



Machine Learning from scratch

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Goals

- Conceive and simulate genetic data under competing demographic scenarios 
- Understand deep learning background and how a CNN works
- How to use deep learning to compare demographic scenarios
- Use CNN to detect regions with selective sweeps on real genomes

Program

Part I: A gentle introduction to supervised deep learning.

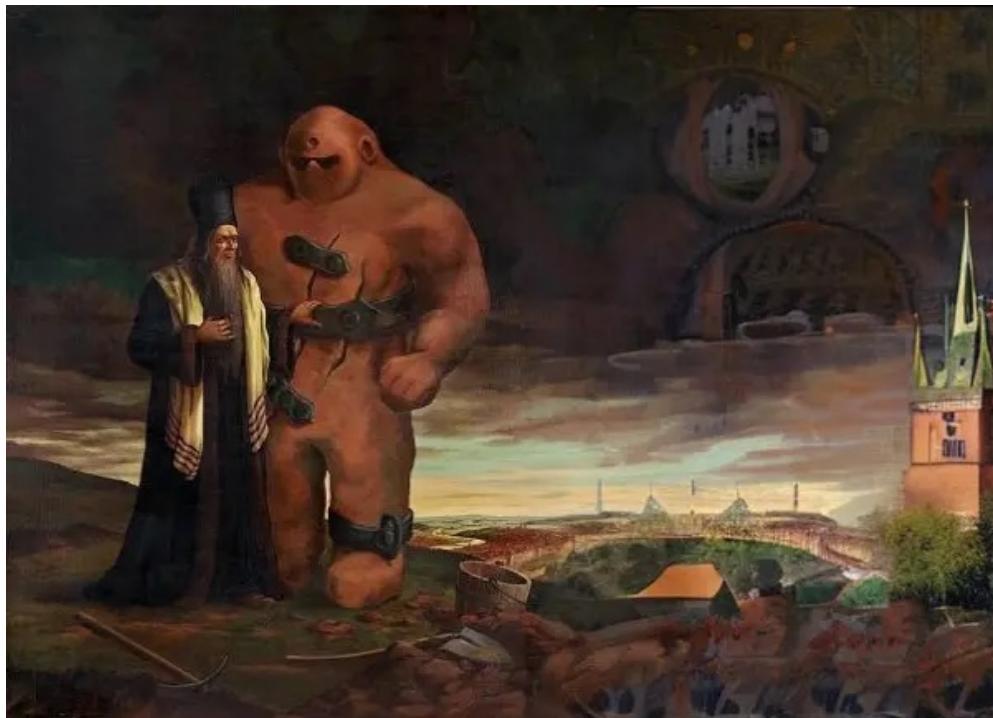
Credit for some slides:
Matteo Fumagalli and Flora Jay

The Golem of Prague

Statistical Rethinking
2023



[https://github.com/rmcelreath/
stat_rethinking_2023](https://github.com/rmcelreath/stat_rethinking_2023)



https://trips-tickets.com/the_golem_of_prague/



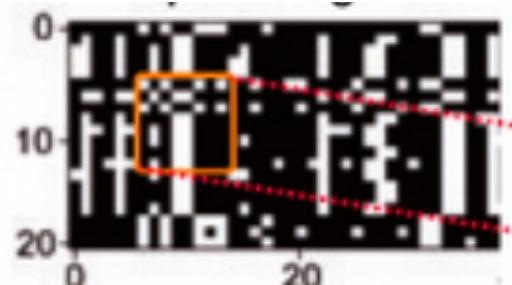
[https://www.atlantajewishtimes.com/
the-golem-of-prague/](https://www.atlantajewishtimes.com/the-golem-of-prague/)

What is machine learning?

TASK:
predict y from x



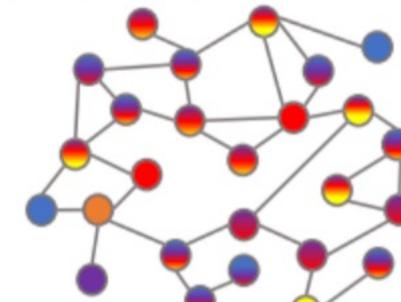
What is the data?



Images

Flagel et al. (2019) *MBE*

Gene interaction network



Graphs

Li et al. (2022) *Nat Biom Eng*

123



[text]

Numerical
Data

Categorical
Data

Time Series
Data

Text
Data

What is the model?

Unsupervised / Supervised Tasks

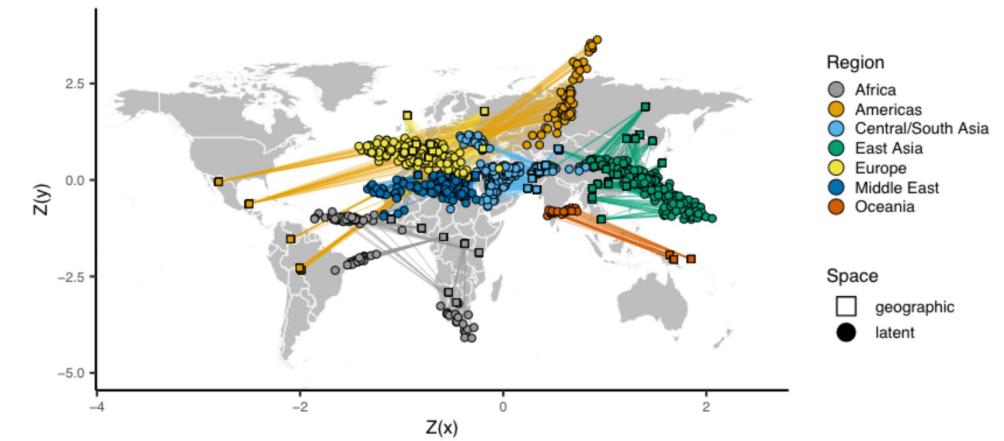
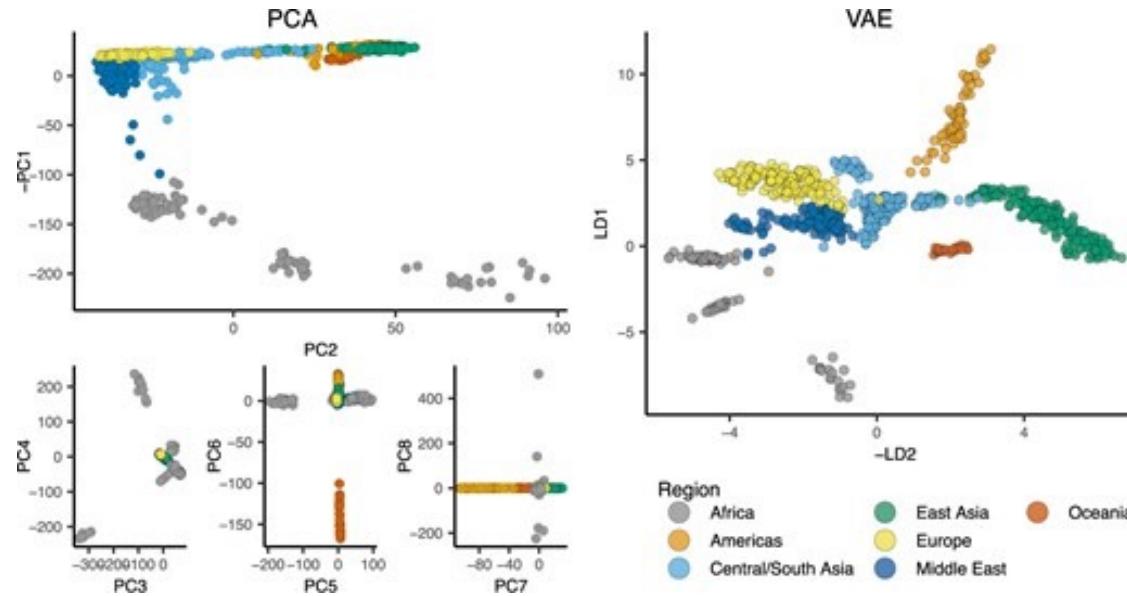
- Learning something from **data**
- Either **unsupervised** (no labels) or **supervised** (discrete or continuous labels)
- What's a label ? a target class (discrete) or a target value (continuous) observed for each sample
*Data are not always labeled. They can also have multiclass labels
ex : pic of dog/person/car..., price of house, level of cholesterol*

What is the model?

.Unsupervised = discovering patterns in data without prior knowledge

You do NOT have labels, or you do NOT use them

- Dimension reduction methods, e.g. PCA, Matrix factorization
- Clustering algorithms, e.g. K-means, hierarchical clustering, ...
- Outlier detection (can be then used for filtering, ..)
- ...



Battey et al. (2021) G3

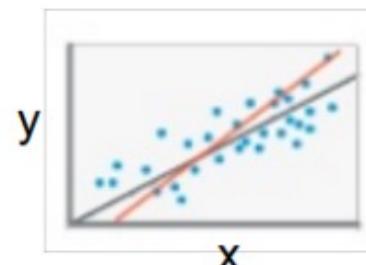
What is the model?

- Supervised = Learn a relationship (a general model) linking input data (or features) to observed labels

Classification (predict a class)



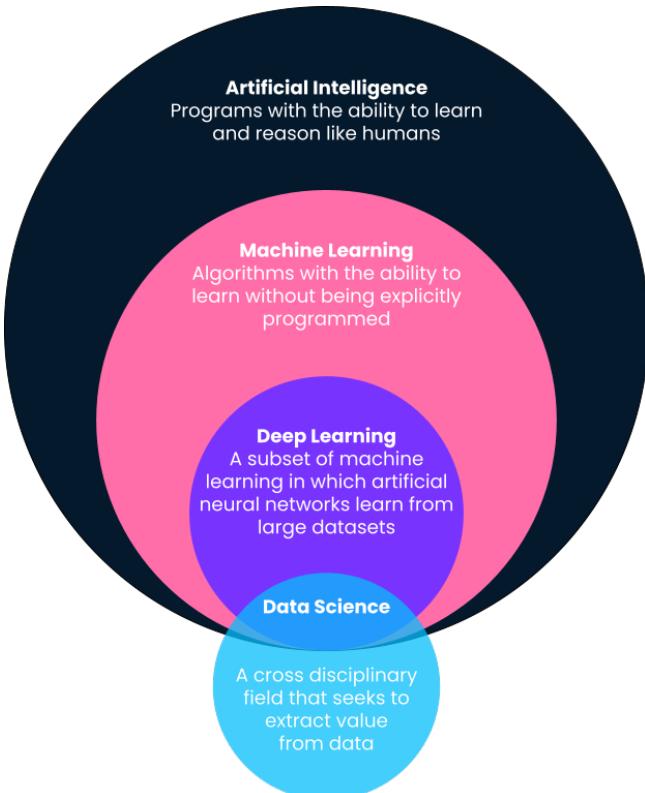
Regression (predict a variable)



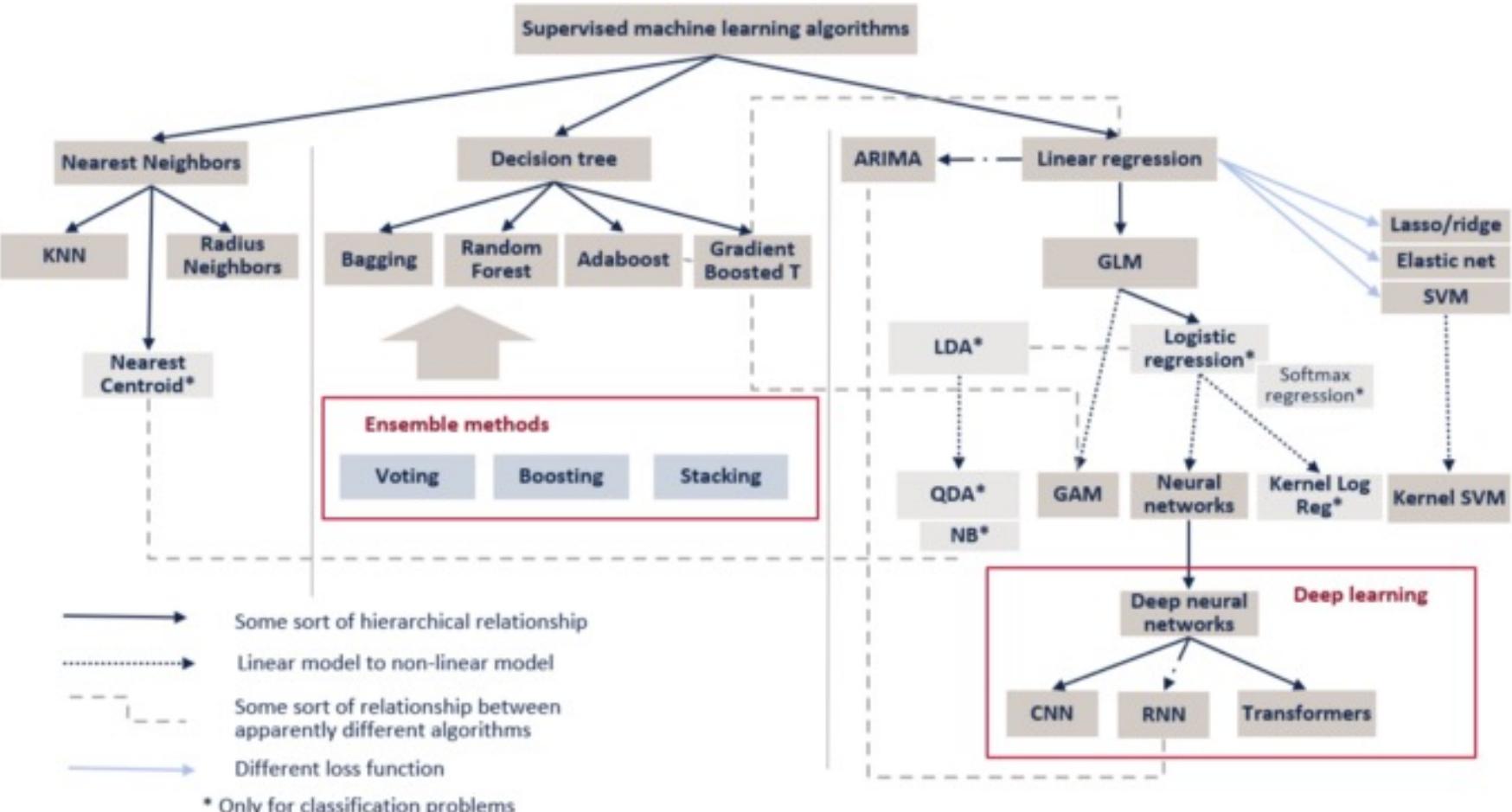
What for:

- Predict labels of new unlabeled samples (eg what's on an image?),
- Understand better the relationship between features and the label (eg understand which set of genes allow to predict a disease risk),
- ...

Deep Neural Networks

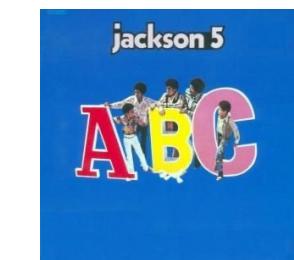


<https://www.datacamp.com/blog/what-is-machine-learning>



<https://towardsdatascience.com/overview-of-supervised-machine-learning-algorithms-a5107d036296>

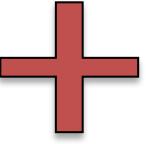
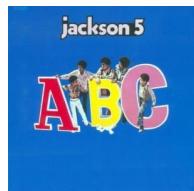
Why Deep Learning?



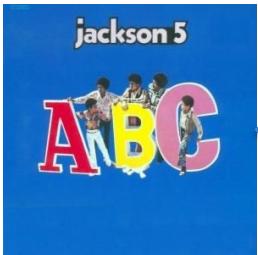
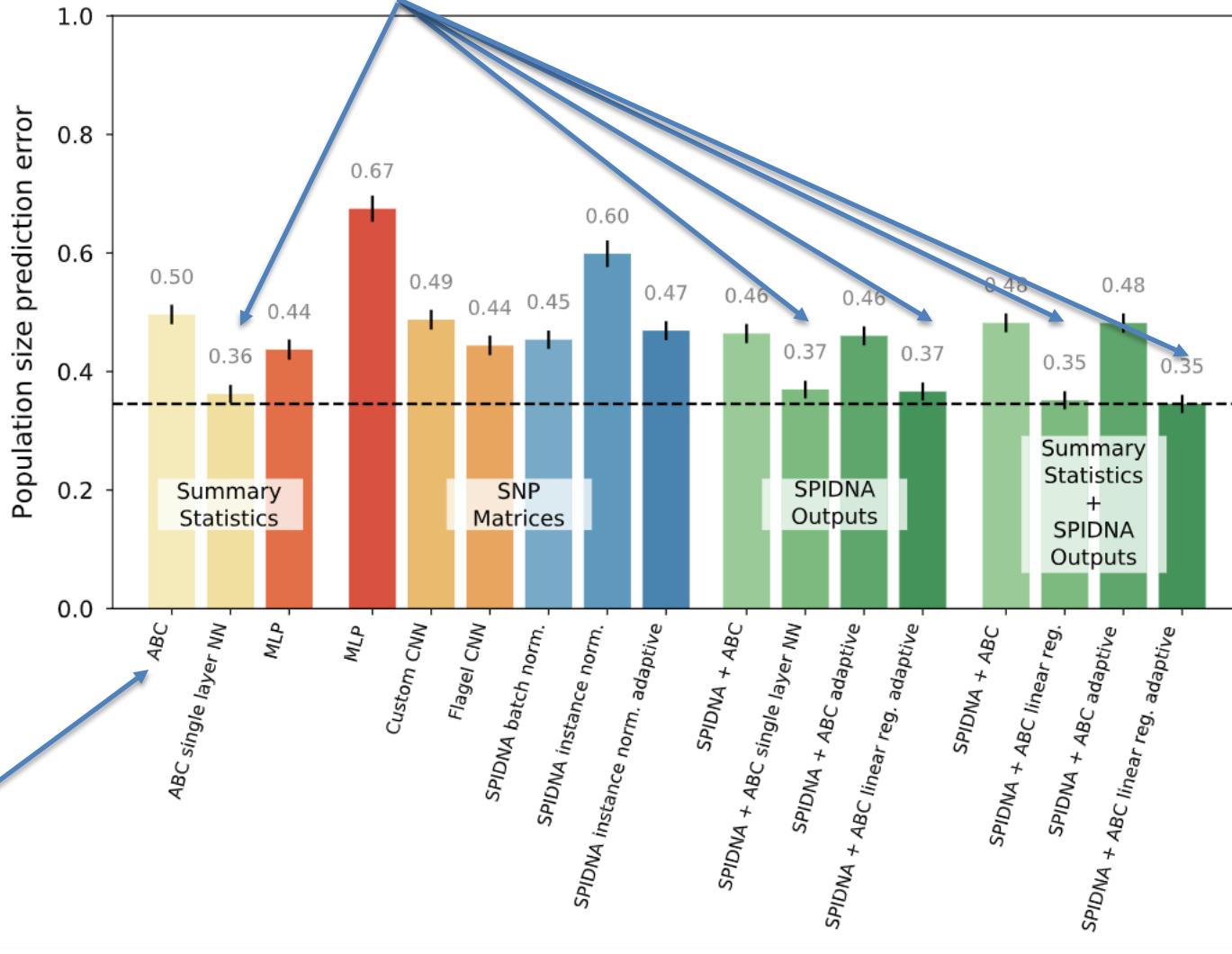
Deep Learning



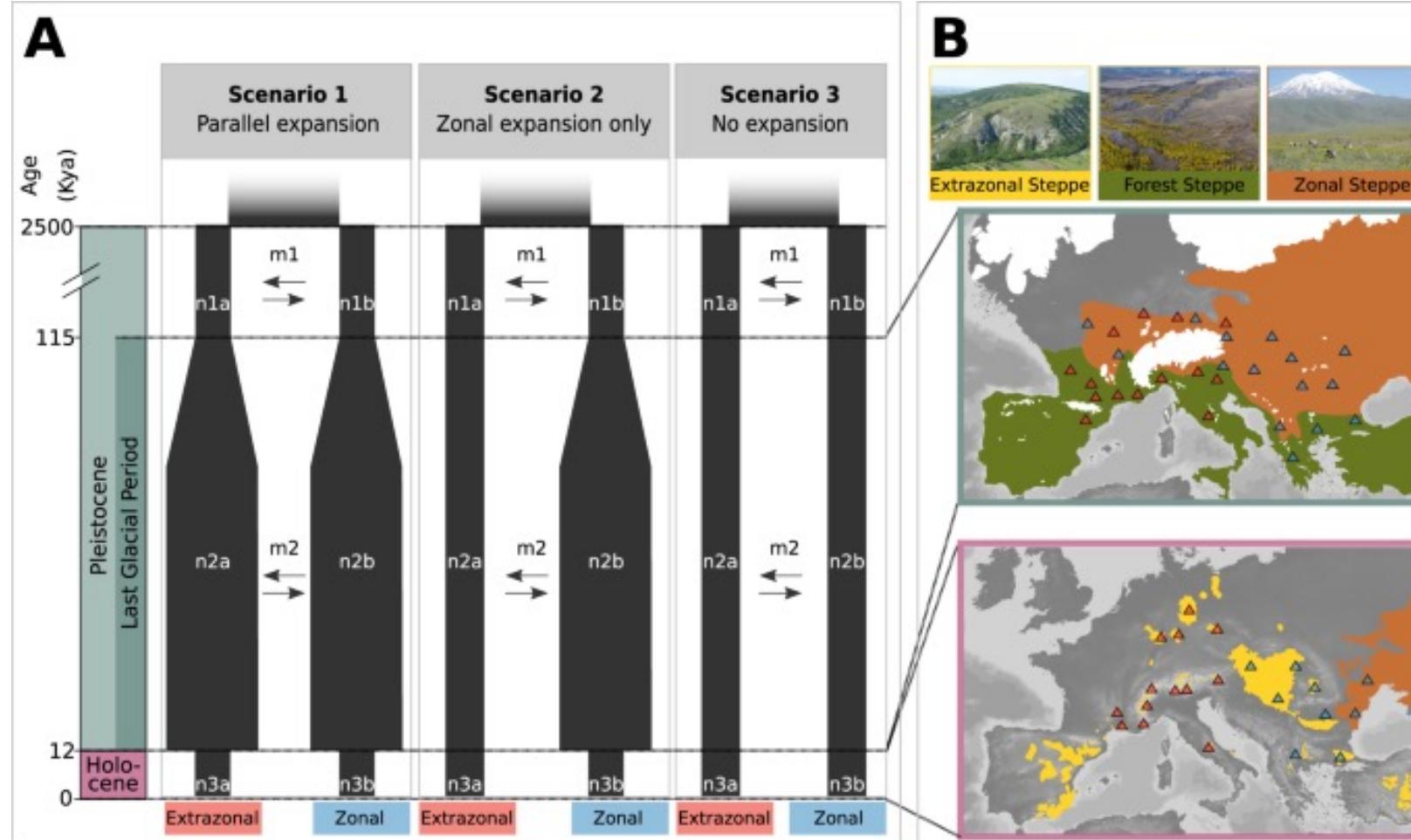
CJ Battey
Twitter 2018



Why Deep Learning?

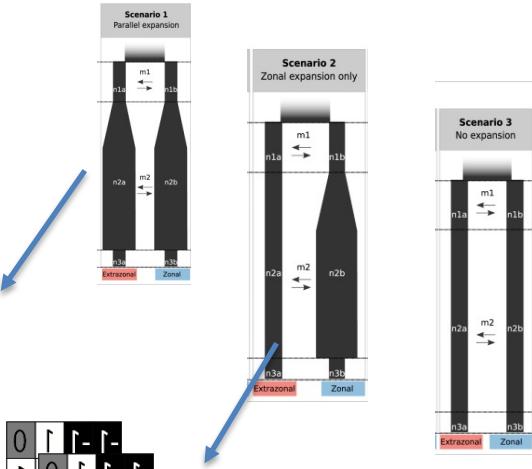


Supervised Deep Learning ~ ABC



Supervised Deep learning ~ ABC

-1	-1	1	0
1	-1	1	0
-1	1	-1	-1
-1	-1	0	1
1	-1	1	-1
0	1	1	-1
0	1	-1	0



Scenario 1

0	1	-1	-1
1	0	1	-1
-1	1	0	1
-1	0	1	-1
1	-1	1	0
0	1	-1	1
0	1	-1	-1

Scenario 2

0	J	-J	-J
J	0	J	-J
-J	J	J	J
J	-J	J	J
-J	J	-J	J
J	-J	J	-J
-J	J	-J	-J

Data is labeled

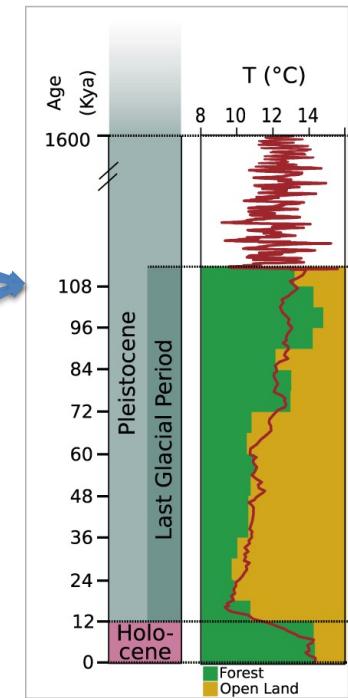
-1	-1	1	0
1	-1	1	1
-1	0	1	-1
1	1	-1	1
0	1	-1	-1

Scenario 3

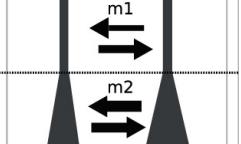
0	J	-J	-J
J	0	J	-J
-J	J	J	J
J	-J	J	J
-J	J	-J	J
J	-J	J	-J
-J	J	-J	-J

θ T1 T2 T3 Ne

Sim1				
Sim2				
Sim3				
Sim4				



PP = 1.00



Supervised Deep Learning ~ ABC

-1	-1	1	0
1	-1	1	0
-1	1	-1	-1
-1	-1	0	1
1	-1	1	-1
0	1	1	-1
0	1	-1	0

Scenario 1

0	1	-1	-1
1	0	1	-1
-1	0	1	1
0	1	-1	1
-1	0	-1	1
1	-1	1	0
-1	0	-1	-1

Scenario 2

0	J	-J	-J
J	0	J	-J
-J	J	J	J
J	-J	J	J
-J	J	-J	J
J	-J	J	-J
-J	J	-J	-J

Data is labeled

-1	-1	1	0
1	-1	1	1
-1	0	1	-1
1	1	-1	1
0	1	-1	-1

Scenario 3

0	J	-J	-J
J	0	J	-J
-J	J	J	J
J	-J	J	J
-J	J	-J	J
J	-J	J	-J
-J	J	-J	-J

Parameters

	θ	T1	T2	T3	Ne
Sim1					
Sim2					
Sim3					
Sim4					

Scenario 1

Parallel expansion

m1 \leftrightarrow m2

n1a \rightarrow n2b

n2a \rightarrow m2

n2b \rightarrow m1

Scenario 2

Zonal expansion only

m1 \rightarrow m2

n1a \rightarrow n2b

n2a \rightarrow m2

n2b \rightarrow m1

Scenario 3

No expansion

m1 \leftrightarrow m2

n1a \rightarrow n2b

n2a \rightarrow m2

n2b \rightarrow m1

Extrazonal

Zonal

DL witchcraft



Cuca - Brazilian Legend

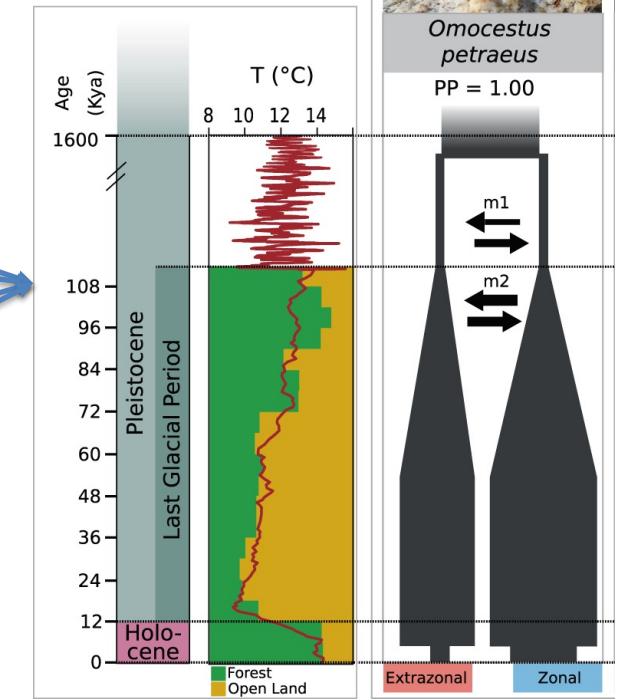


Image recognition

What the computer sees?

What do you see?



Challenges

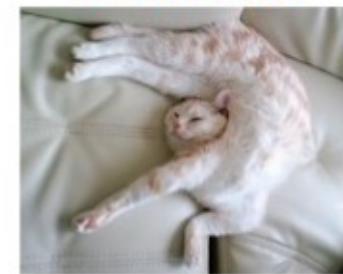
Viewpoint variation



Scale variation



Deformation



Occlusion



Illumination conditions



Background clutter



Intra-class variation



Matteo Fumagalli and Flora Jay. Machine learning and deep learning for demographic and selection inference. Lecture

Image recognition

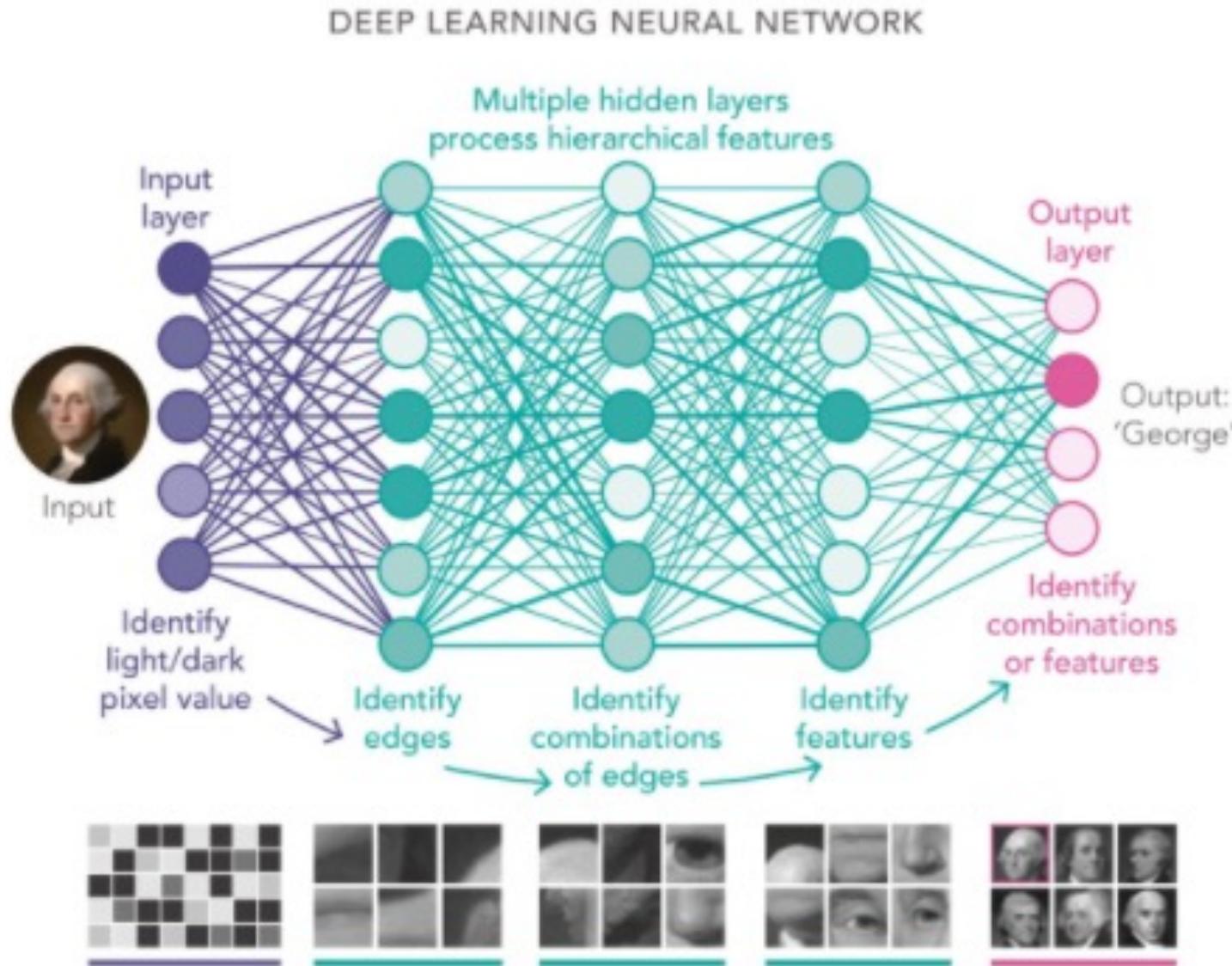
Data-Driven approach (need a large training set)

The MNIST dataset (70,000 handwritten numbers)



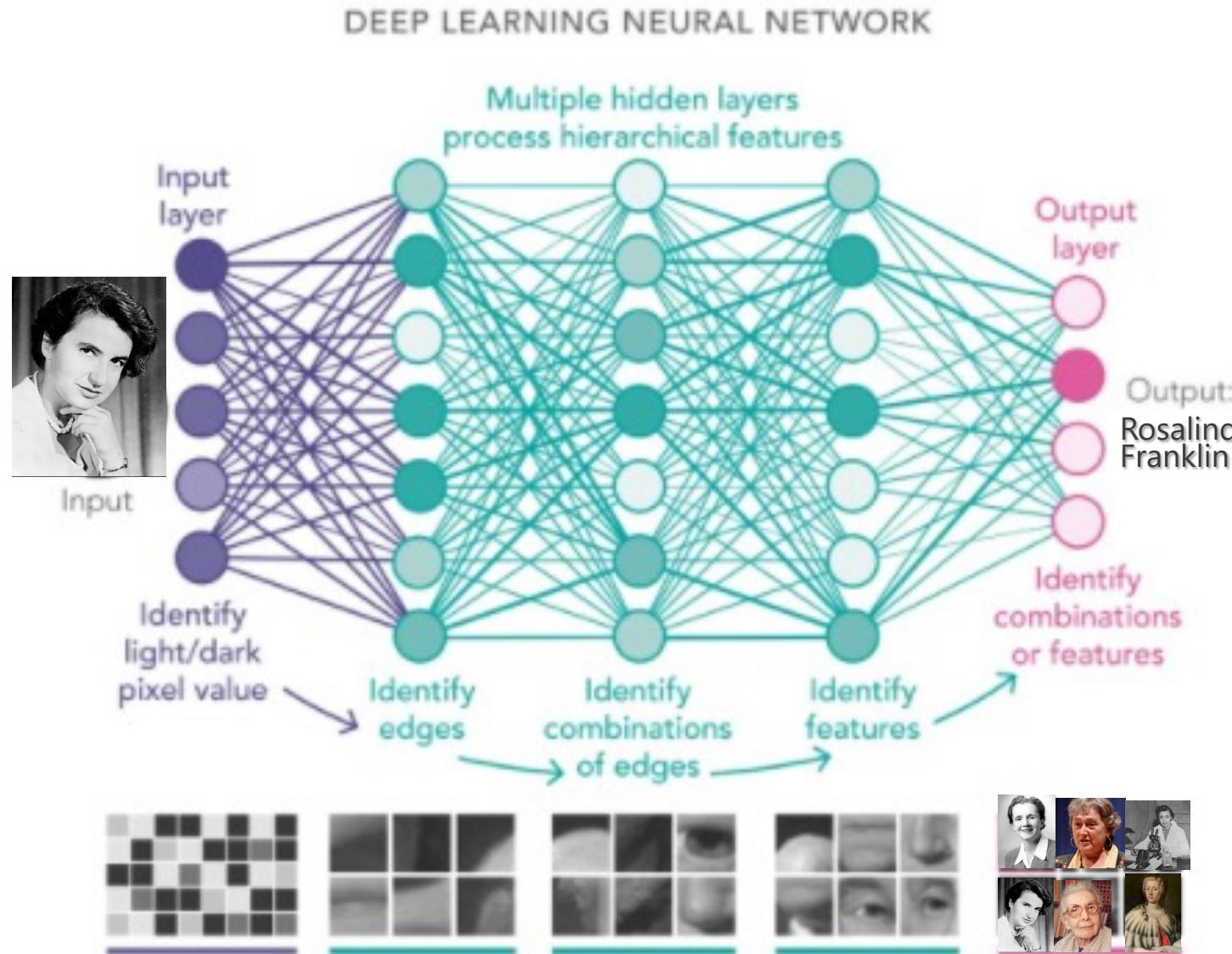
<https://blog.filestack.com/api/from-mnist-classification-to-intelligent-check-processing/>

Deep Neural Networks



Multi-Layer Perceptron (MLP)

Deep Neural Networks

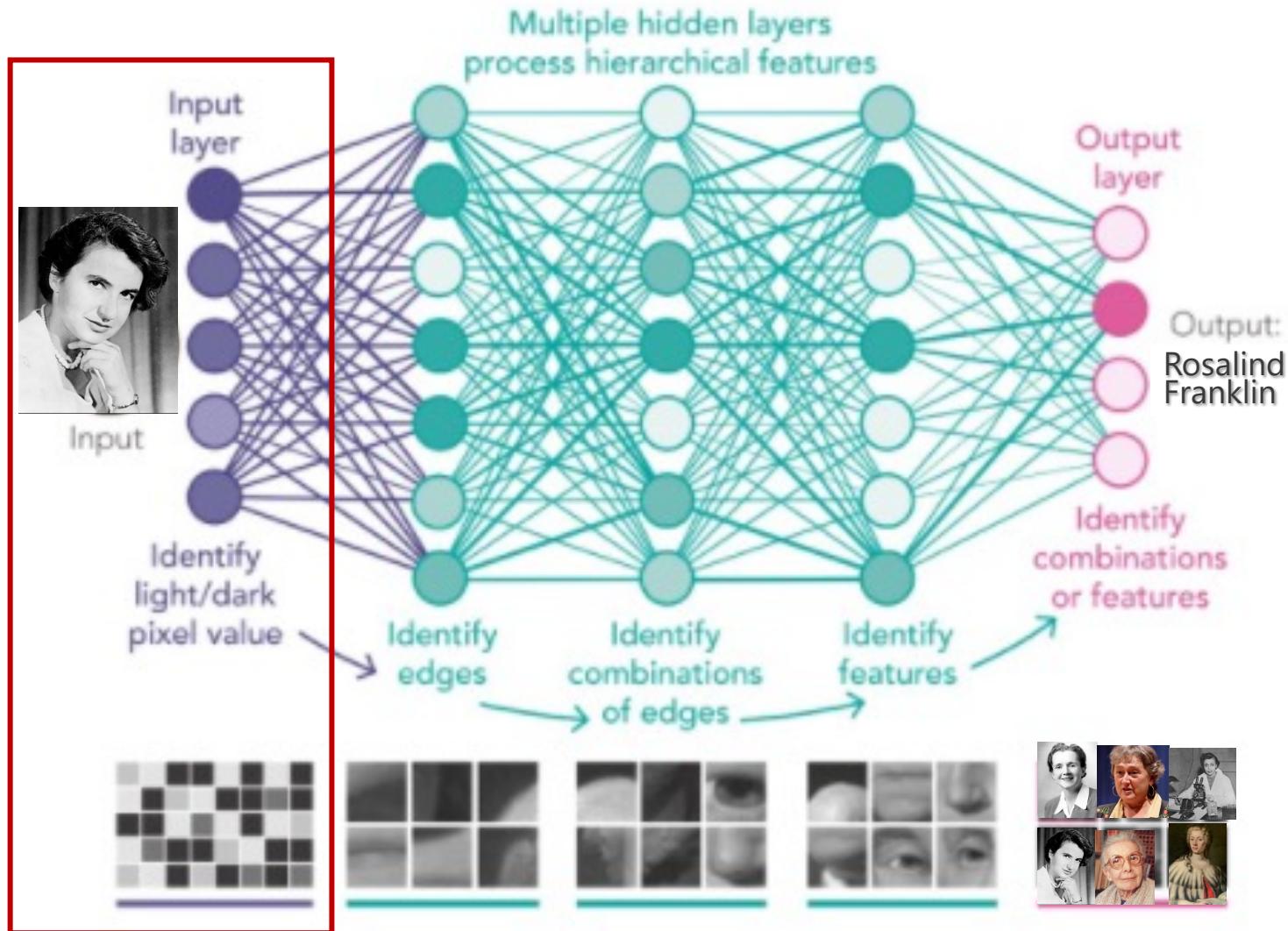


Multi-Layer Perceptron (MLP)

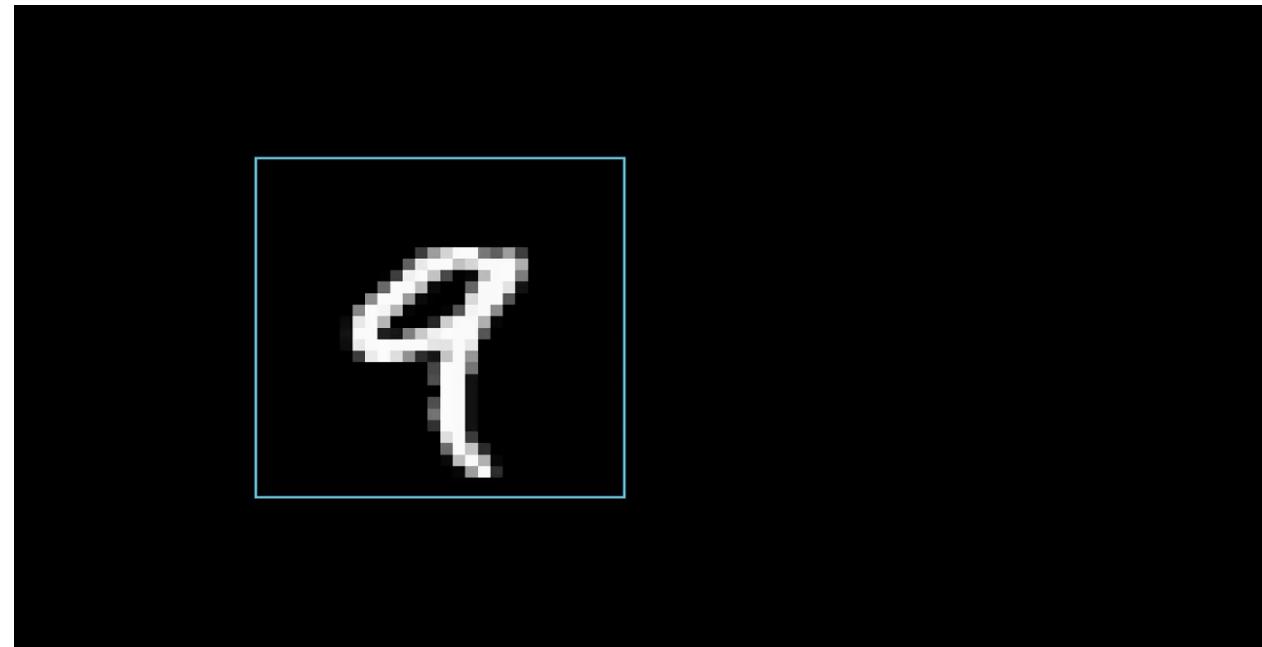
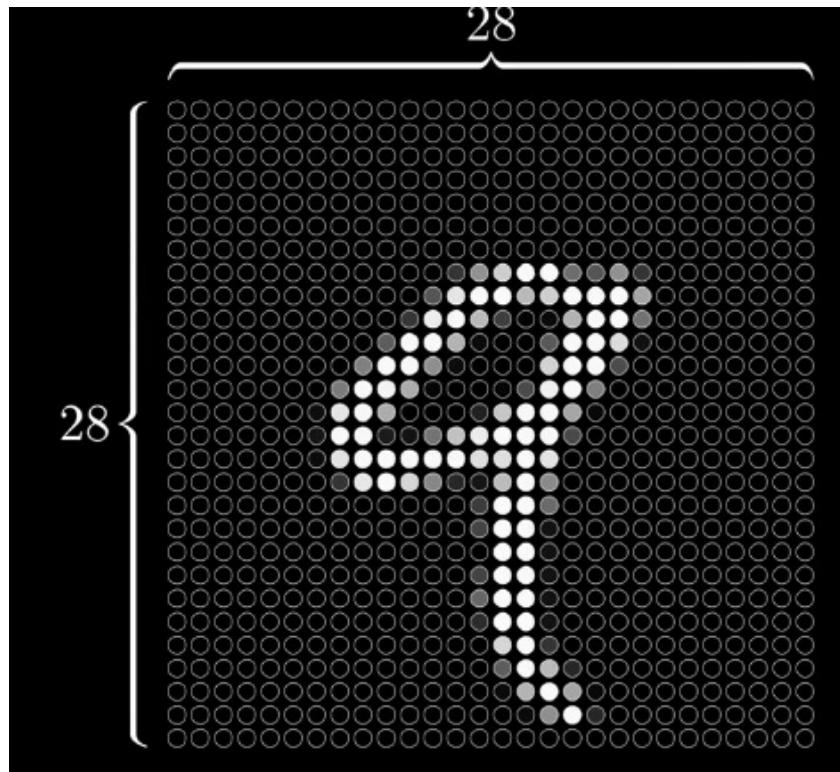
Adapted from Waldrop (2019)
PNAS

Deep Neural Networks

DEEP LEARNING NEURAL NETWORK

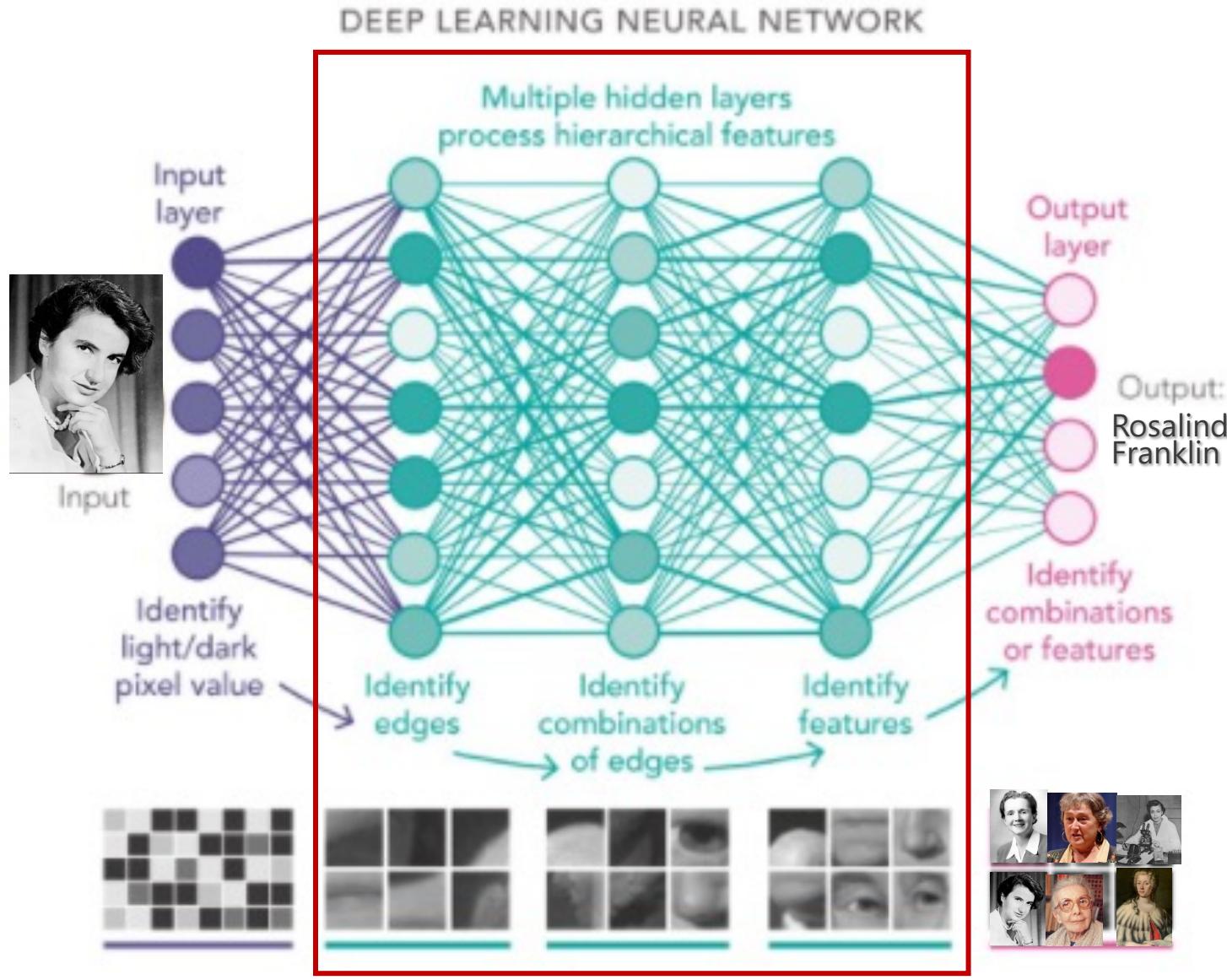


Adapted from Waldrop (2019) PNAS



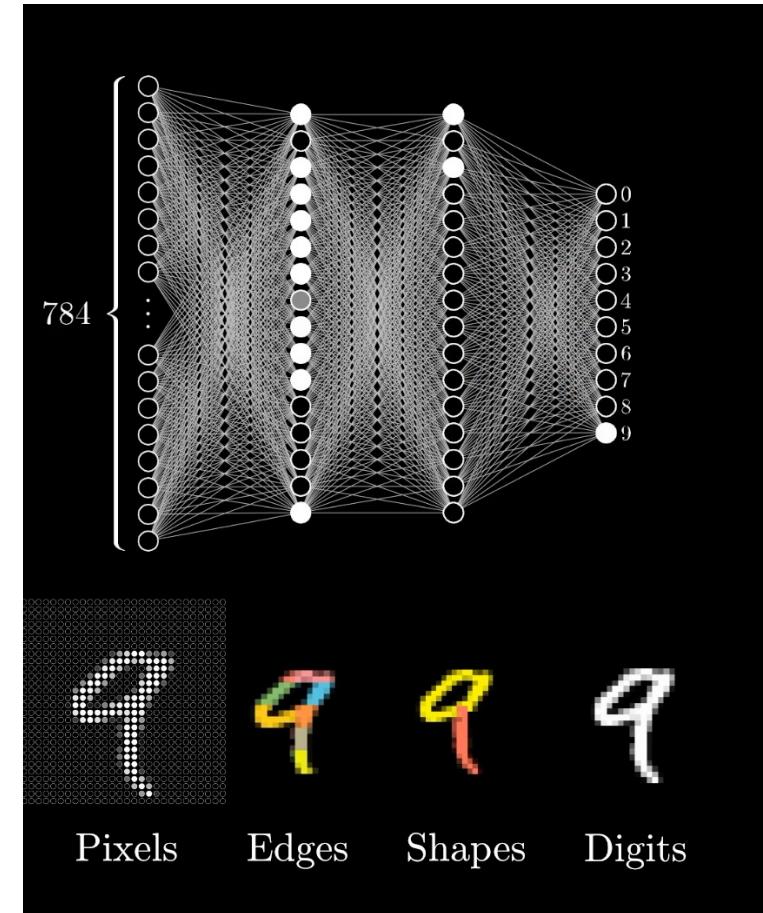
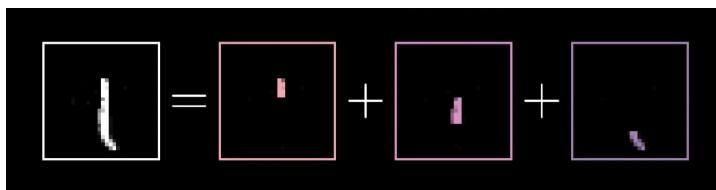
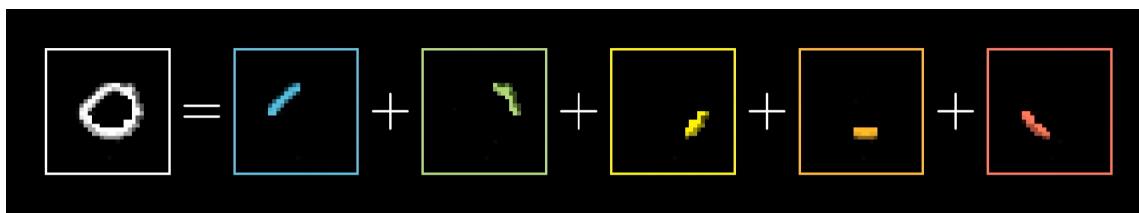
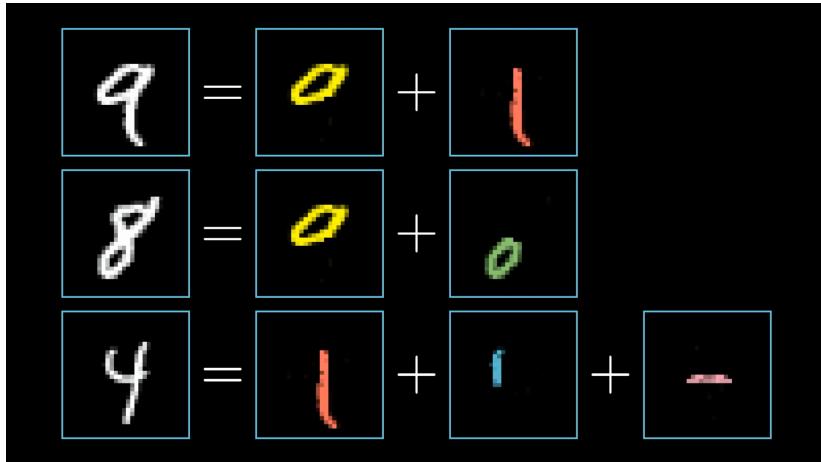
Input Layer

Deep Neural Networks

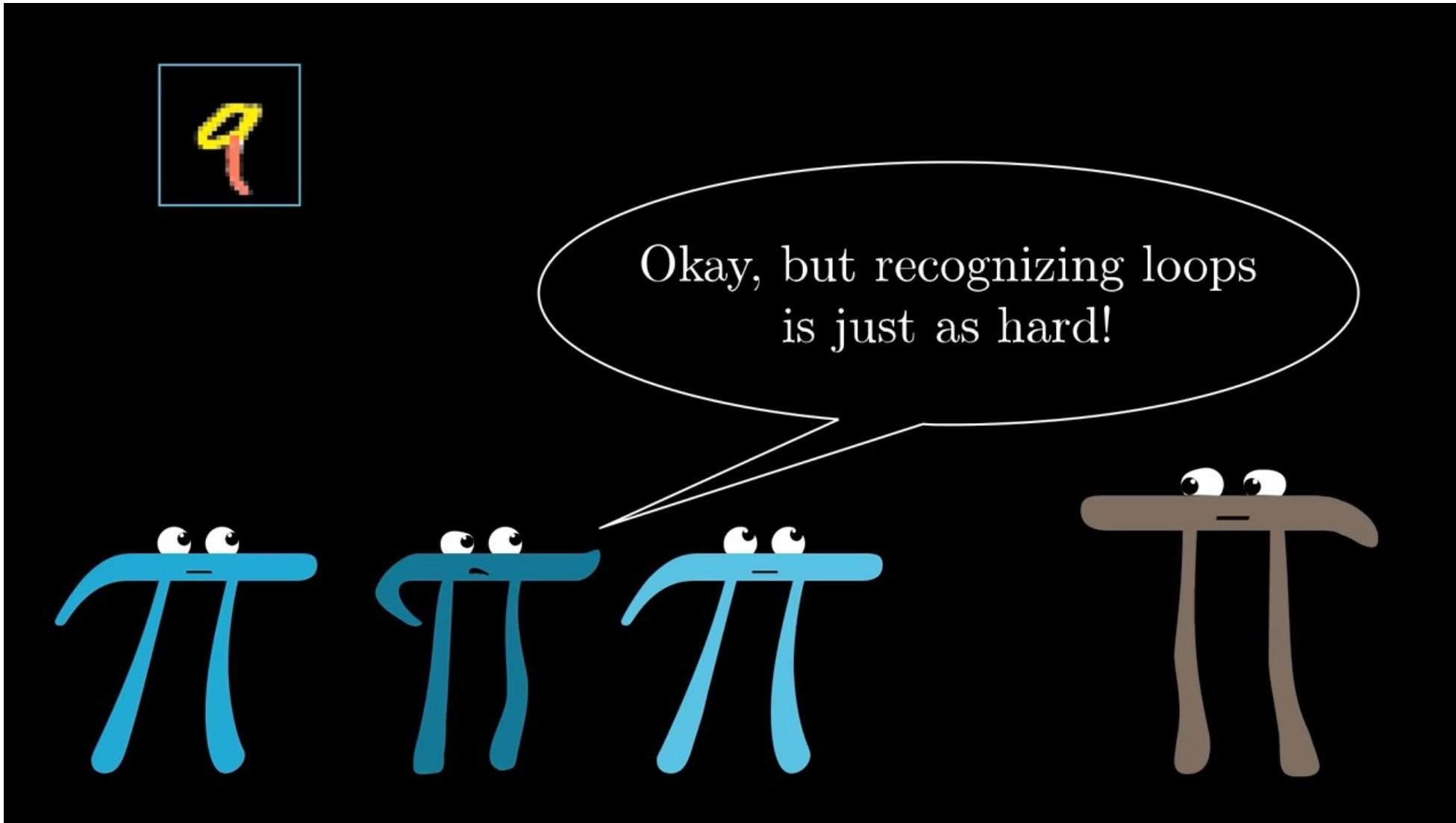


Adapted from Waldrop (2019)
PNAS

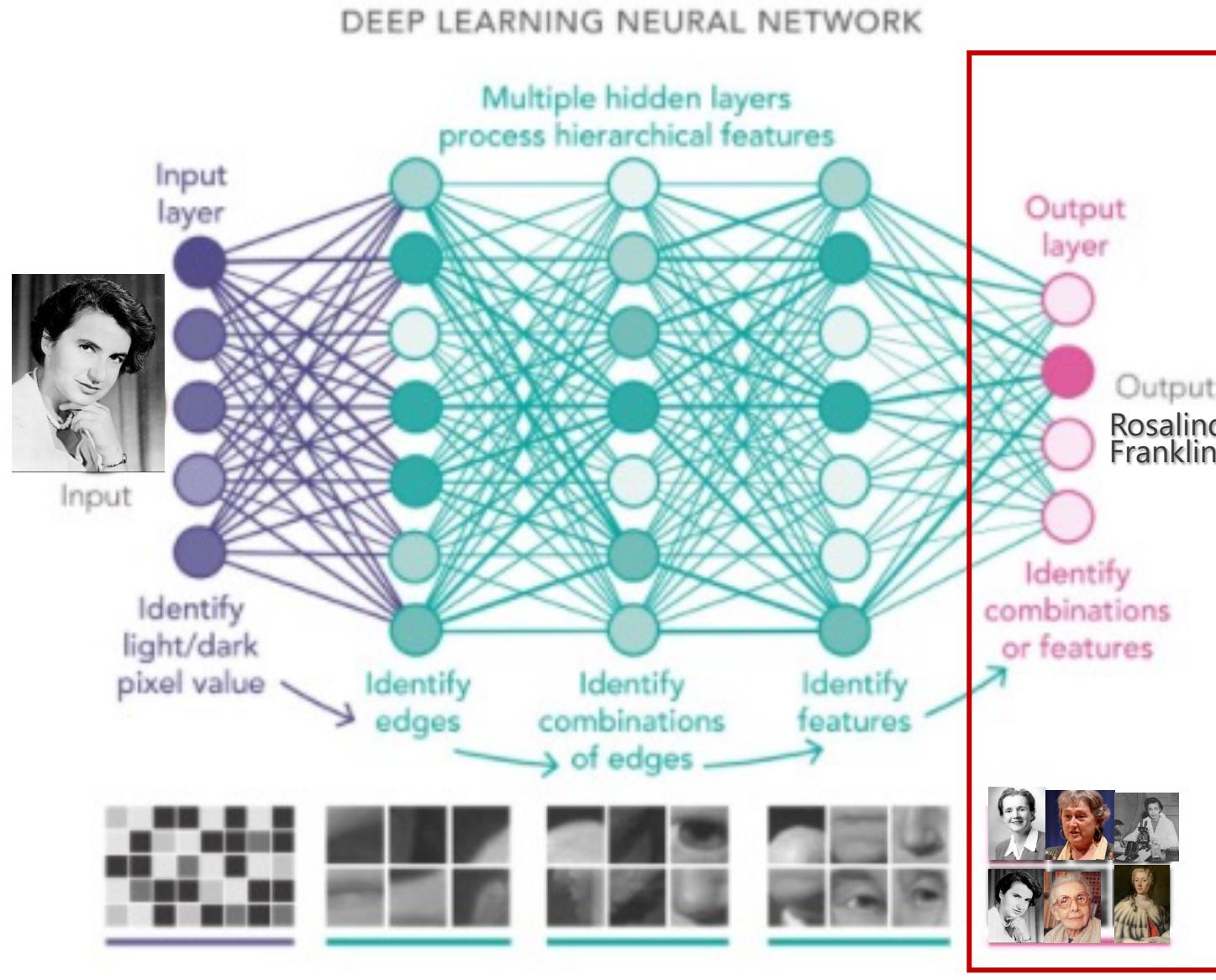
Hidden Layers process hierarchical features



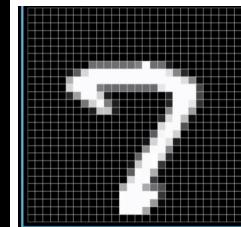
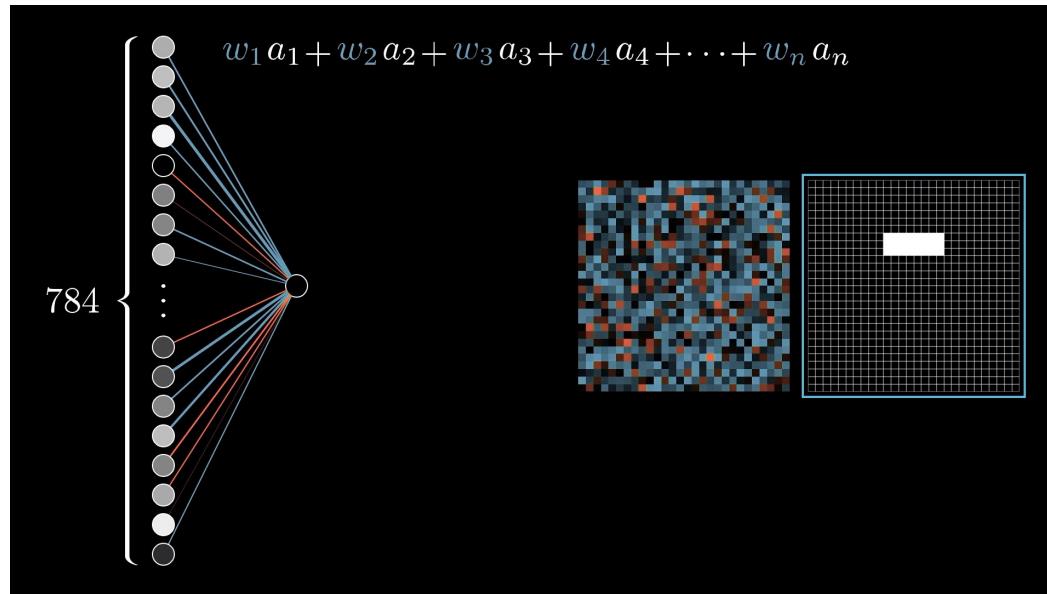
Hidden Layers process hierarchical features



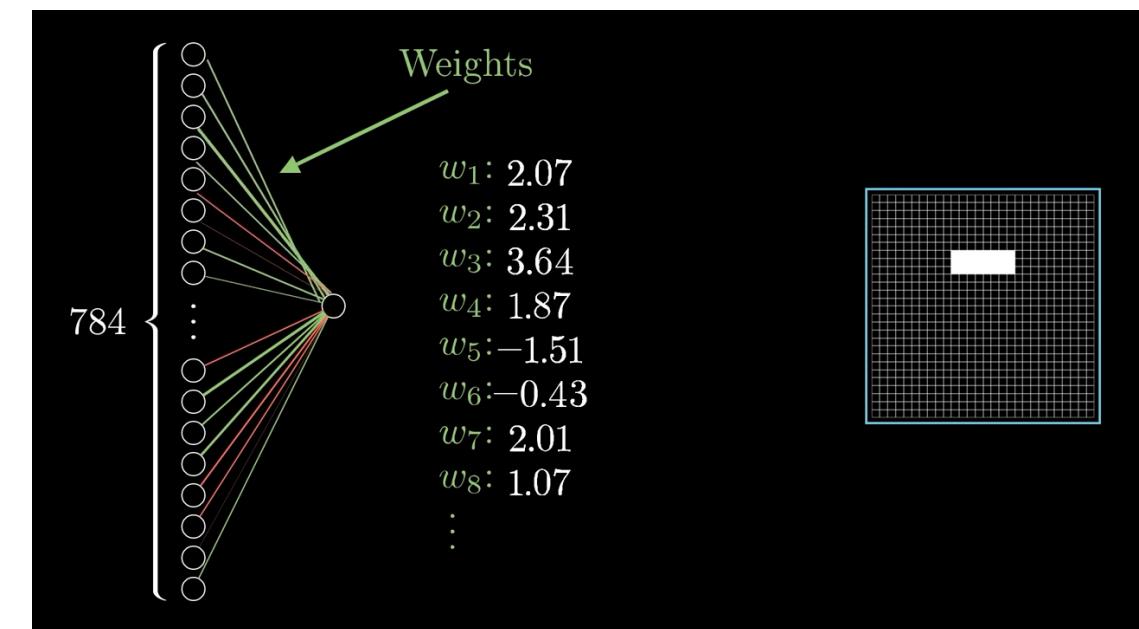
Deep Neural Networks



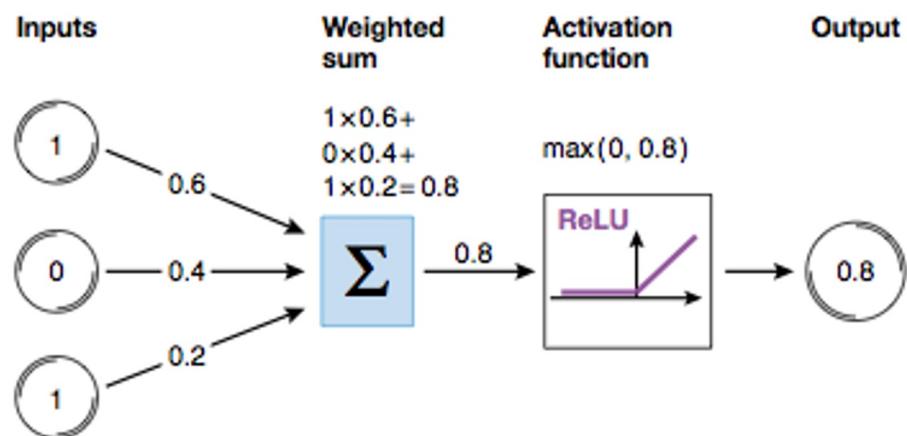
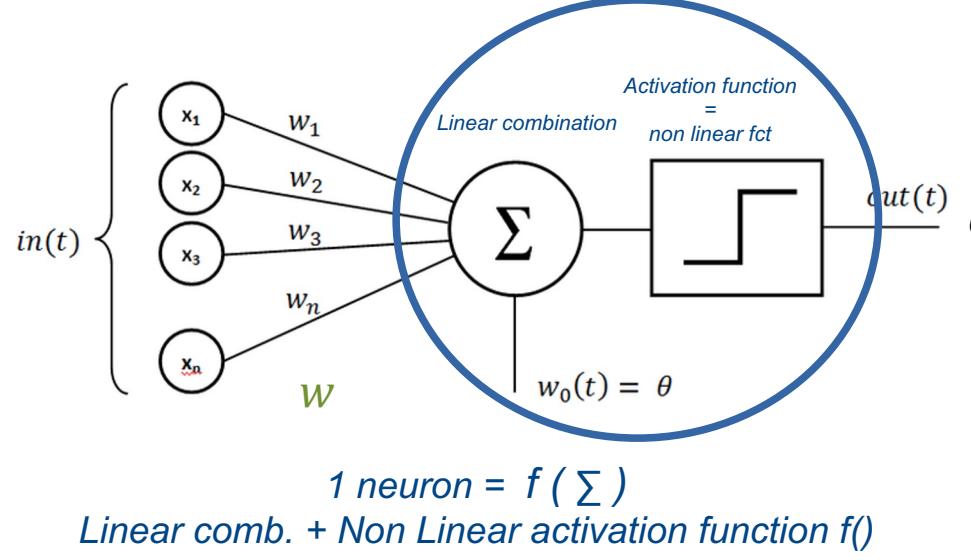
Network Weights



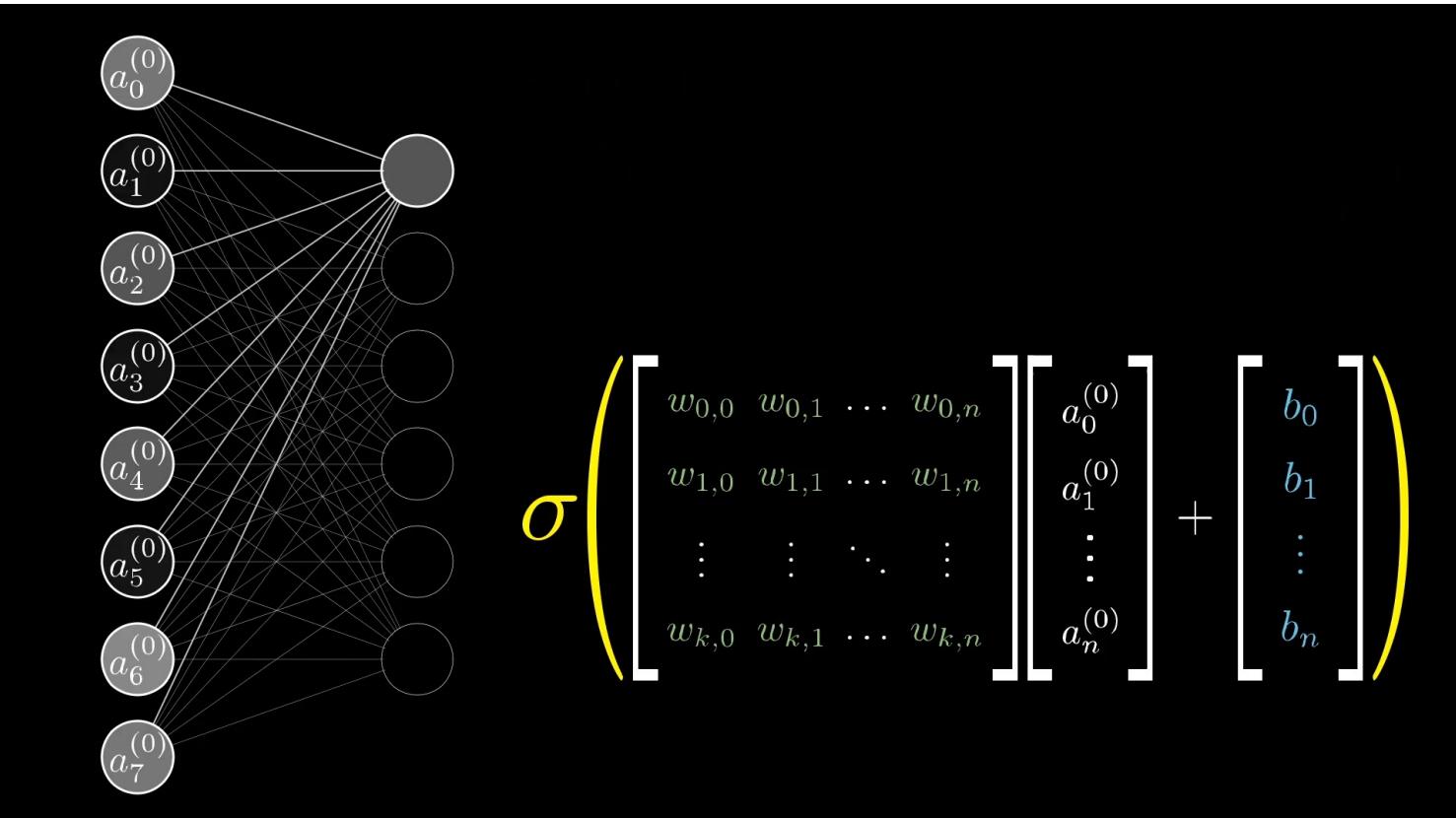
Neuron in the second layer to check whether the image contains this one, specific edge.



Network Weights



$$out = f(w_0 + w_1x_1 + w_2x_2 + \dots)$$

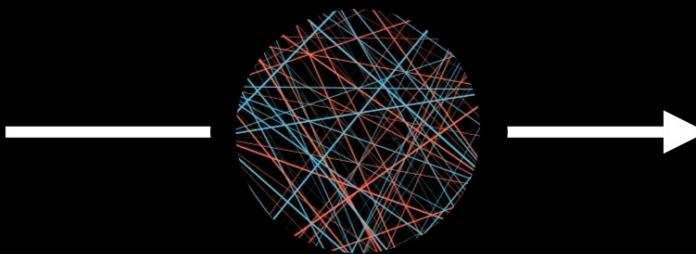


Score function

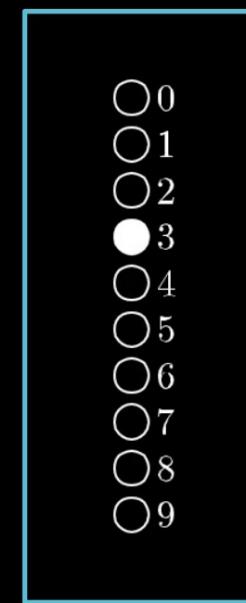
Neural network function



784 inputs



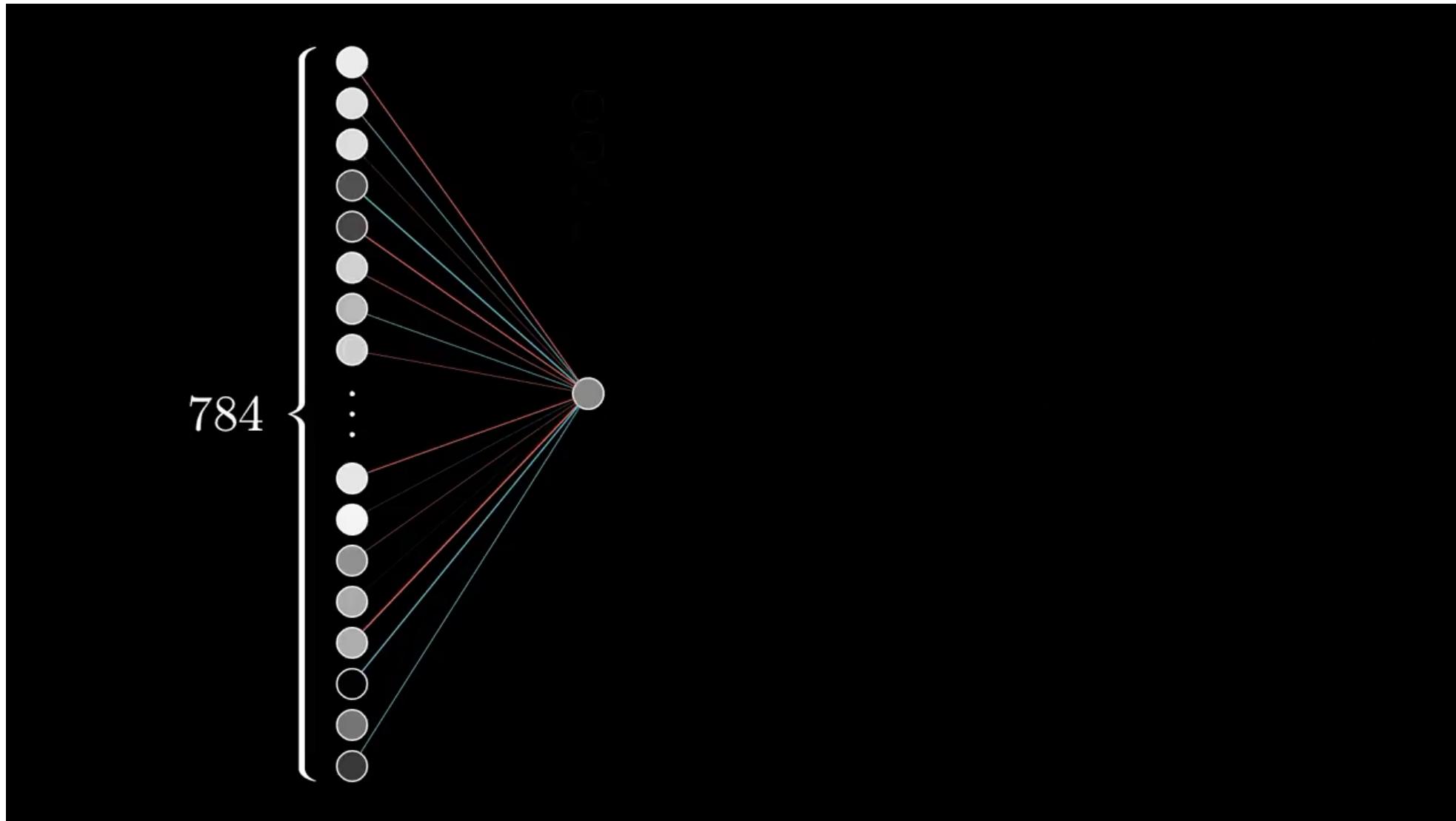
13,002 weights
and biases



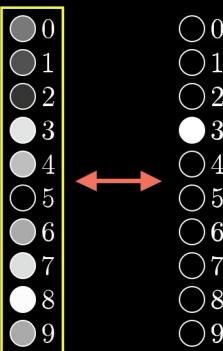
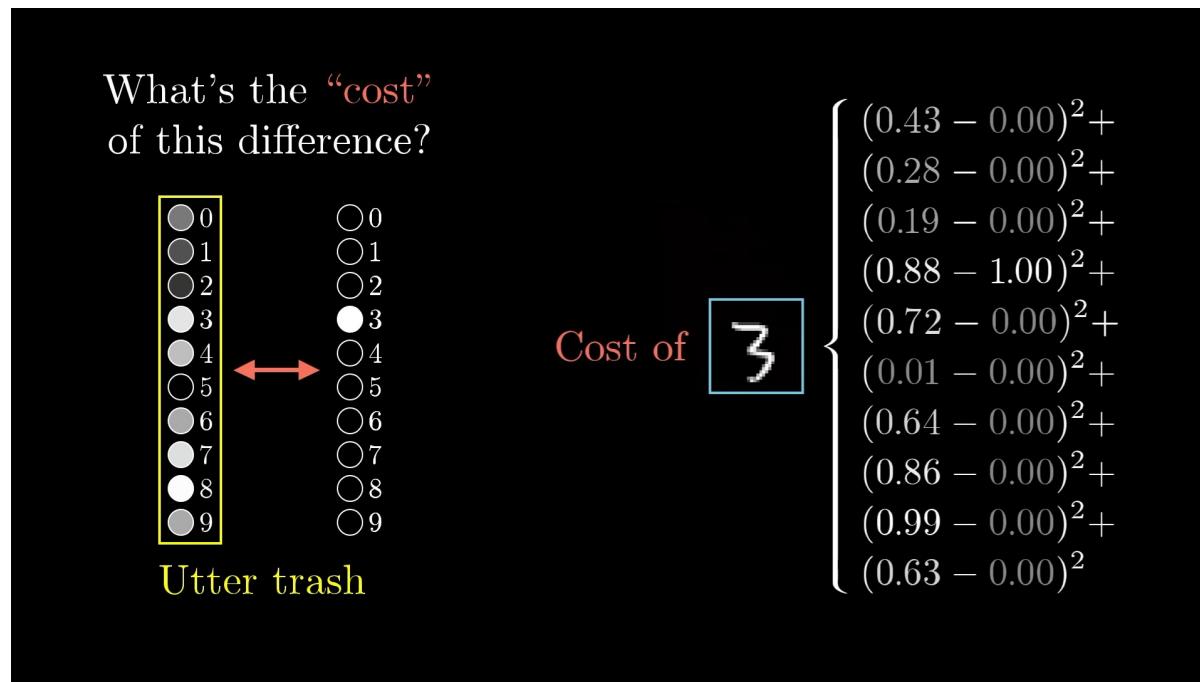
10 outputs

How the network learns?

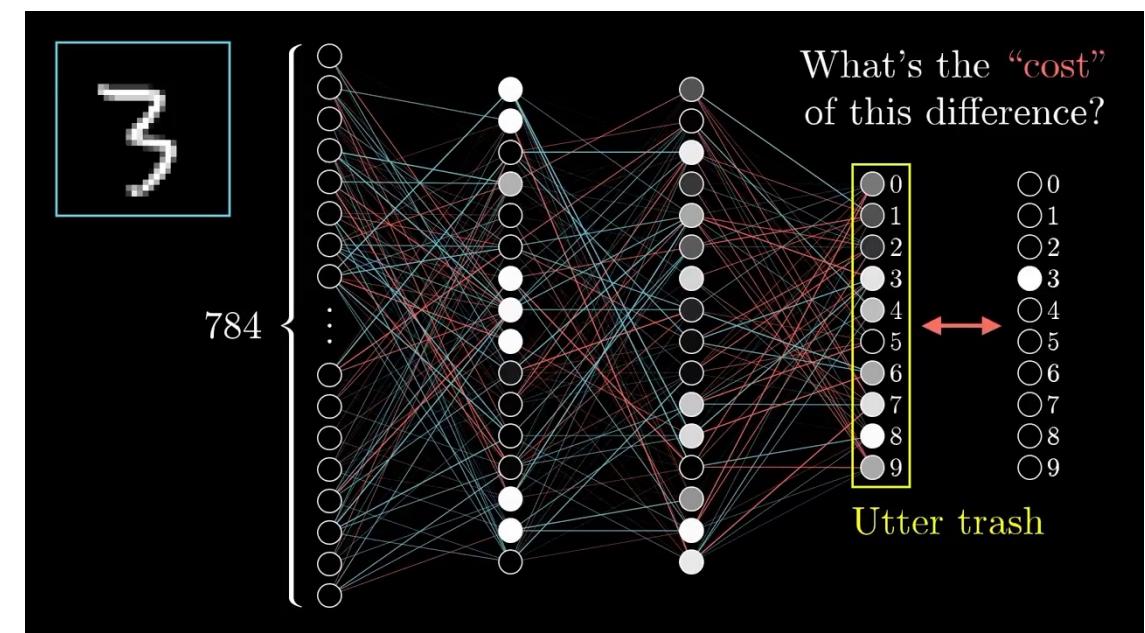
Cost function



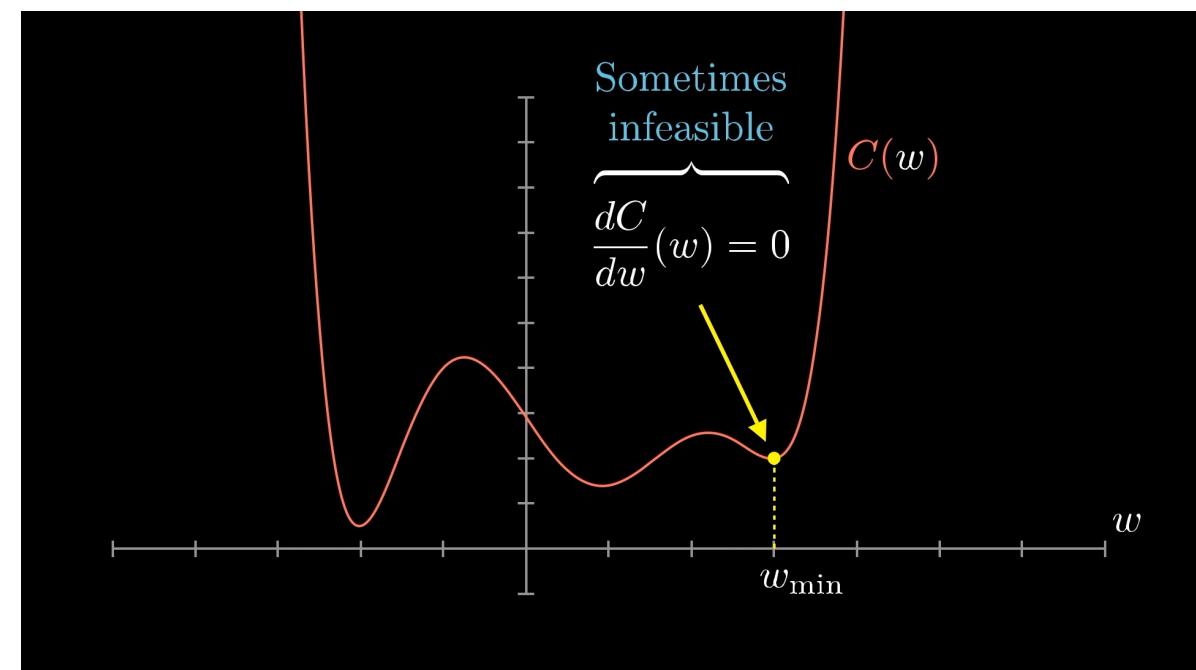
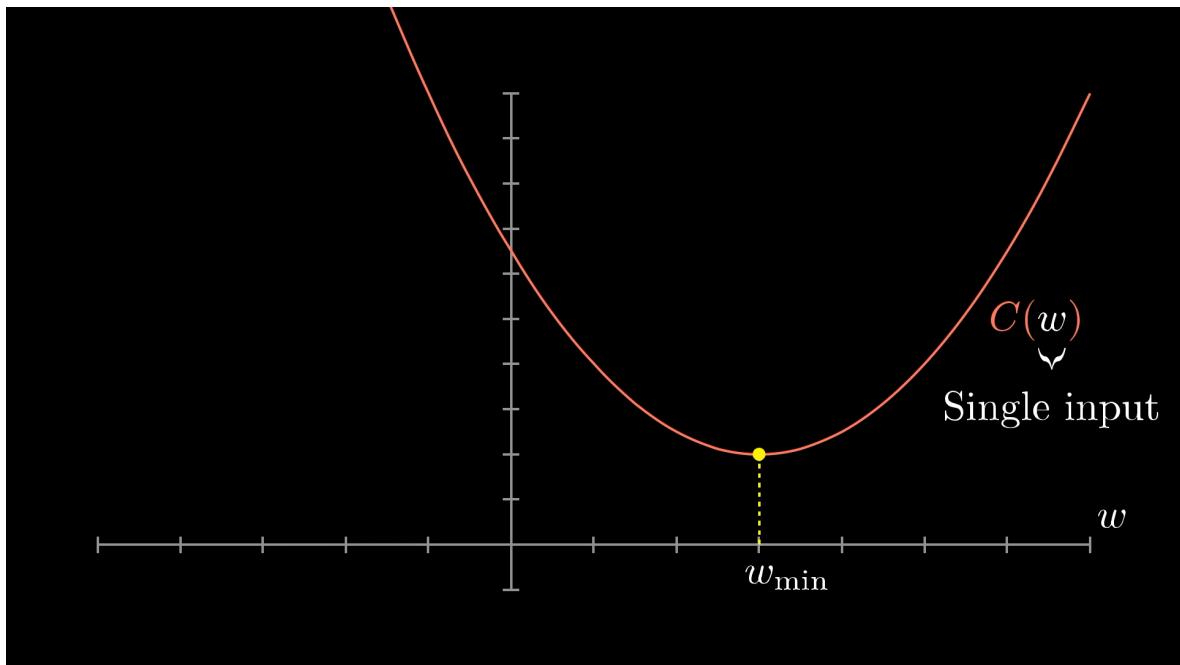
Cost Function



Utter trash

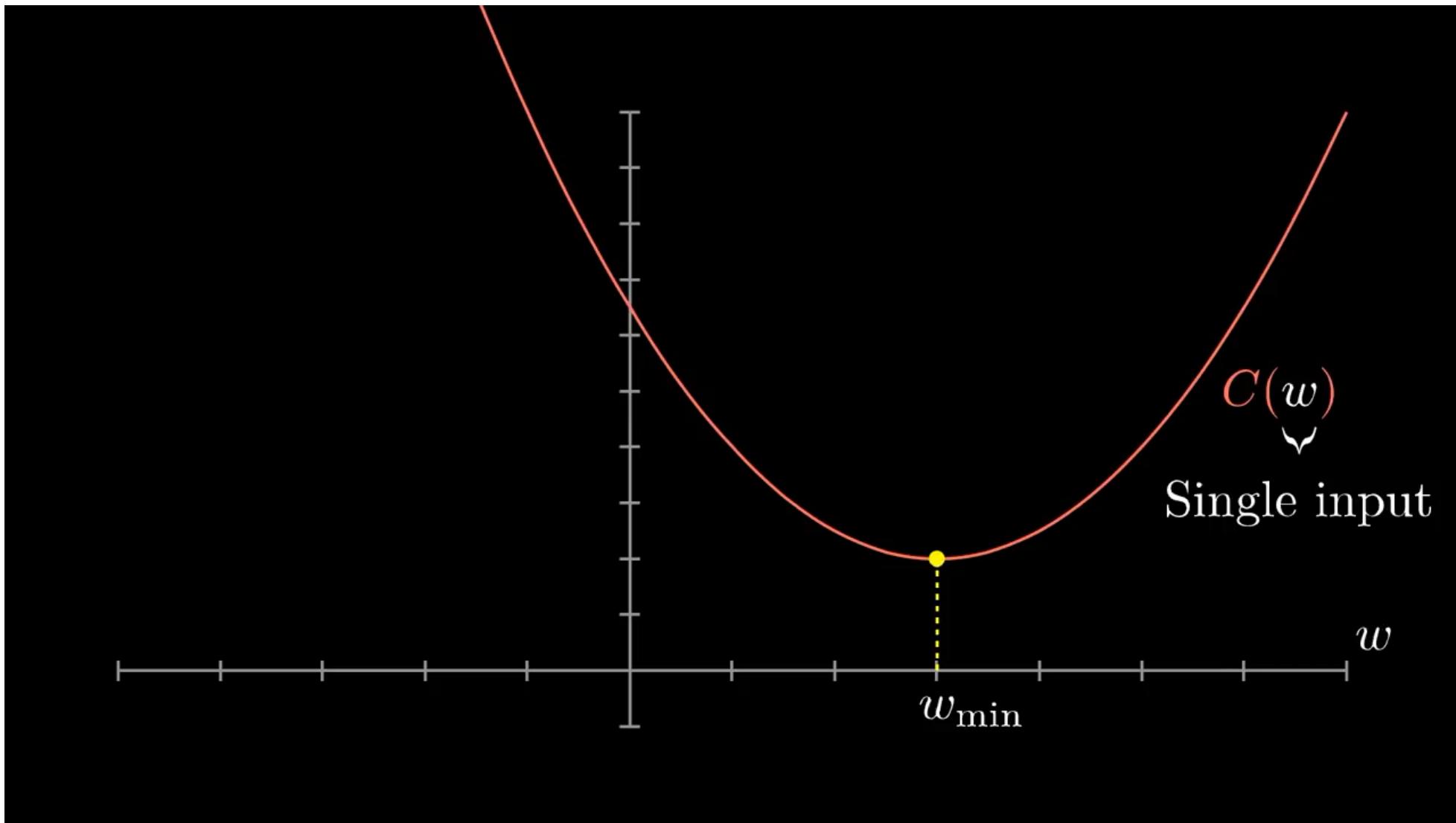


Cost Function

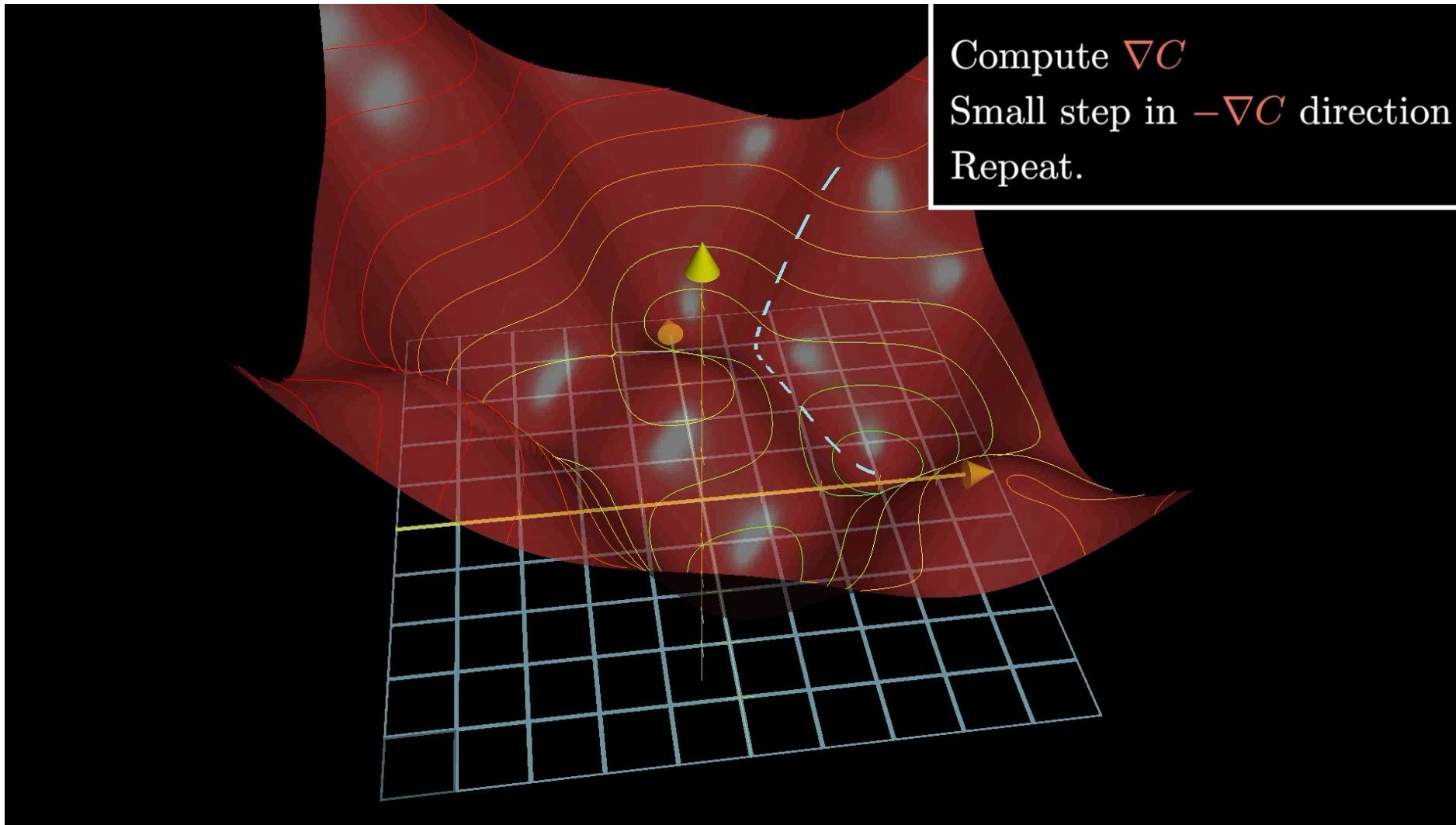


Optimization

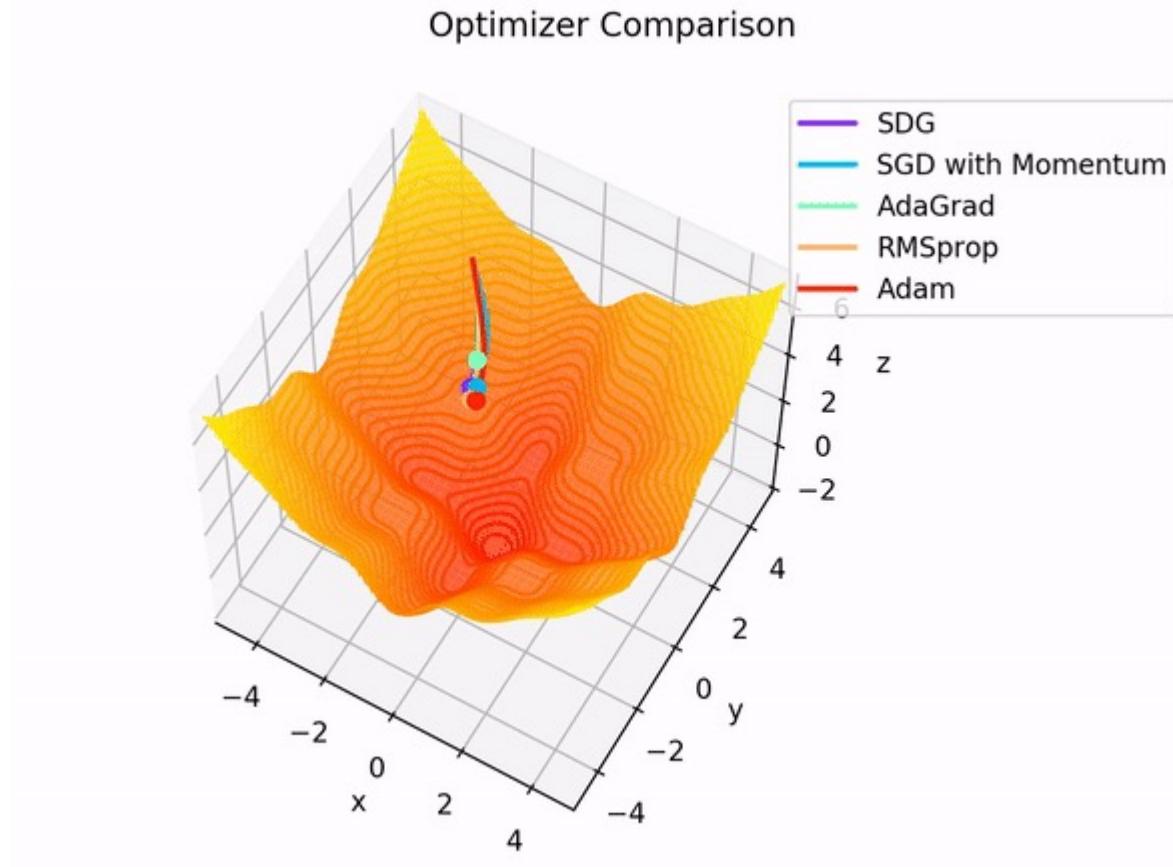
Gradient Descent



Gradient Descent



Gradient Descent



<https://towardsdatascience.com/complete-guide-to-adam-optimization-1e5f29532c3d>

Gradient Descent

13,002 weights and biases

$$\vec{\mathbf{W}} = \begin{bmatrix} 2.25 \\ -1.57 \\ 1.98 \\ \vdots \\ -1.16 \\ 3.82 \\ 1.21 \end{bmatrix}$$

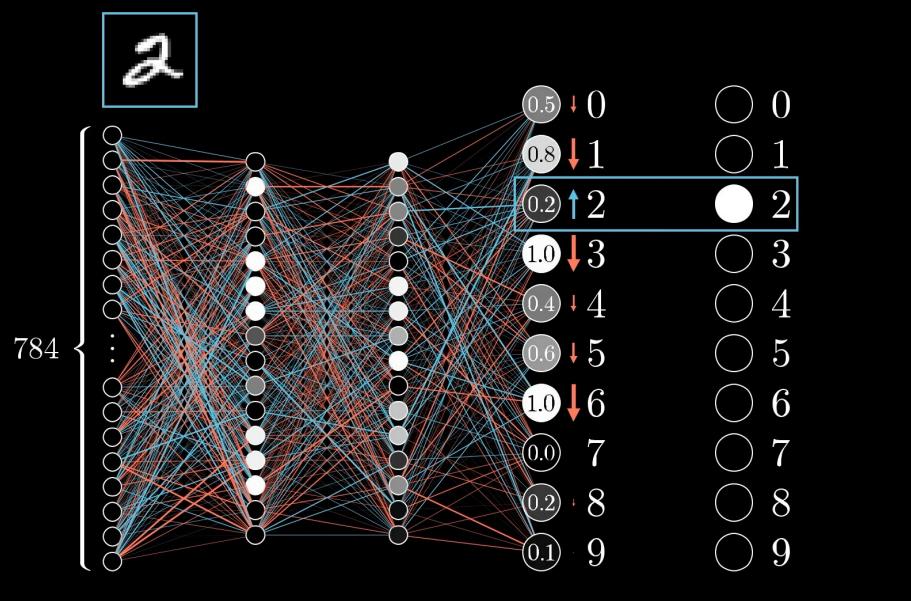
$$-\nabla C(\vec{\mathbf{W}}) = \begin{bmatrix} 0.31 \\ 0.03 \\ -1.25 \\ \vdots \\ 0.78 \\ -0.37 \\ 0.16 \end{bmatrix}$$

w_0 should increase somewhat
 w_1 should increase a little
 w_2 should decrease a lot
 $w_{13,000}$ should increase a lot
 $w_{13,001}$ should decrease somewhat
 $w_{13,002}$ should increase a little

Gradient Descent

$$\vec{\mathbf{W}} = \begin{bmatrix} w_0 \\ w_1 \\ w_2 \\ \vdots \\ w_{13,000} \\ w_{13,001} \\ w_{13,002} \end{bmatrix}$$
$$-\nabla C(\vec{\mathbf{W}}) = \left. \begin{bmatrix} 0.31 \\ 0.03 \\ -1.25 \\ \vdots \\ 0.78 \\ -0.37 \\ 0.16 \end{bmatrix} \right\} \text{Example gradient}$$

Backpropagation

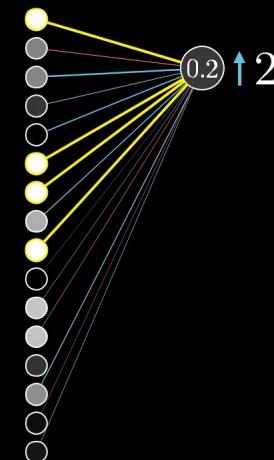


$$(0.2) = \sigma(w_0 a_0 + w_1 a_1 + \dots + w_{n-1} a_{n-1} + b)$$



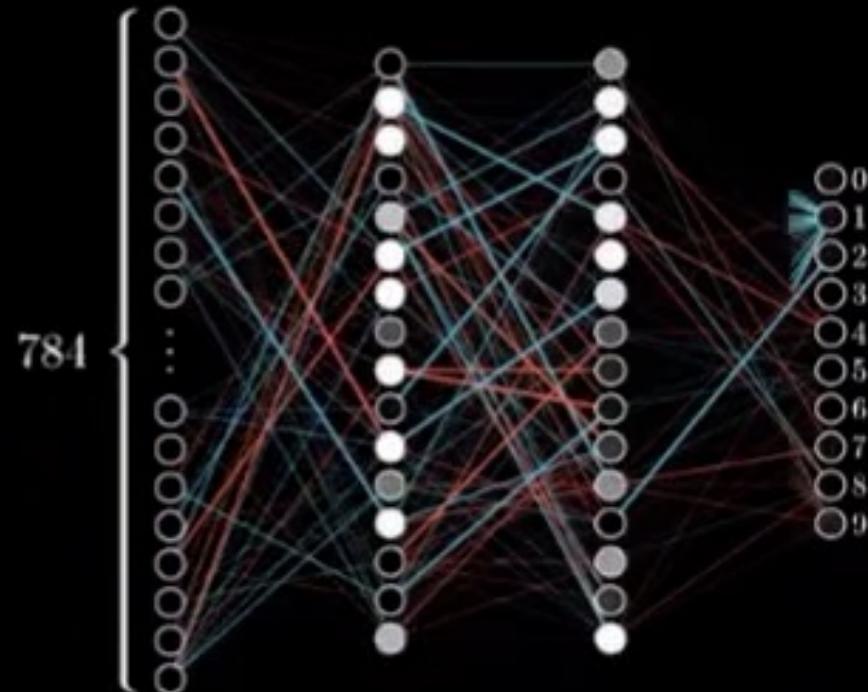
Increase b

Increase w_i
in proportion to a_i



Backpropagation

Training in progress. . .



Training NNs

- Training = estimating all the weights $w_{ij}^{(l)}$ for all layers (l) with the aim of minimizing the loss or cost function
- Loss/cost function: how well your classifier/regressor do ?
→ define a function quantifying how far you are from the truth (e.g., Mean Squared Error)

$$loss = \frac{1}{n} \sum_{examplei=1}^n (y_i^{predicted} - y_i^{truth})^2$$

- Training algorithm :

- Step 1 Initialize randomly the weights

For each epoch :

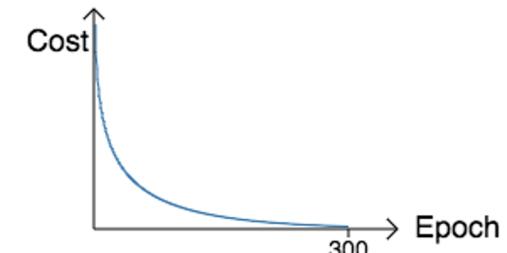
Step 2 Forward pass your examples (eg labeled images of cats and birds) through nnet to compute predicted values (as previously explained)

Step 3 Compute loss

Step 4 Backward propagation

Step 5 Update weights (gradient descent algorithm)

Repeat from step 2 until a plateau is reached



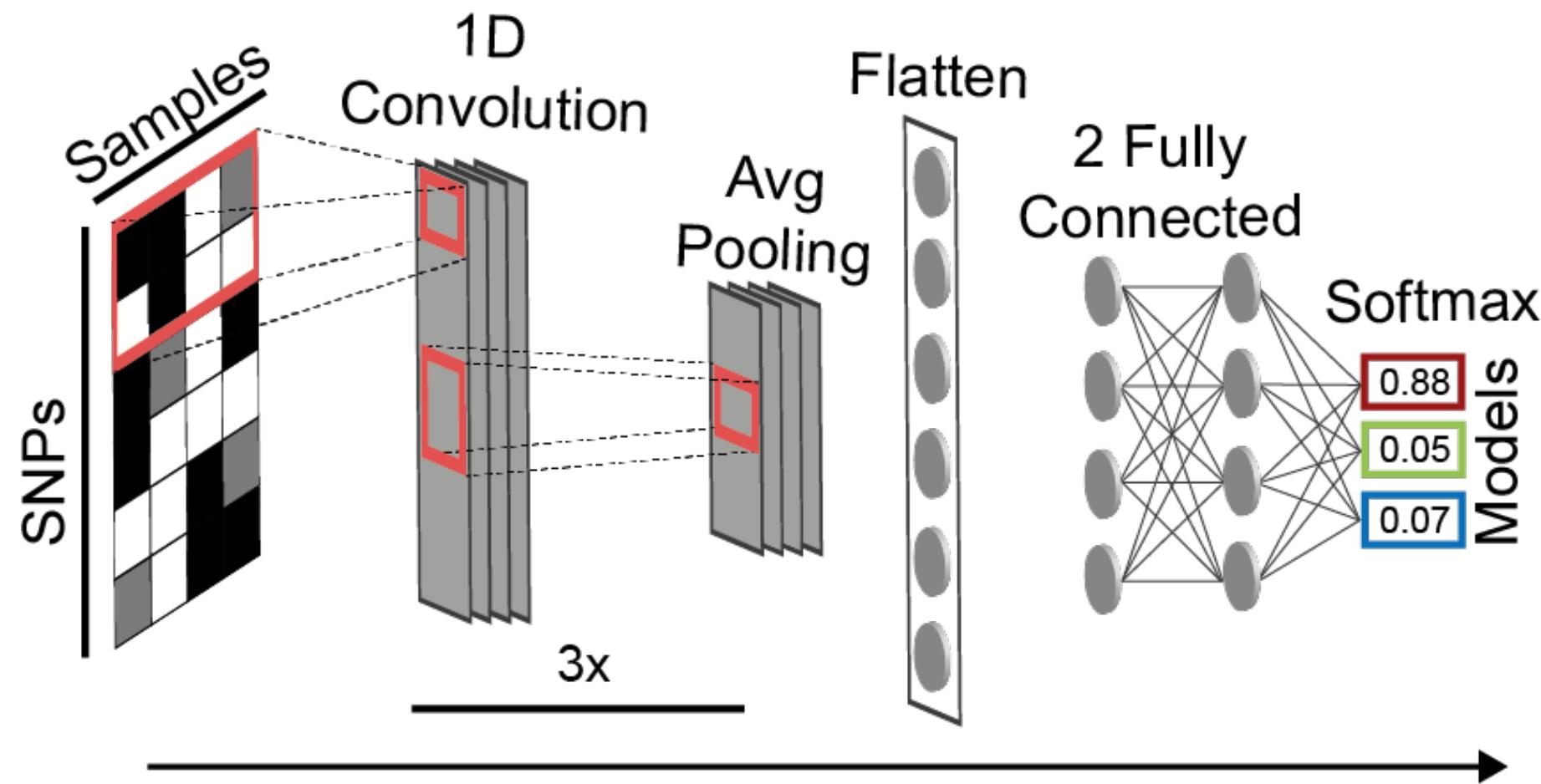
- **Practical Exercise 1:**
- Access <https://playground.tensorflow.org>.
- Use the graphical interface to see how the neural network results changes when you modify the number of neurons, the input features, and the number of hidden layers.
- Compare the learning capacity when using a sigmoid and a ReLU activation. We will talk about these functions later.

Goals

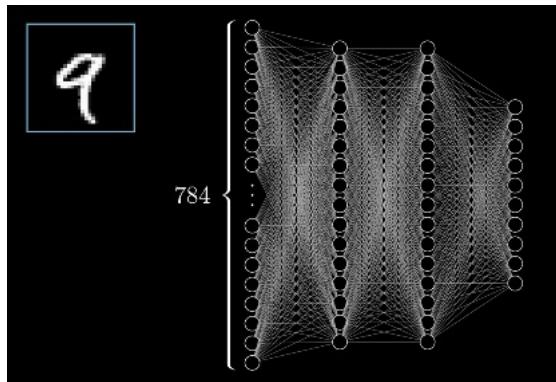
- Conceive and simulate genetic data under competing demographic scenarios 
- Understand deep learning background and how a CNN works 
- How to use deep learning to compare demographic scenarios
- Use CNN to detect regions with selective sweeps on real genomes

Part II: Understanding the basic CNN architecture for image recognition.

CNN architecture

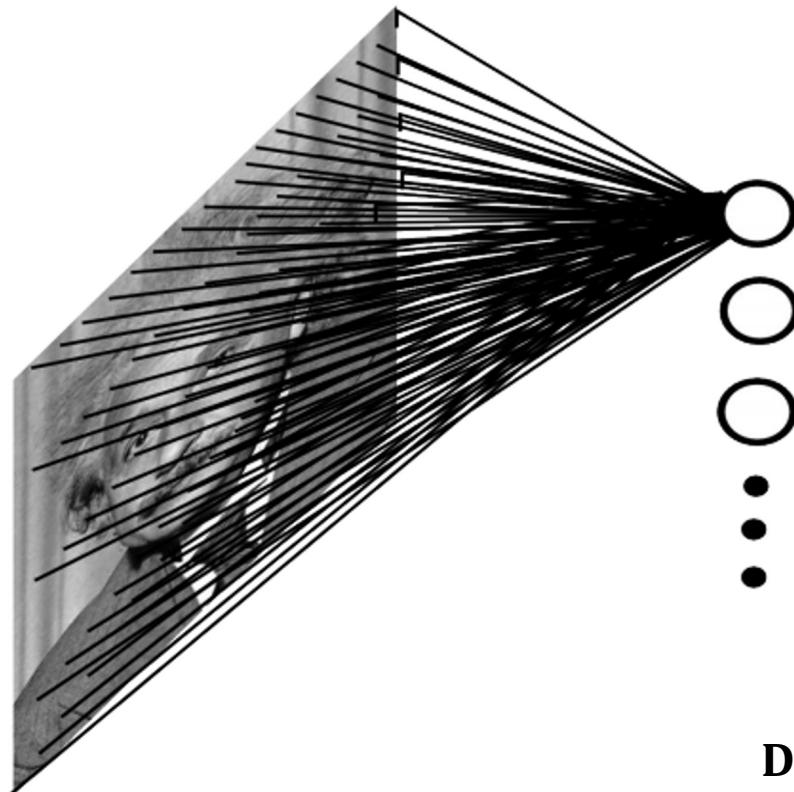


Convolutional Neural Networks (CNNs)

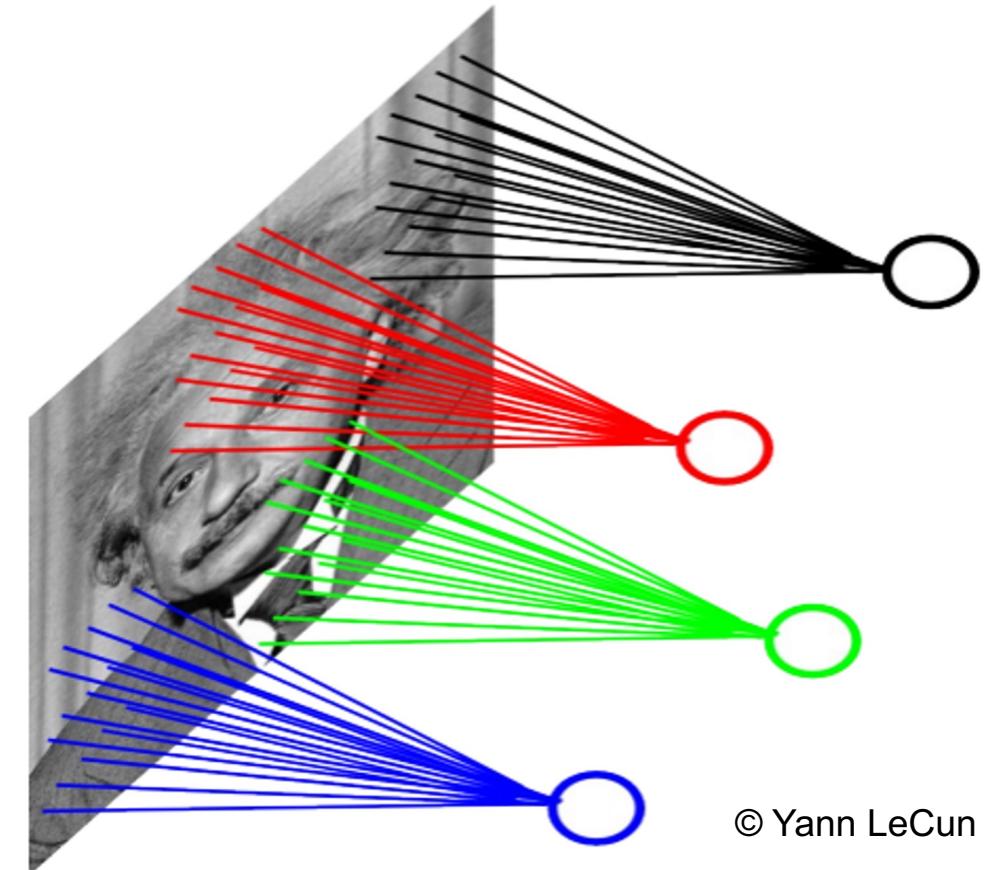


MLP
Fully connected

Convnet
locally connected
→ smaller number of parameters to learn

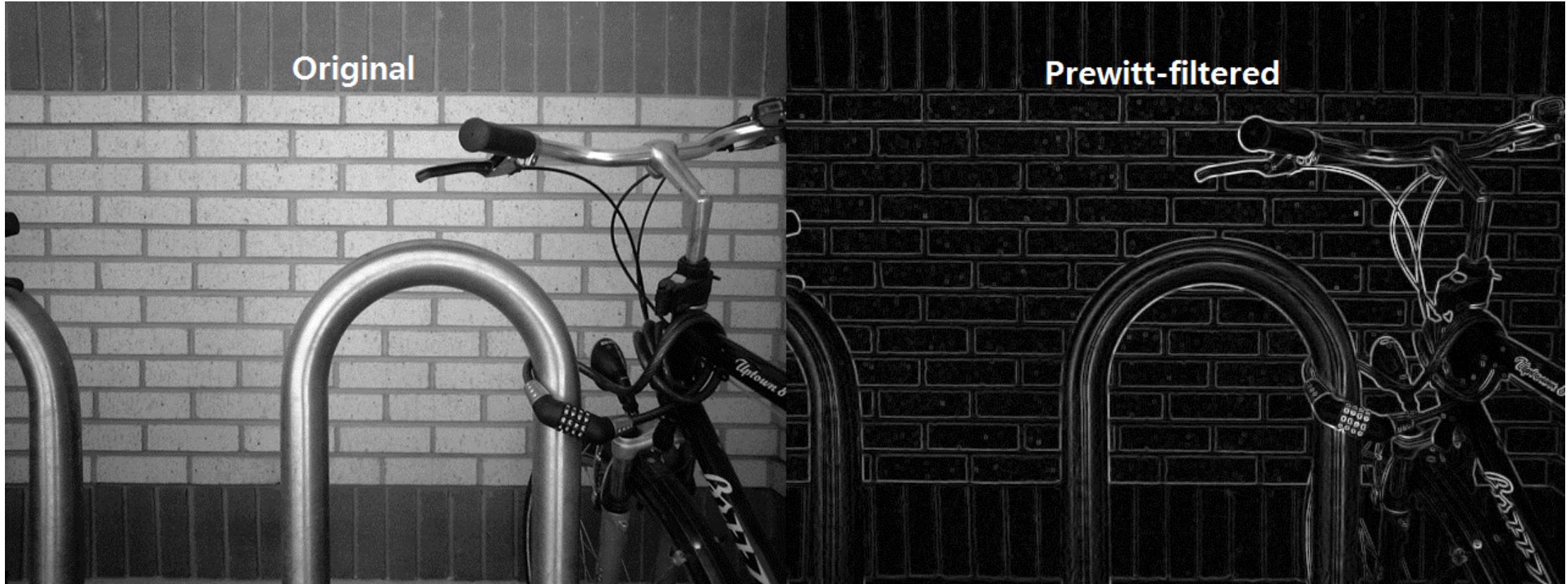


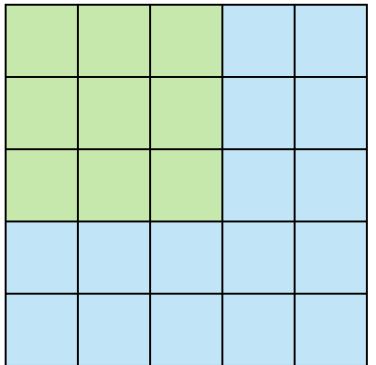
DL witchcraft



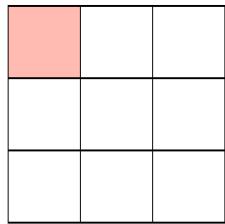
© Yann LeCun

Convolutional Layers



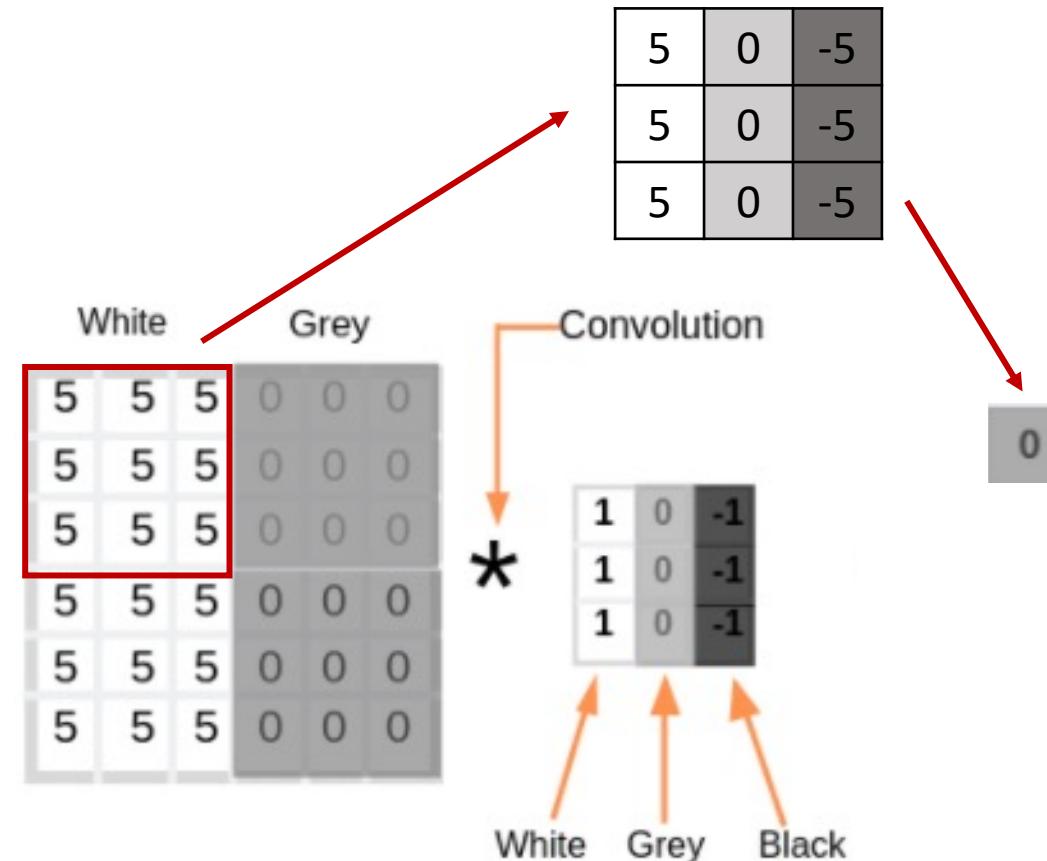


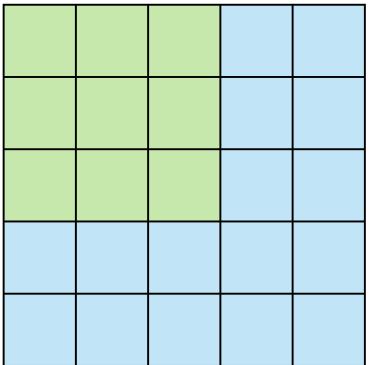
Stride 1



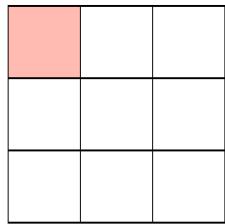
Feature Map

Convolutional Layers



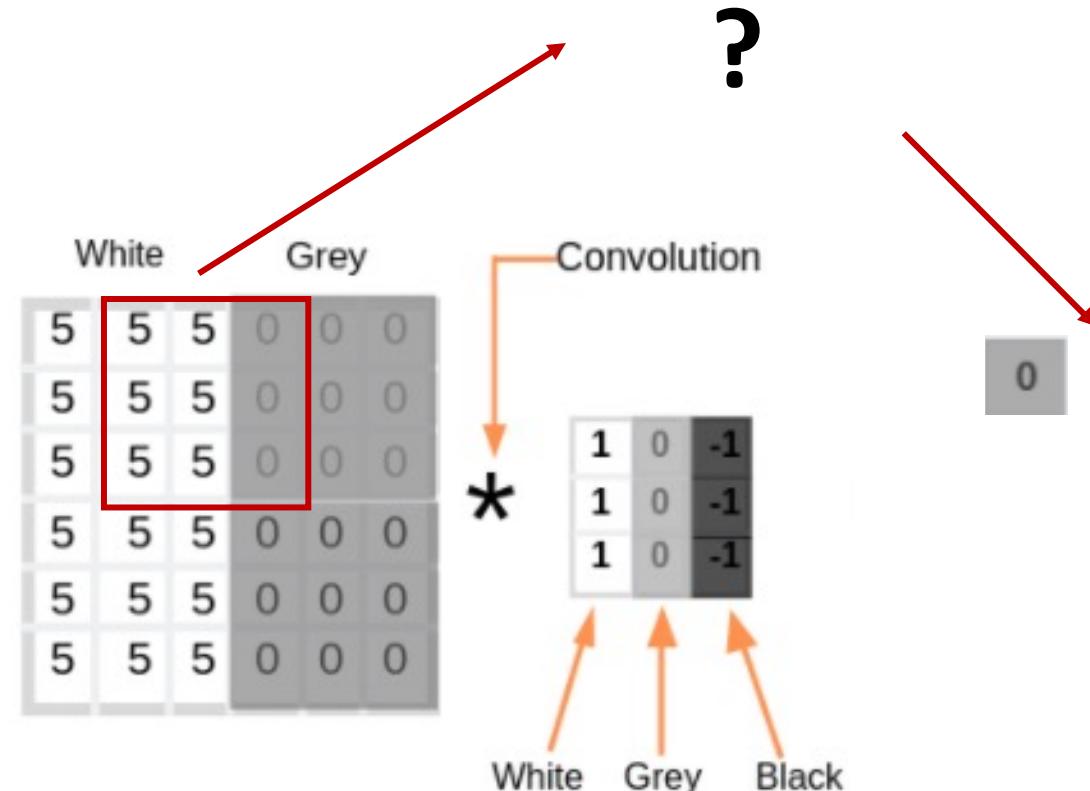


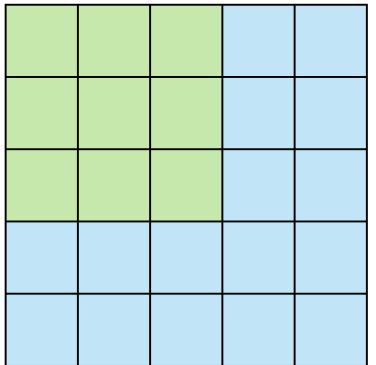
Stride 1



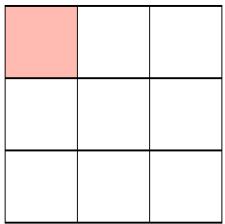
Feature Map

Convolutional Layers





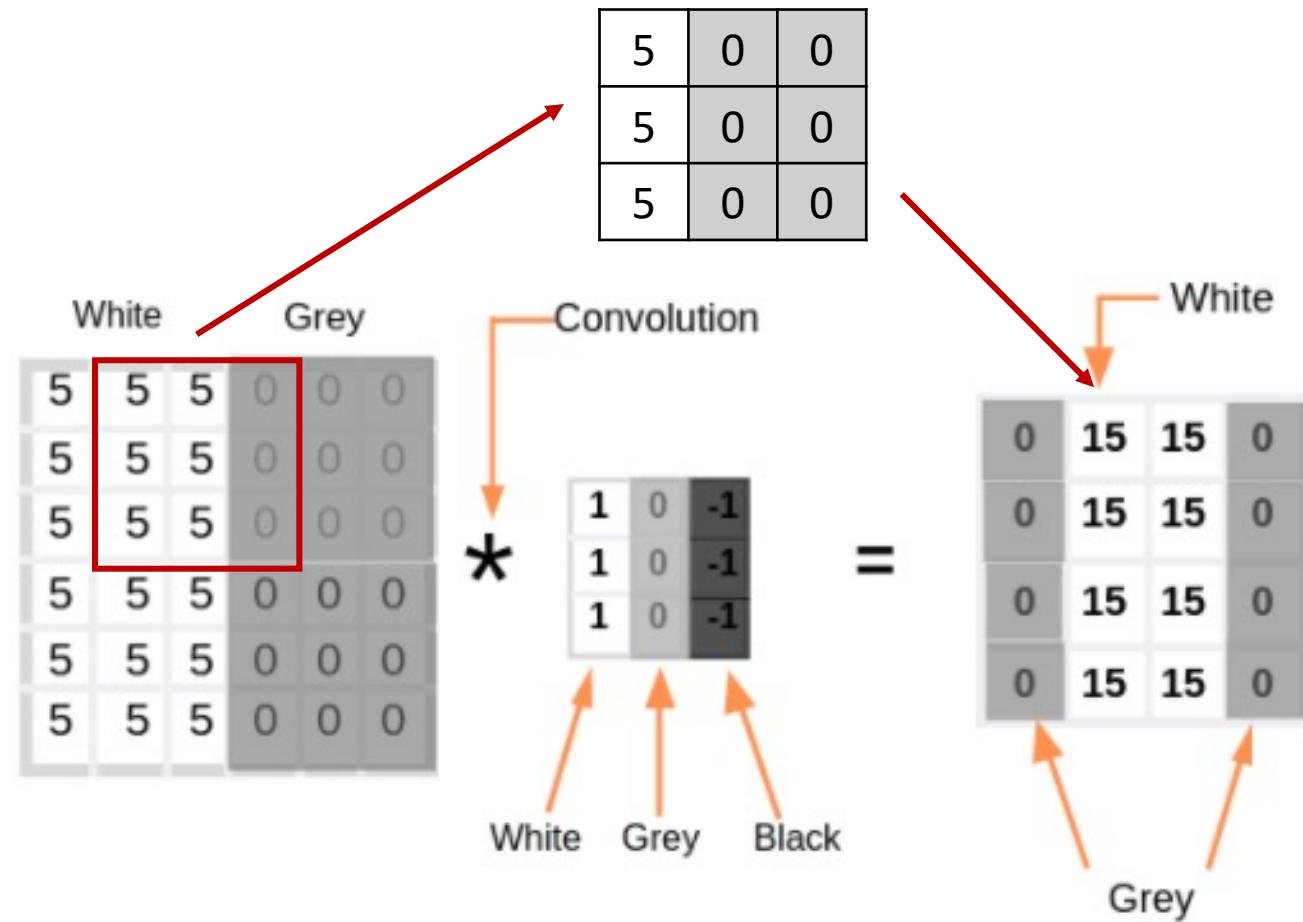
Stride 1



Feature Map

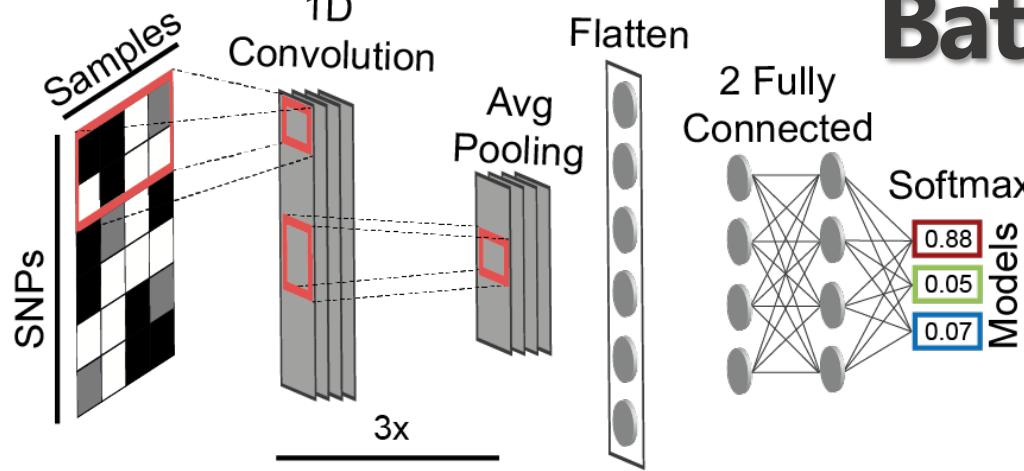


Convolutional Layers

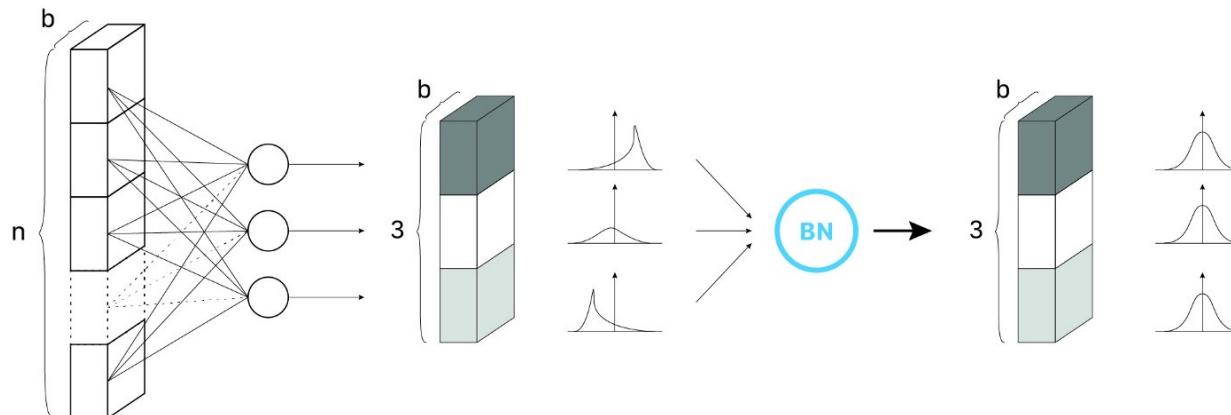




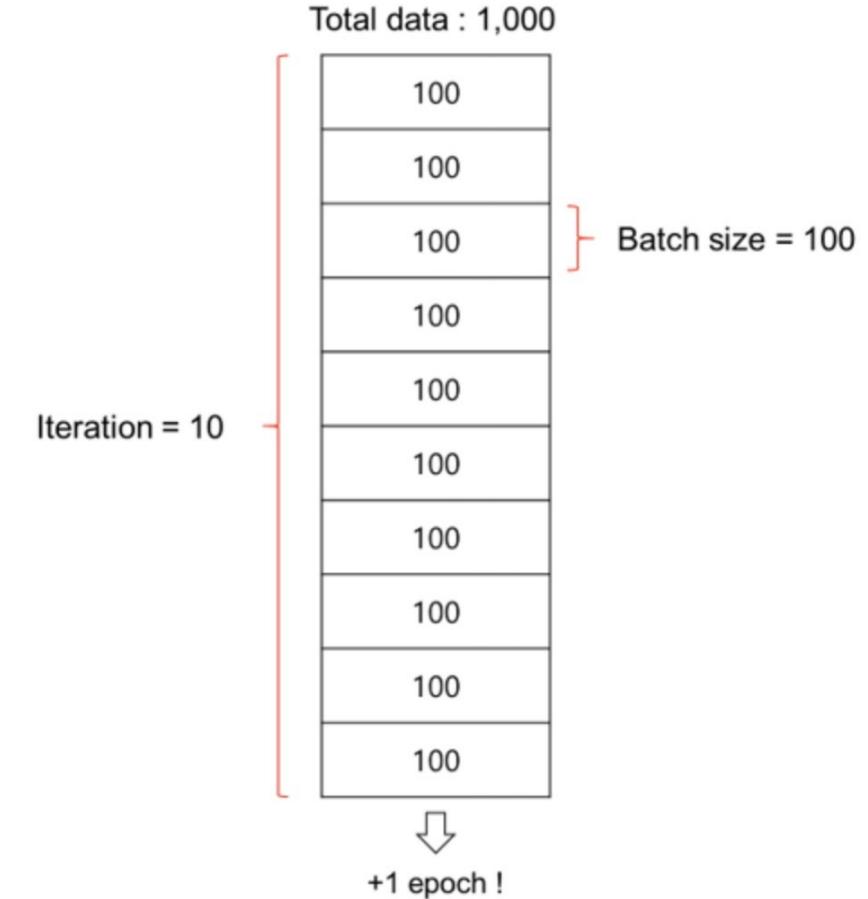
Batches and Batch Normalization



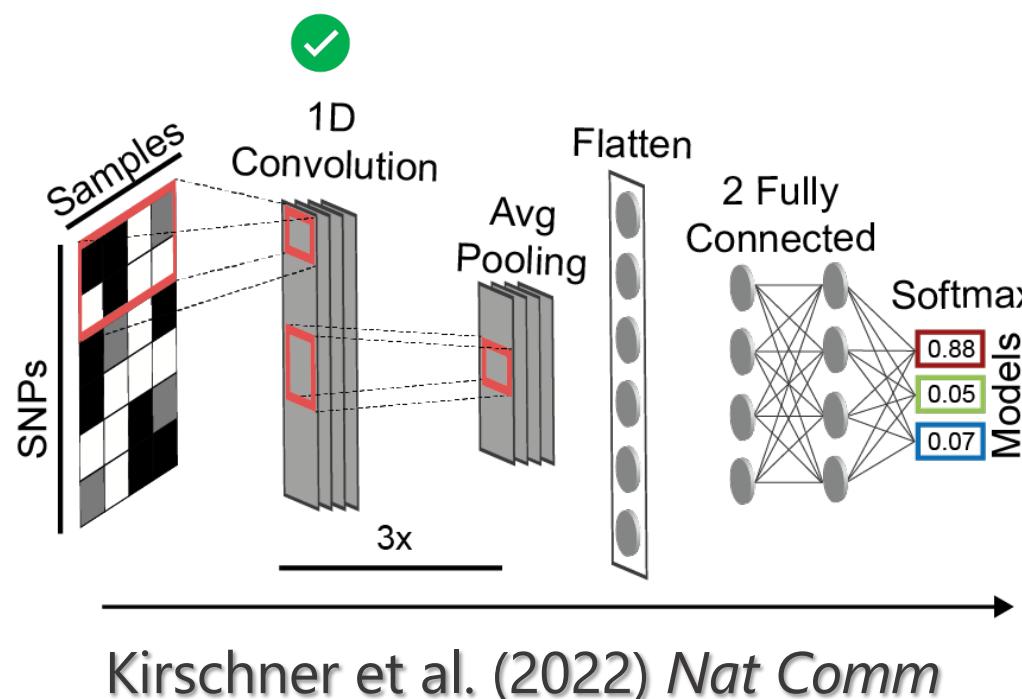
Kirschner et al. (2022) *Nat Comm*



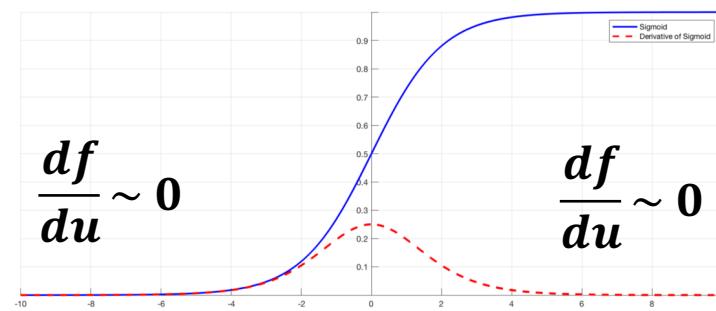
<https://towardsdatascience.com/batch-normalization-in-3-levels-of-understanding-14c2da90a338>



<https://jerryan.medium.com/batch-size-a15958708a6>



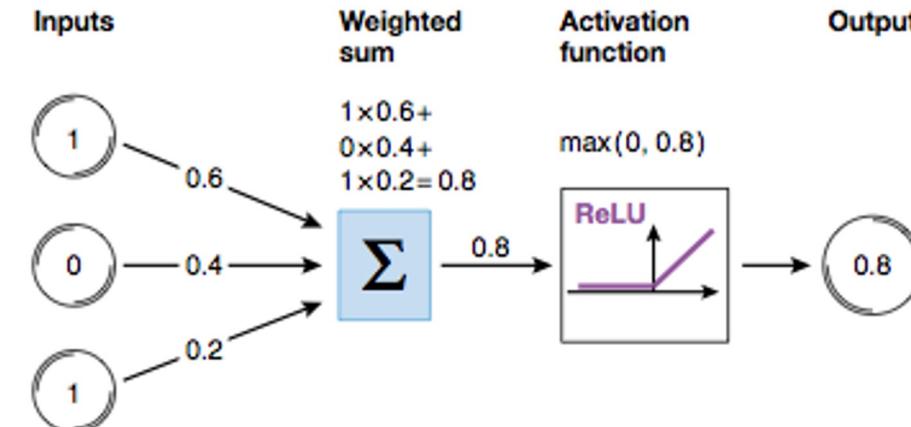
Sigmoid – Vanishing gradients



<https://towardsdatascience.com/the-vanishing-gradient-problem-69bf08b15484>

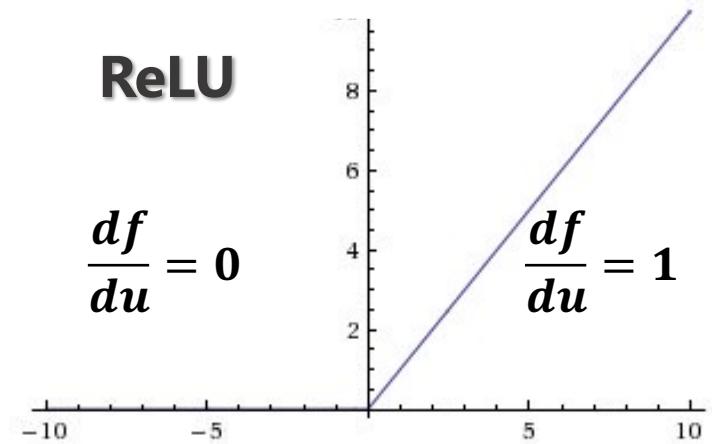
Activation Function

DL witchcraft



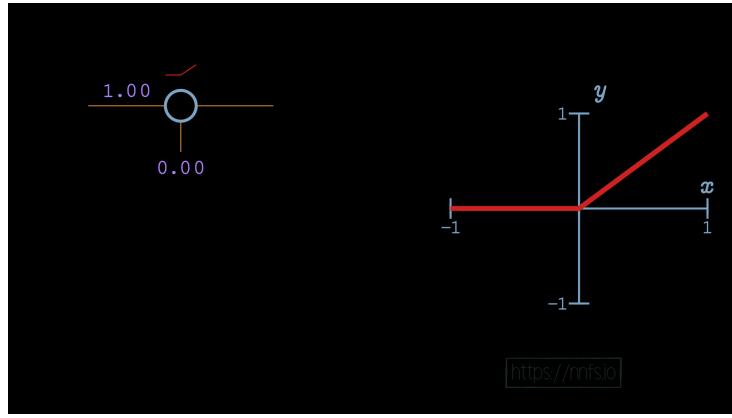
ReLU

$$\frac{df}{du} = 0$$

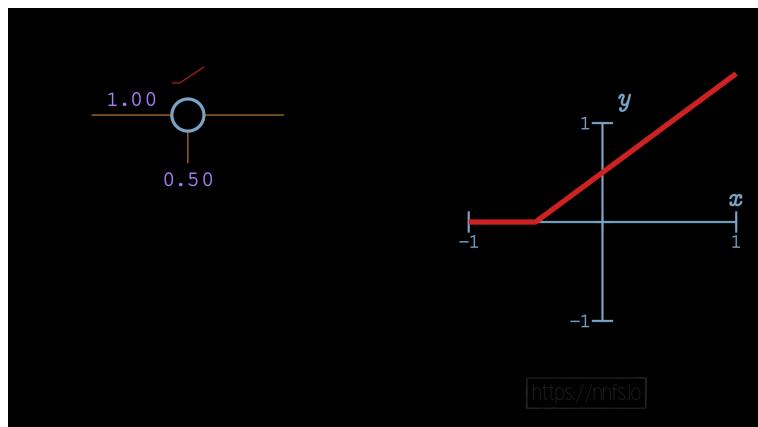


<https://www.kaggle.com/code/dansbecker/rectified-linear-units-relu-in-deep-learning/notebook>

CNN Script – ReLU



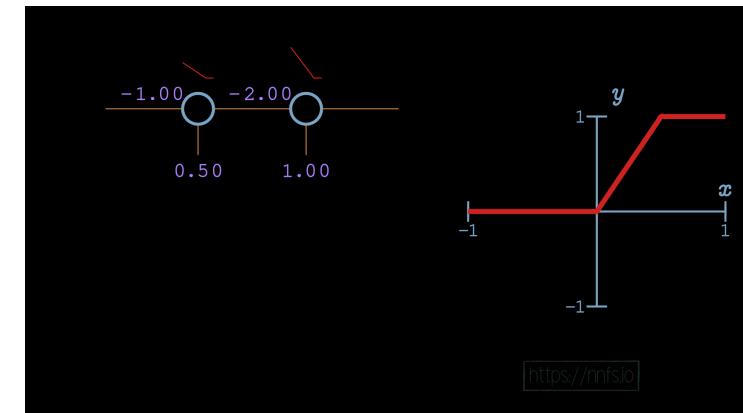
**Weight = 1
Bias = 0**



**Weight = 1
Bias = 0.5**



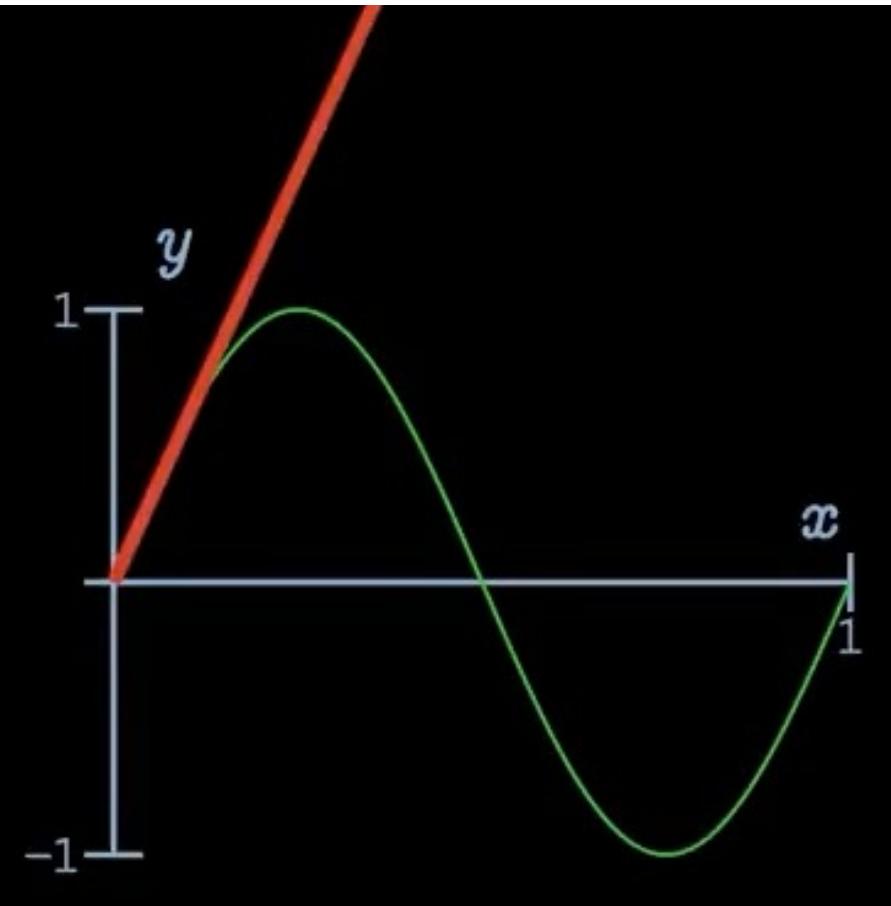
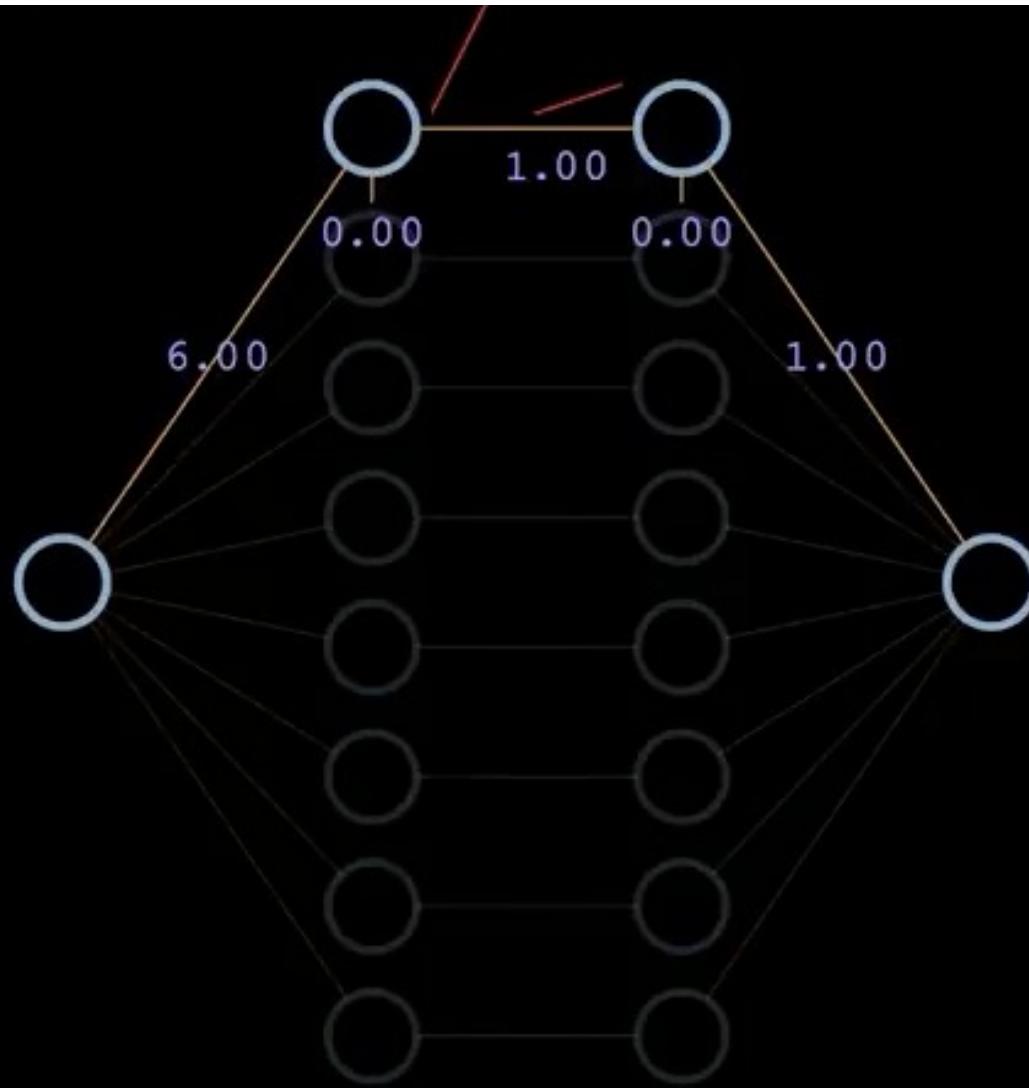
**Weight = -1
Bias = 0.5**



2 neurons

<https://nnfs.io/mvp/>

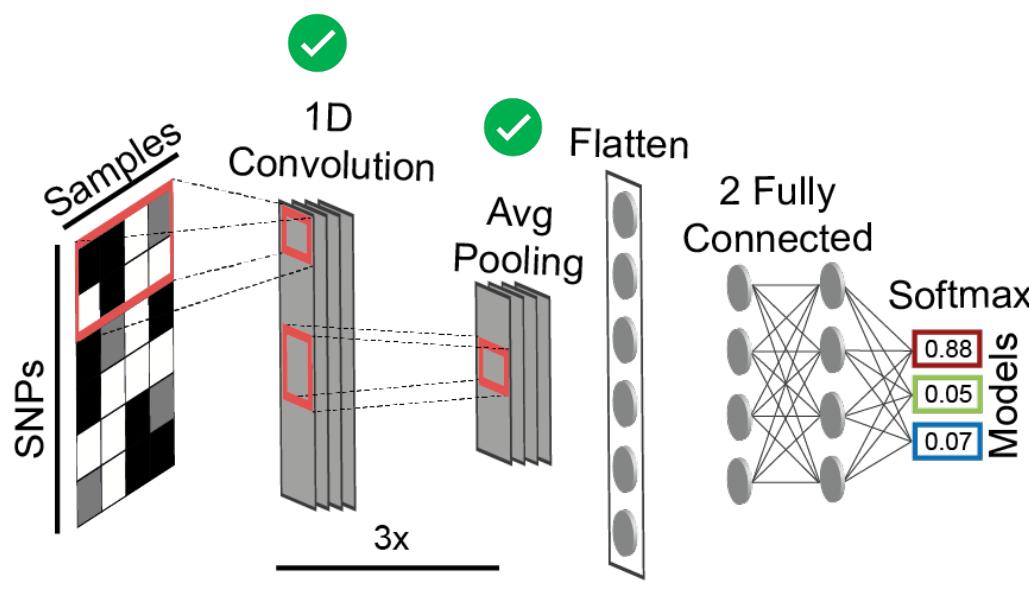
CNN Script – ReLU



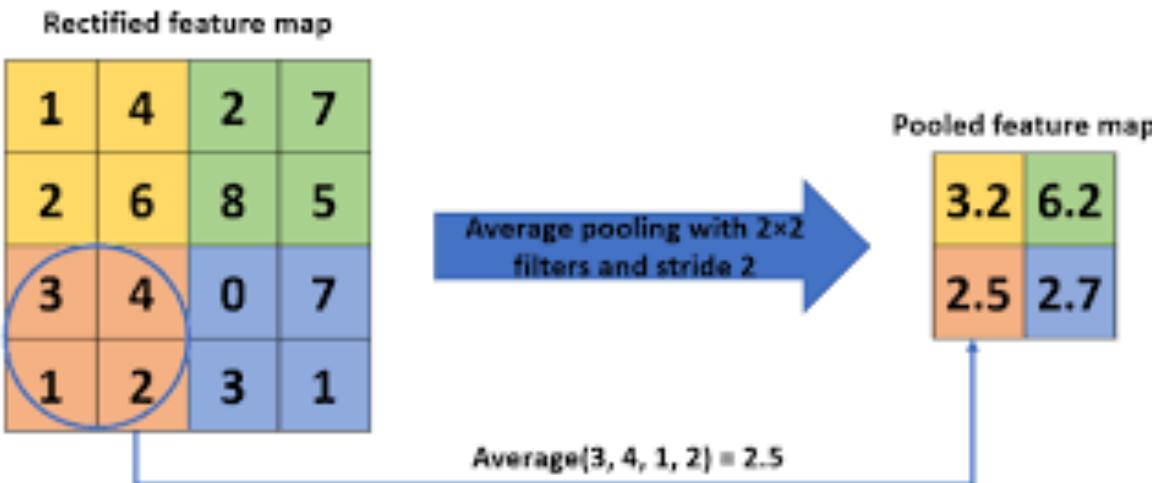
<https://nnfs.io>

<https://nnfs.io/mvp/>

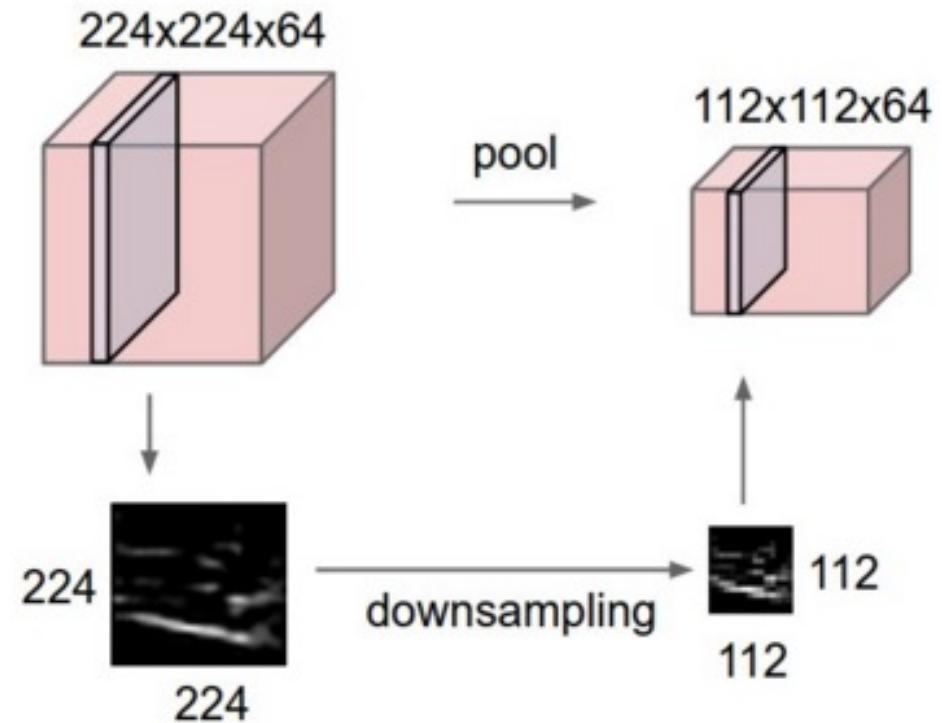
Pooling



Kirschner et al. (2022) *Nat Comm*

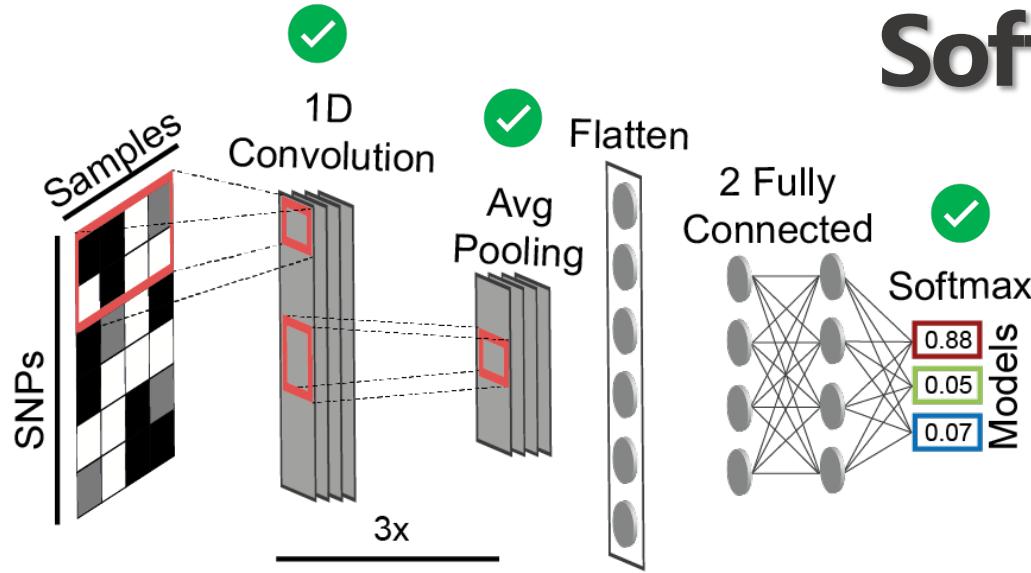


Gholamalinezhad & Khosravi
(2020) *arXiv*

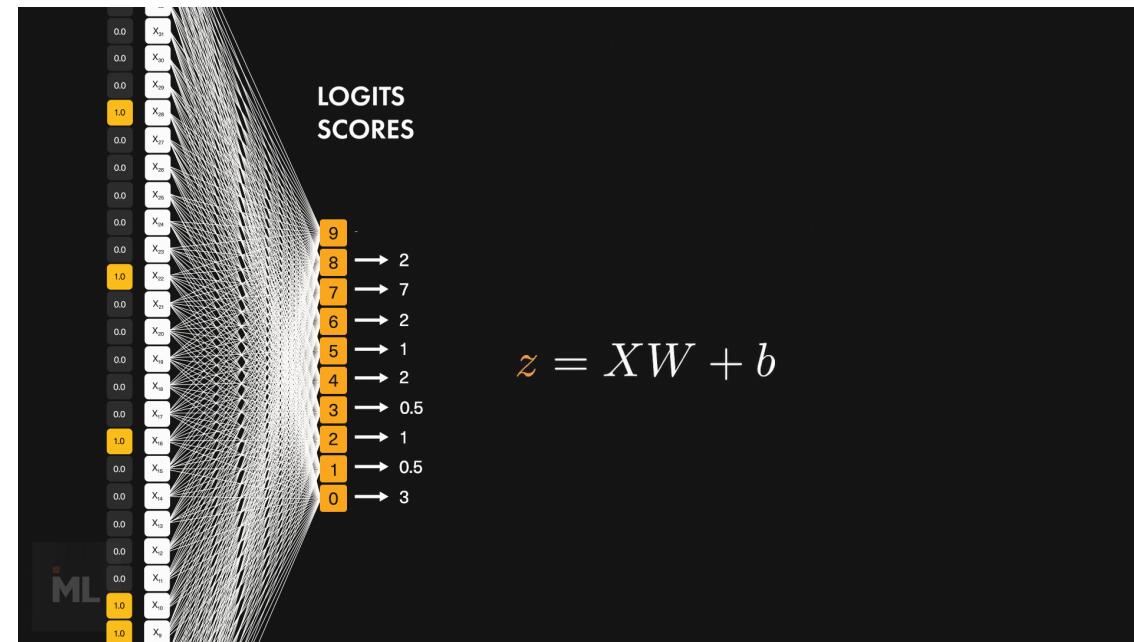


https://leonardoaraujosantos.gitbook.io/artificial-intelligence/machine_learning/deep_learning/pooling_layer

Softmax layer for Classification



Kirschner et al. (2022) *Nat Comm*



Libraries for deep Learning:
Keras, Tensorflow, pyTorch



TensorFlow

Table 2. Central parameters of a neural network and recommended settings.

Name	Range	Default value
Learning rate	0.1, 0.01, 0.001, 0.0001	0.01
Batch size	64, 128, 256	128
Momentum rate	0.8, 0.9, 0.95	0.9
Weight initialization	Normal, Uniform, Glorot uniform	Glorot uniform
Per-parameter adaptive learning rate methods	RMSprop, Adagrad, Adadelta, Adam	Adam
Batch normalization	Yes, no	Yes
Learning rate decay	None, linear, exponential	Linear (rate 0.5)
Activation function	Sigmoid, Tanh, ReLU, Softmax	ReLU
Dropout rate	0.1, 0.25, 0.5, 0.75	0.5
L1, L2 regularization	0, 0.01, 0.001	

Hyperparameters

Some of the best hyperparameter optimization libraries are:

1. Scikit-learn
2. Scikit-Optimize
3. Optuna
4. Hyperopt
5. Ray.tune
6. Talos
7. BayesianOptimization
8. Metric Optimization Engine (MOE)
9. Spearmint
10. GPyOpt
11. SigOpt
12. Fabolas

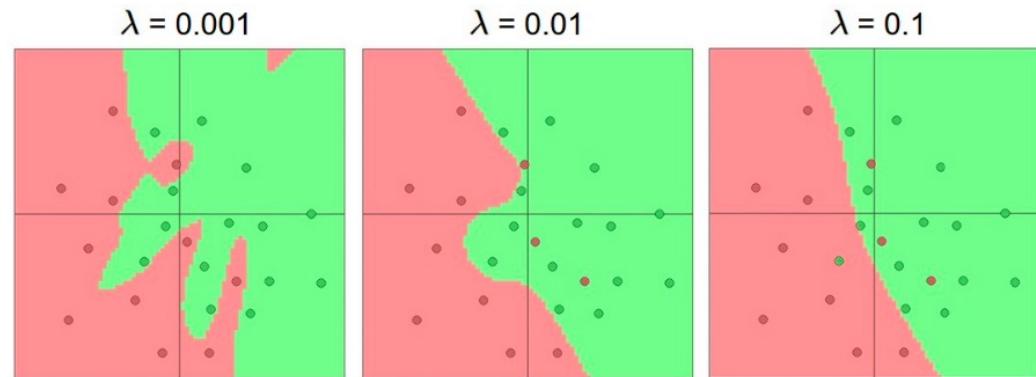
<https://neptune.ai/blog/hyperparameter-tuning-in-python-complete-guide#hyperopt>

Hyperparameters

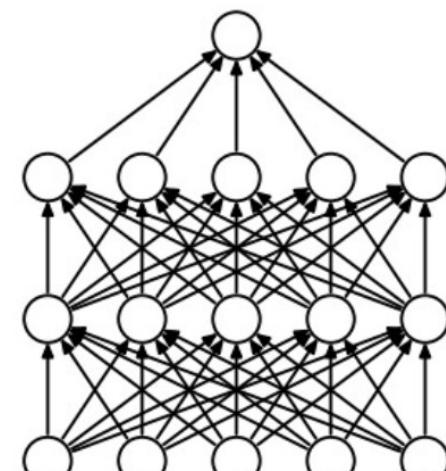
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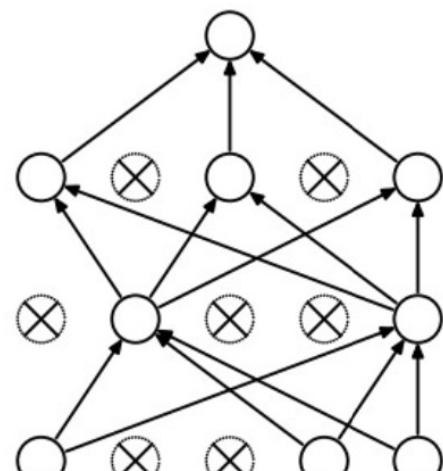
Regularization



Options: L2, L1, maxnorm and **dropout**.



(a) Standard Neural Net

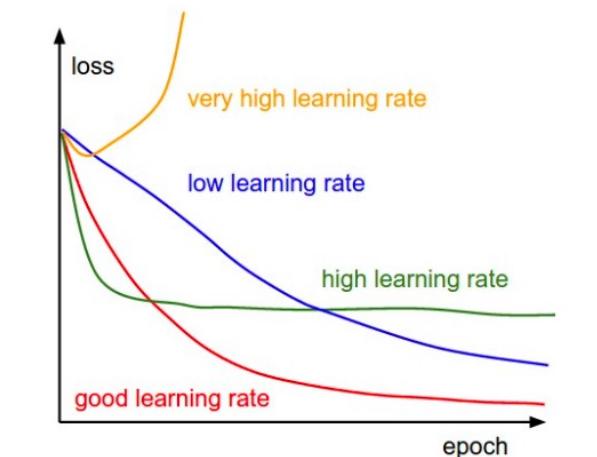


(b) After applying dropout.

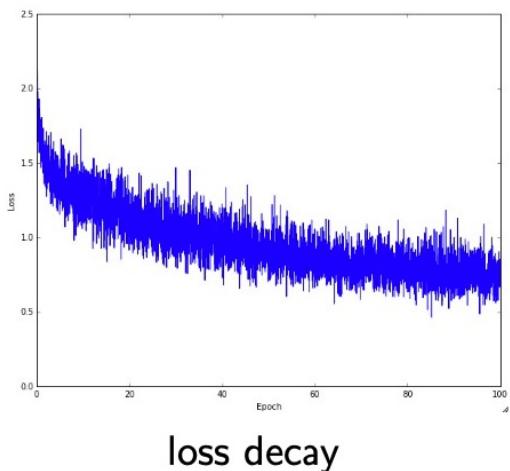
Hyperparameters

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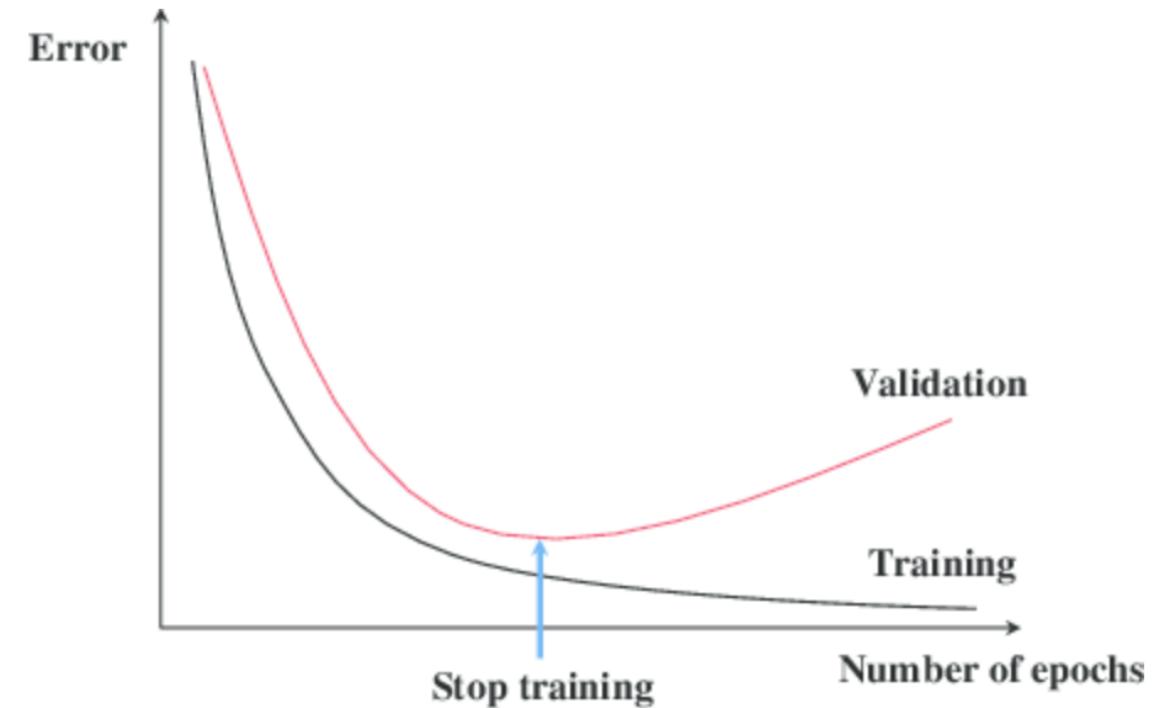
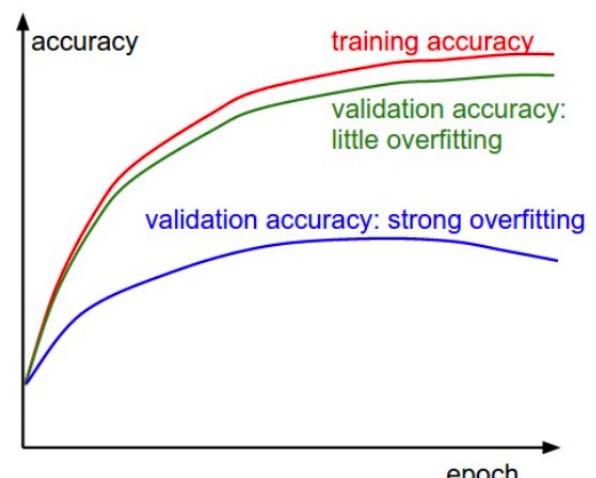
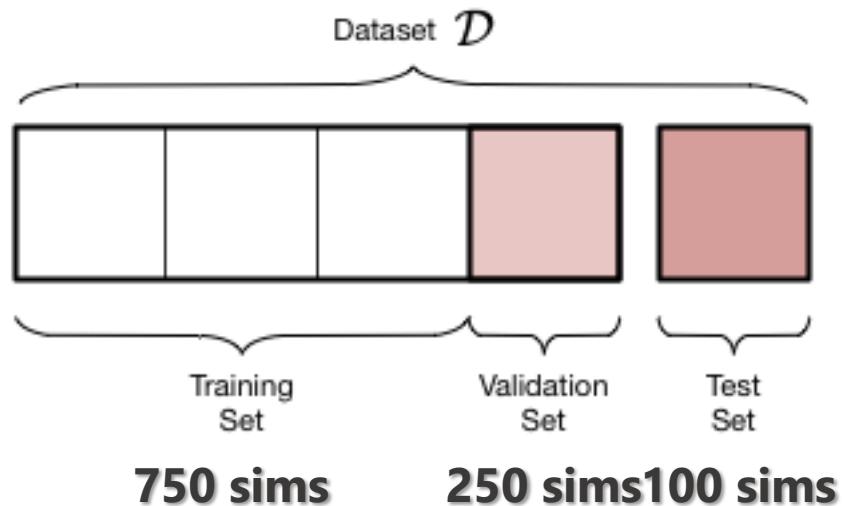


effects of different learning rates



Early Stop to avoid overfitting

<https://se-education.org/learningresources/contents/ai/ml.html>



<https://towardsdatascience.com/a-practical-introduction-to-early-stopping-in-machine-learning-550ac88bc8fd>

Part III: Practical on Image classification with CNN.

- **Practical Exercise 2:**
- Access <https://poloclub.github.io/cnn-explainer/>
- Scroll down to the Understanding hyperparameters section. Try to understand what is kernel size, padding, and stride.
- Use the graphical interface to try to better understand how convolutions work and what features are being extracted from the images.
- You can also upload the alignment images (Model1 to Model3.png) from different scenarios (but notice the network was not trained with that type of image). Does the network give an output prediction for the alignments?

Goals

- Conceive and simulate genetic data under competing demographic scenarios 
- Understand deep learning background and how a CNN works 
- How to use deep learning to compare demographic scenarios
- Use CNN to detect regions with selective sweeps on real genomes

