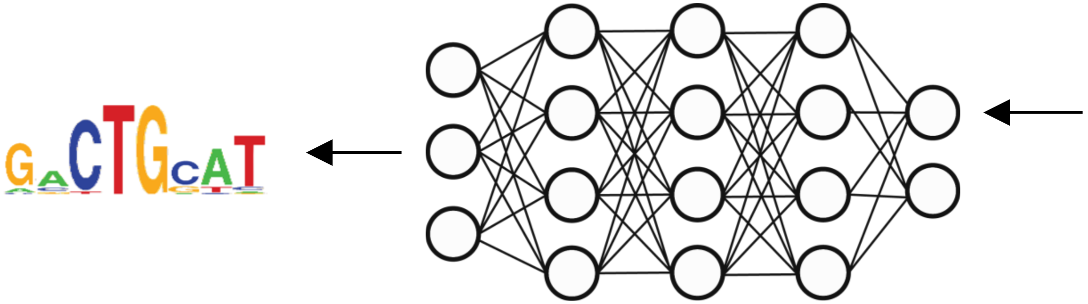
positive binding site for TF “CBX3”

$$\arg\max_X S_+(X) + \lambda\|X\|_2^2$$

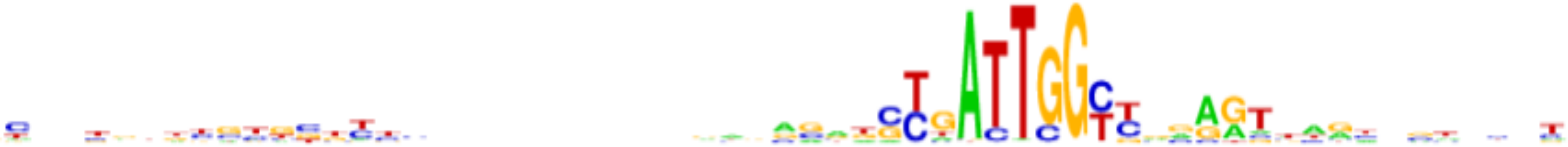
Where X is the input sequence and the score S_+ is probability of sequence X being a positive binding site

Deep Inside Convolutional Networks: Visualising Image Classification Models and Saliency Maps, ICLR 2013

3. Class Optimization



positive binding site for TF “CBX3”

Optimal binding site for TF “CBX3”	

Visualization Methods

Sequence Specific

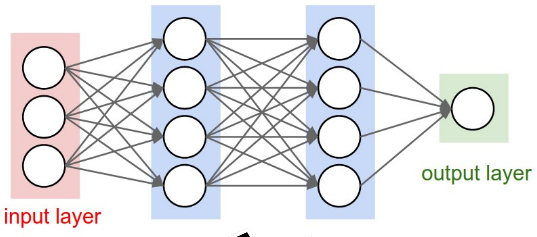
1. Saliency Maps – (CNN kind)
2. Temporal Output Values – (RNN kind)

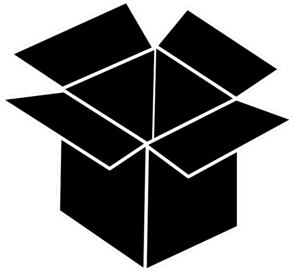
TF Specific

3. Class Optimization – (CNN kind)

code available at: **deepmotif.org**

Related Work to Post-Understand DNN

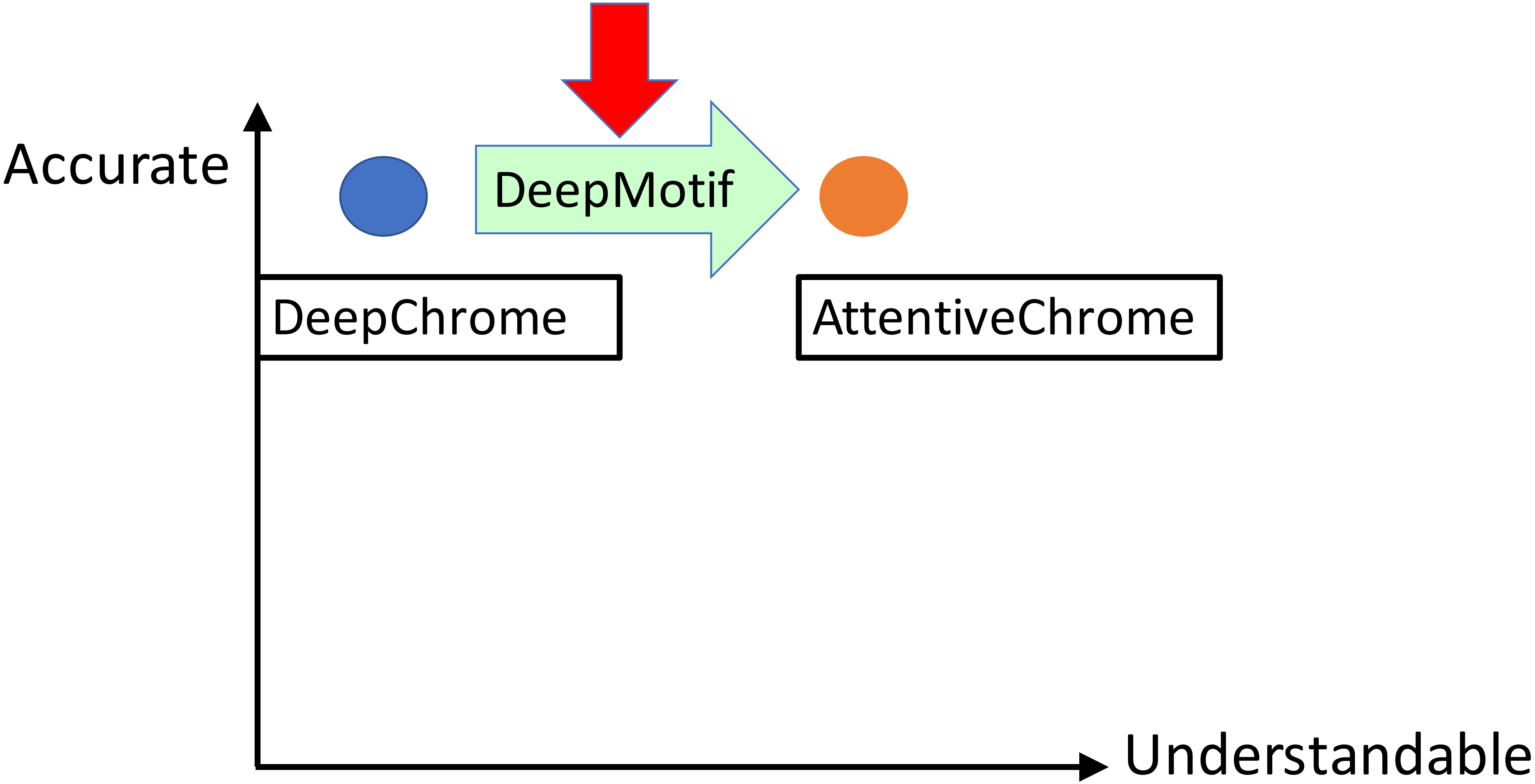




- Deconvolution
- Perturbation-based — Temporal Output Values
- Backpropagation-based — Saliency Map; Class Optimization
- Difference to Reference — DeepLift
- Influence based — Influential Function / ICML27 Best Paper

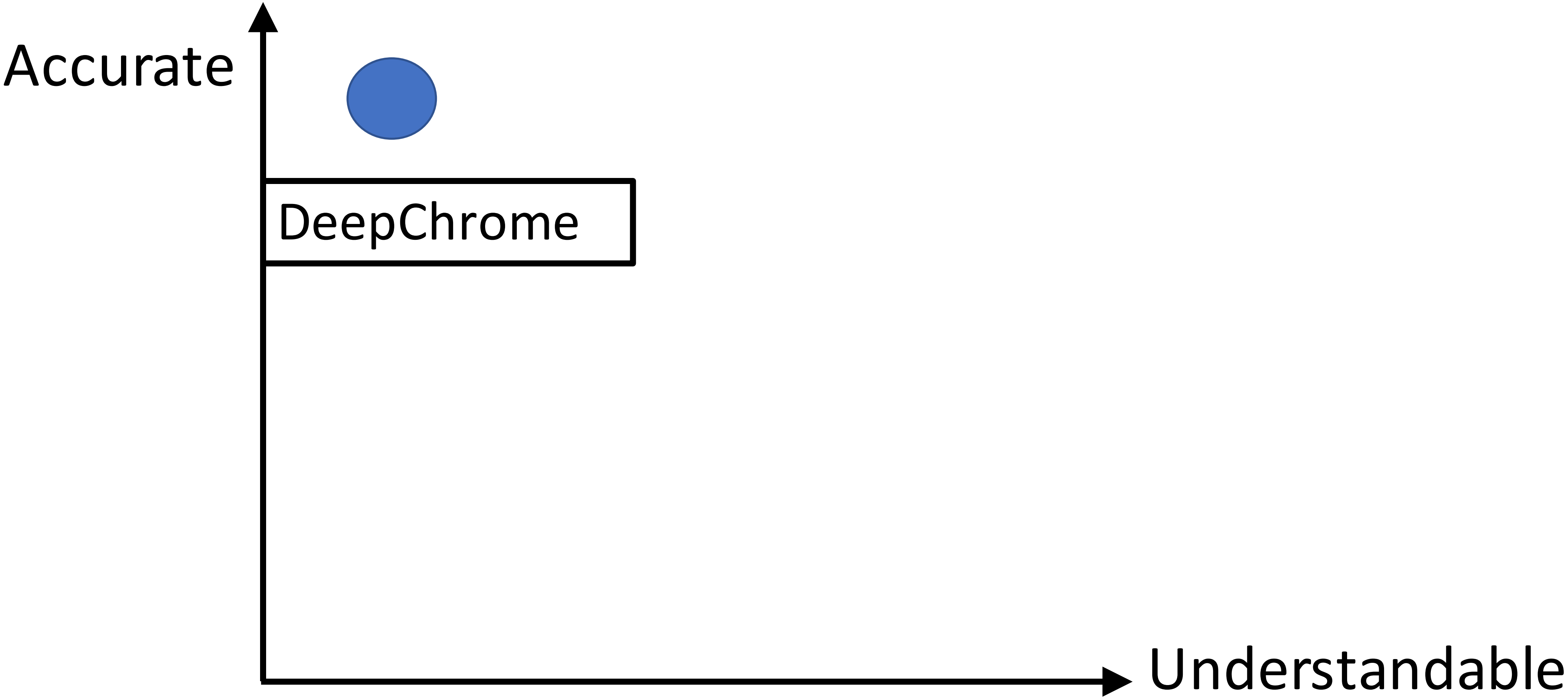
https://www.deepchrome.org

Summary of tools



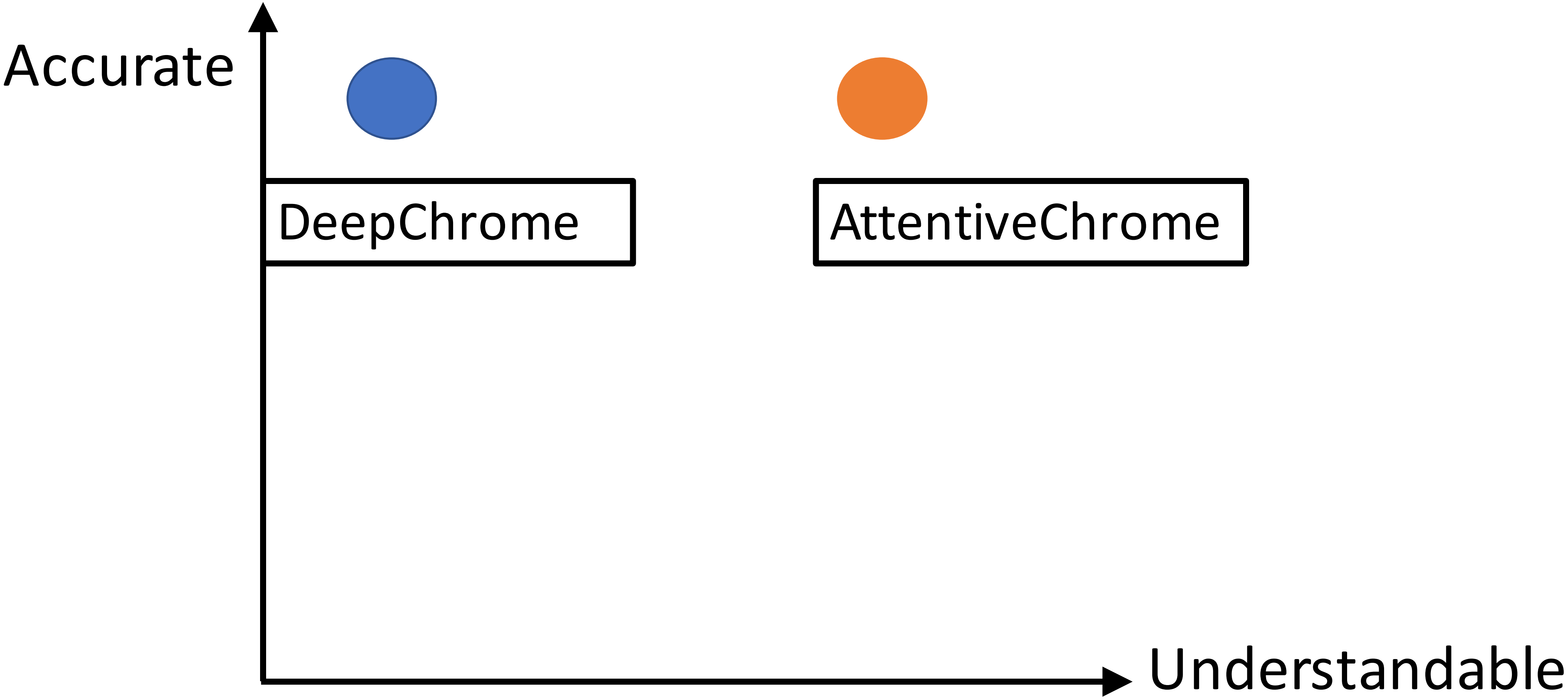
https://www.deepchrome.org

Recap

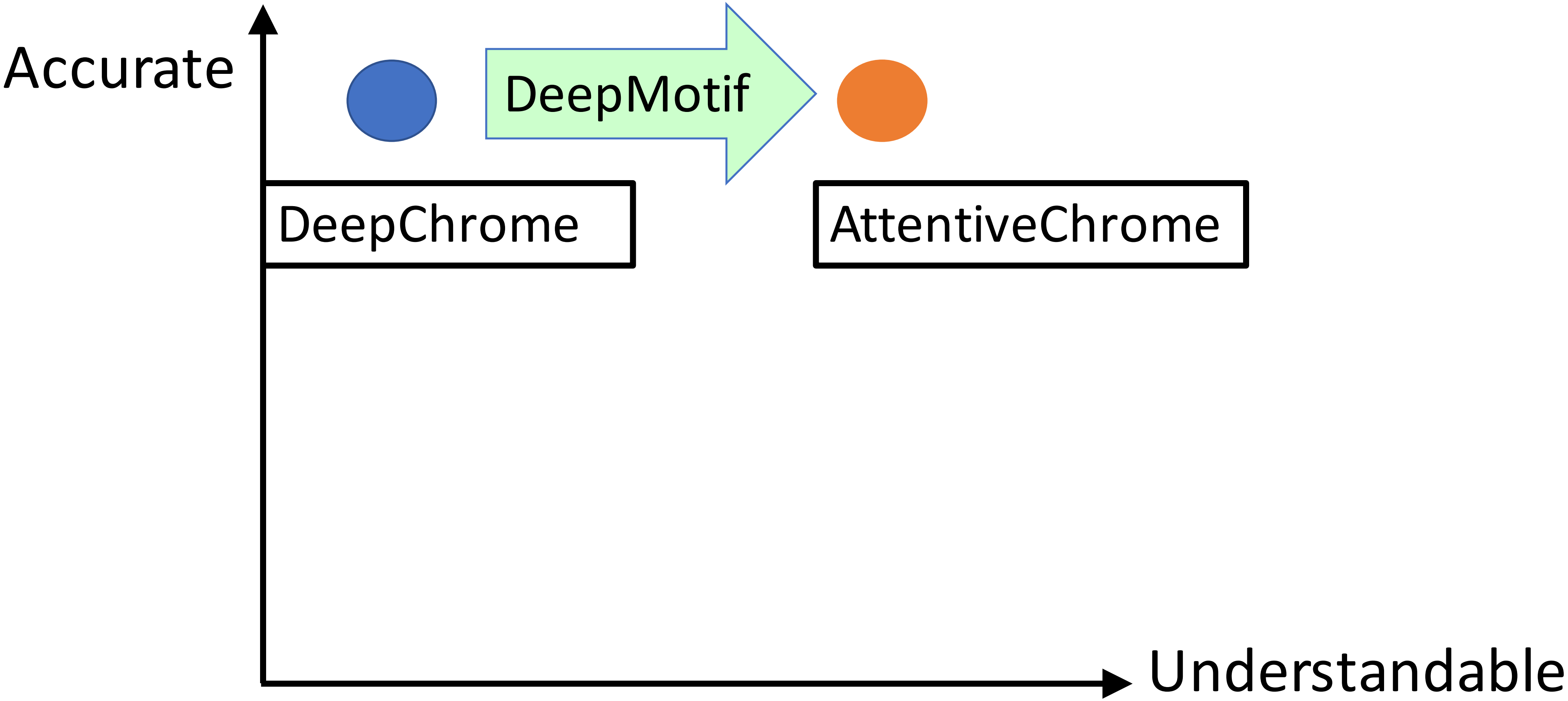


https://www.deepchrome.org

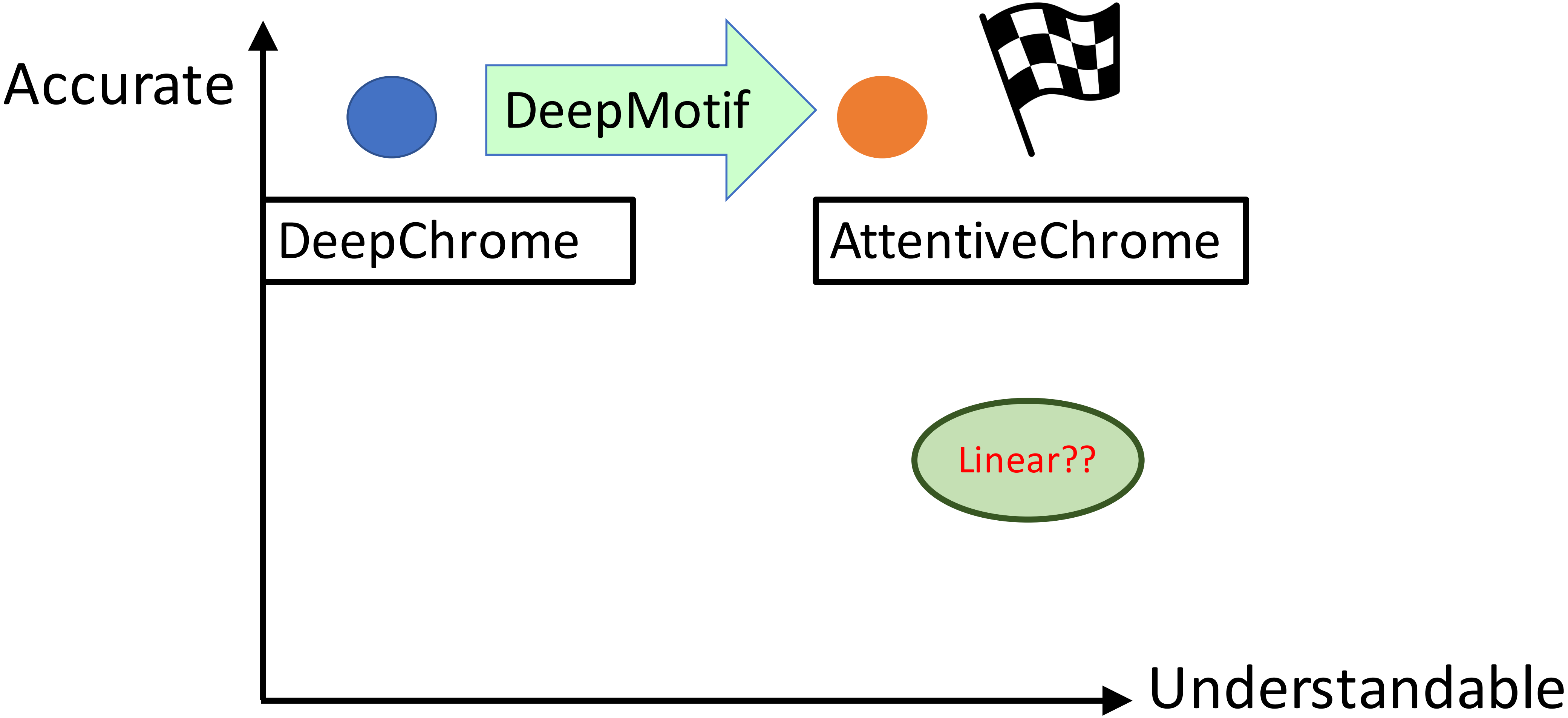
Recap



Recap


Accurate
DeepMotif
DeepChrome
AttentiveChrome
Understandable

Recap


Accurate
DeepMotif
DeepChrome
AttentiveChrome
Linear??
Understandable

Acknowledgements

Ritambhara Singh

Jack Lanchantin

Arshdeep Sekhon

Beilun Wang

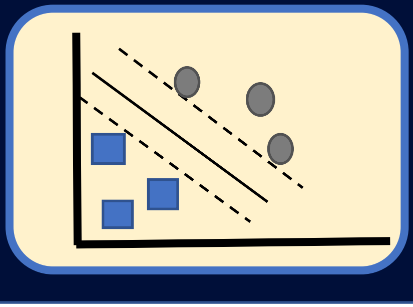
UVA Department of Biochemistry and Molecular Genetics: Dr. Mazhar Adli

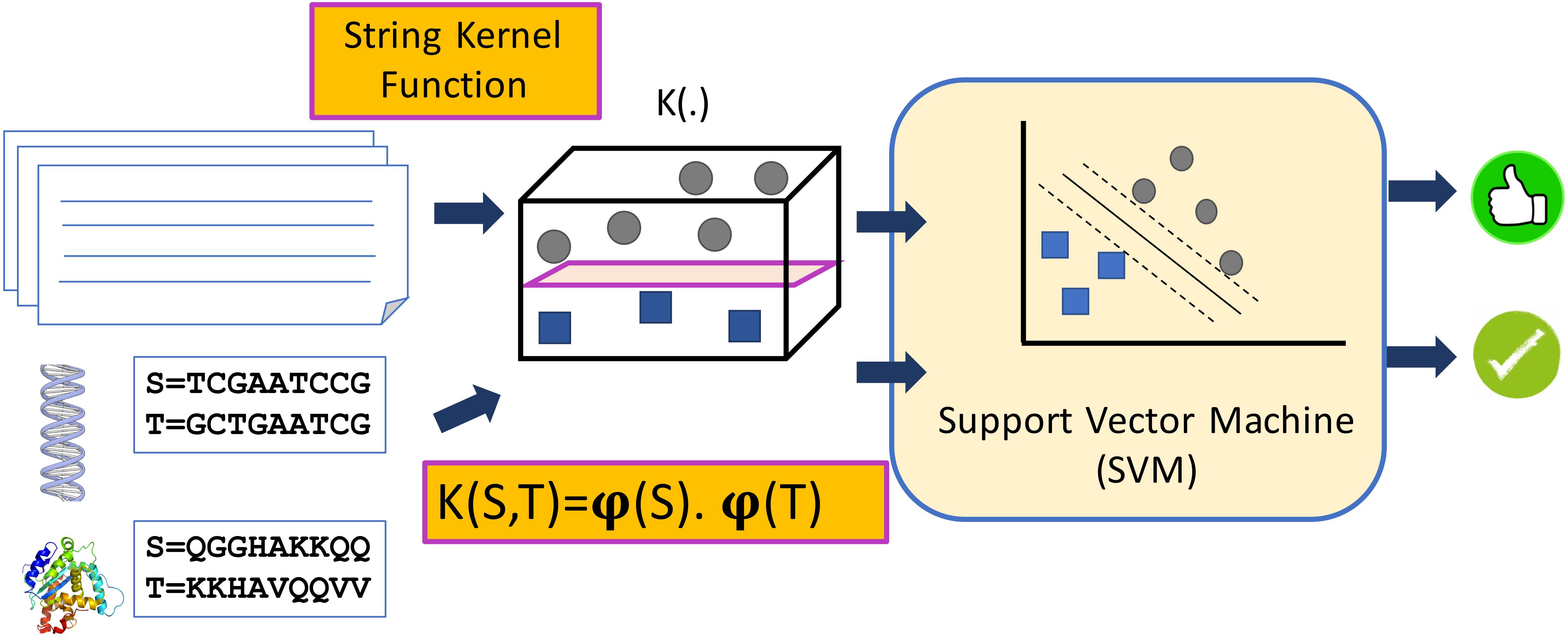
Thank you

More Tools: A Fast and Scalable Tool to Classify Biological Sequences

https://github.com/QData/iGakco-SVM

String Kernel + SVM





String Kernel Function

K(.)

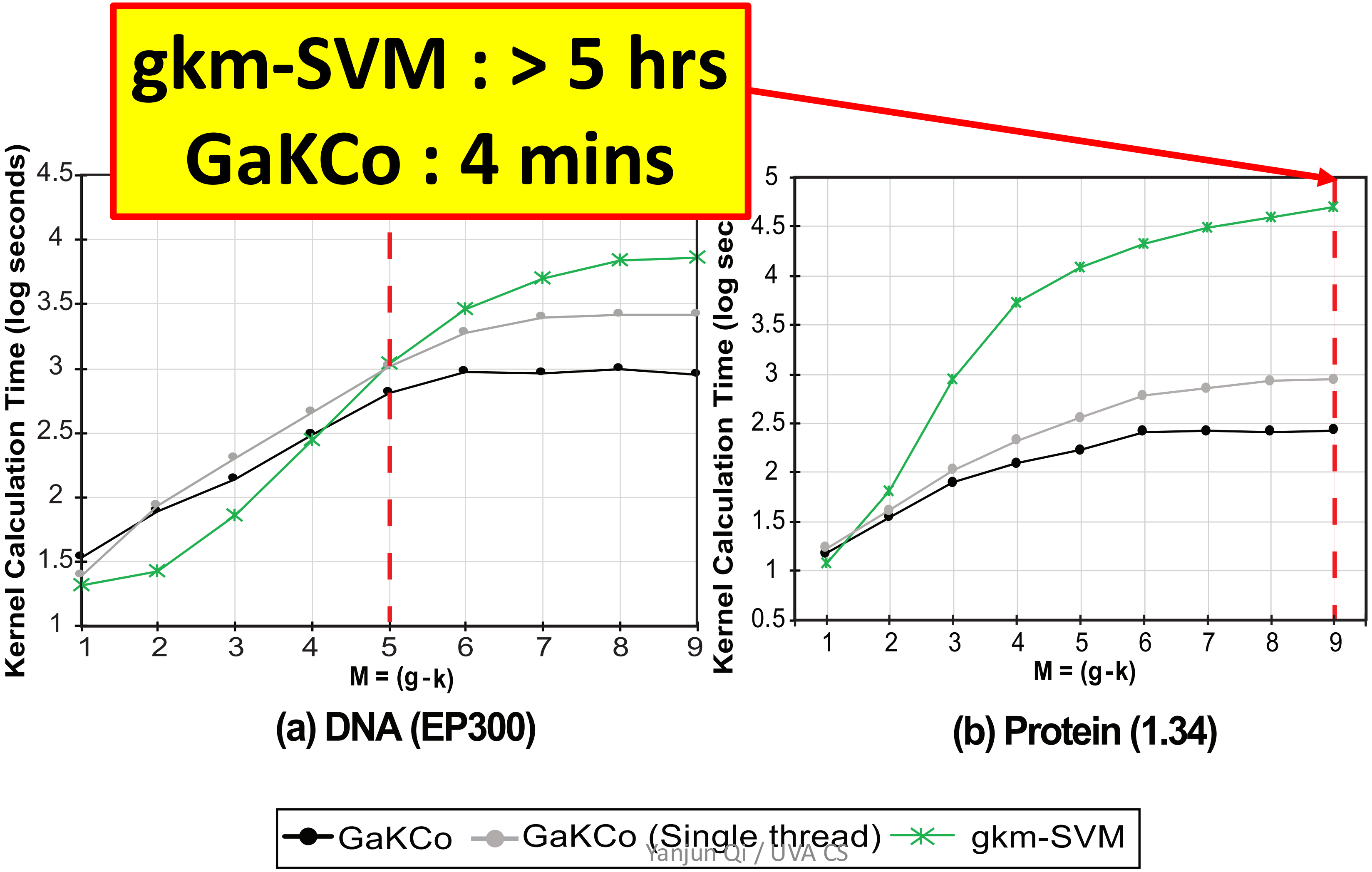
S=TCGAATCCG
T=GCTGAATCG

S=QGGHAKKQQ
T=KKHAVQQVV

$K(S,T)=\varphi(S).\ \varphi(T)$

Support Vector Machine (SVM)

Our Tool Scales well with increasing ∑ and m



gkm-SVM : > 5 hrs
GaKCo : 4 mins

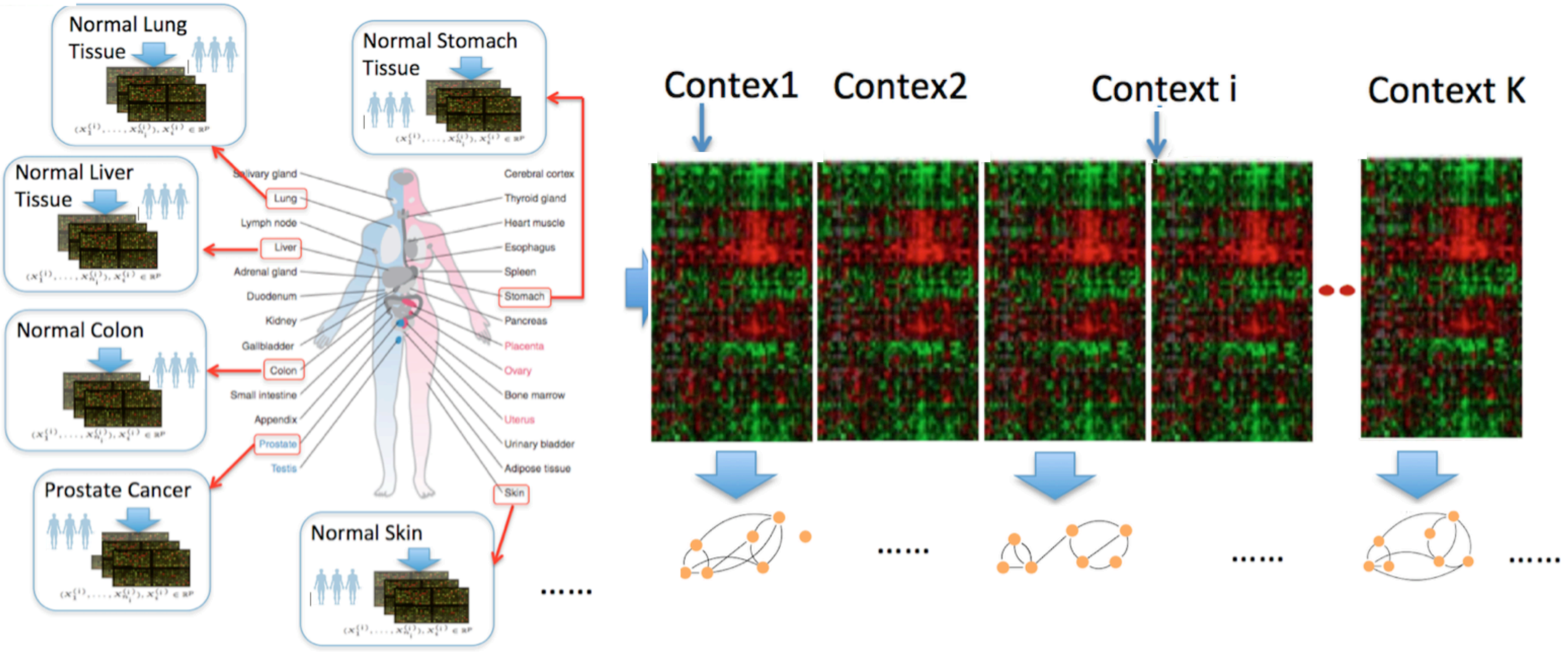
(a) DNA (EP300)

(b) Protein (1.34)

More Tools: Extracting graphs from data

https://www.jointggm.org

Motivation: Graphs vary across contexts



Limitation of Previous Methods : Storage

e.g., calculate the gradient

$$\Sigma = \mathrm{Cov}(X) = \boxed{\begin{bmatrix} \sigma_{11} & \sigma_{12} & \cdots & \sigma_{1n} \\ \sigma_{21} & \sigma_{22} & \cdots & \sigma_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ \sigma_{n1} & \sigma_{n2} & \cdots & \sigma_{nn} \end{bmatrix}}$$

$$\Sigma = \mathrm{Cov}(X) = \boxed{\begin{bmatrix} \sigma_{11} & \sigma_{12} & \cdots & \sigma_{1n} \\ \sigma_{21} & \sigma_{22} & \cdots & \sigma_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ \sigma_{n1} & \sigma_{n2} & \cdots & \sigma_{nn} \end{bmatrix}}$$

$$\Sigma = \mathrm{Cov}(X) = \boxed{\begin{bmatrix} \sigma_{11} & \sigma_{12} & \cdots & \sigma_{1n} \\ \sigma_{21} & \sigma_{22} & \cdots & \sigma_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ \sigma_{n1} & \sigma_{n2} & \cdots & \sigma_{nn} \end{bmatrix}}$$

When K contexts= 91, p nodes= 30K

$O(Kp^2)$ in memory

Double type: 65 TB

Limitation of Previous Methods: Speed

Suppose they have the same iteration number T

K = 91, p= 30K

Traditional Optimization Method

---- Block Coordinate Descent : $O(K^3p^4)$ / Itera

more than 2 billion years

Current Optimization: ADMM based

---- Still needs SVD for each covariance matrix

SVD for the matrices needs $O(Kp^3)$ / Itera → 3.5 days

Our Tools

- Fast and scalable estimators for joint graph discovery from heterogeneous samples
- Parallelizable algorithms
- Sharp convergence rate (sharp error bounds)

More details at: http://www.jointggm.org/