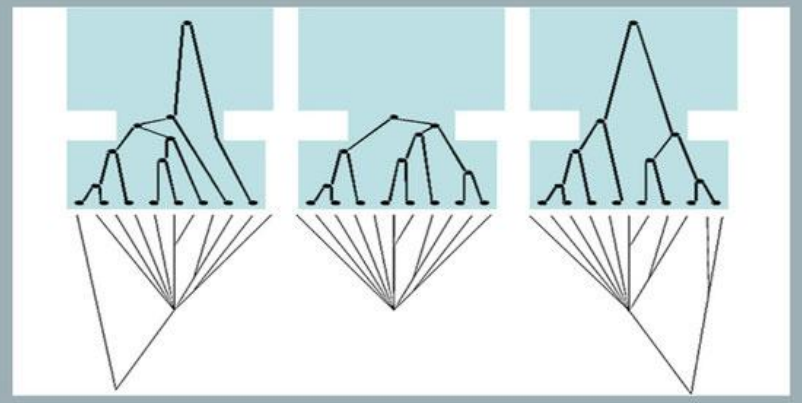


Deep learning methods in population genomics and phylogeography

Manolo Fernandez Perez

Departent of Life Sciences, Imperial College London

@ManoloLearning

manolofperez@gmail.com

sites.google.com/site/manolofperez

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

Program

Program

- *Part I: A gentle introduction to supervised deep learning and how to apply it to genomic data.*
- *Part II: Understanding the basic CNN architecture for image recognition.*
- *Part III: Practical on Image classification with CNN.*

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://trips-tickets.com/the_golem_of_prague/

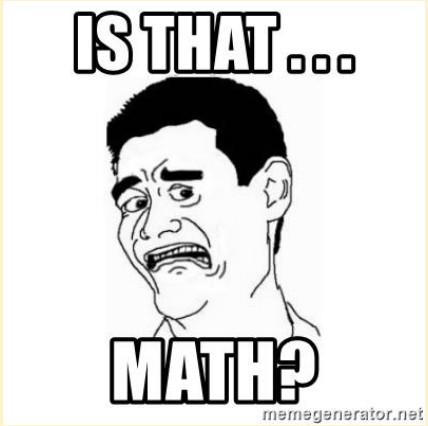
https://www.atlantajewishtimes.com/the-golem-of-prague/

Likelihood-free methods

Complex evolutionary processes -> too many posible models and parameters to estimate the likelihood function (ML and Bayesian methods).

Post. Prob. **Likelihood** Prior

$$Pr(M|data) = \frac{\mathbf{Pr(data|M)}*Pr(M)}{Pr(data)}$$



Likelihood-free methods

Posible solutions:

Use a few (simple) models for all species/datasets (IM; Migrate-n…)

Likelihood-free methods

- ABC;
- Approximate Likelihoods;
- Deep Learning

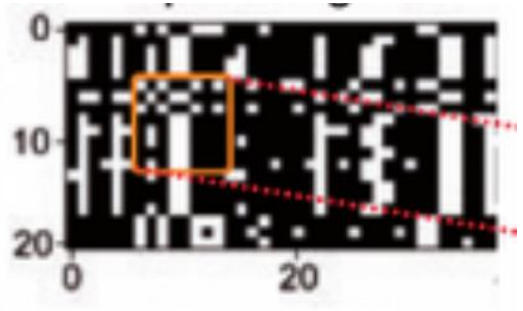
What is machine learning?

TASK:
predict y from x

Angermueller et al Mol Syst Biol. (2016) 12: 878

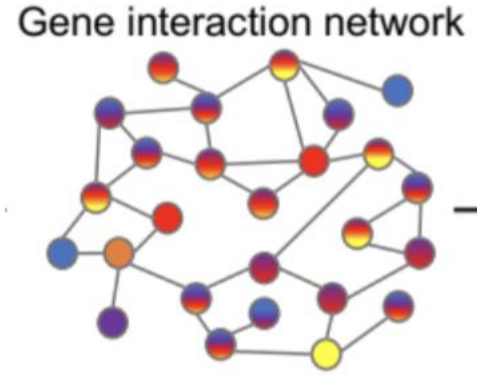
Matteo Fumagalli and Flora Jay. Machine learning and deep learning for demographic and selection inference. Lecture

What is the data?



Flagel et al. (2019) *MBE*

Images



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

Graphs

https://www.datarobot.com/blog/the-importance-of-machine-learning-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

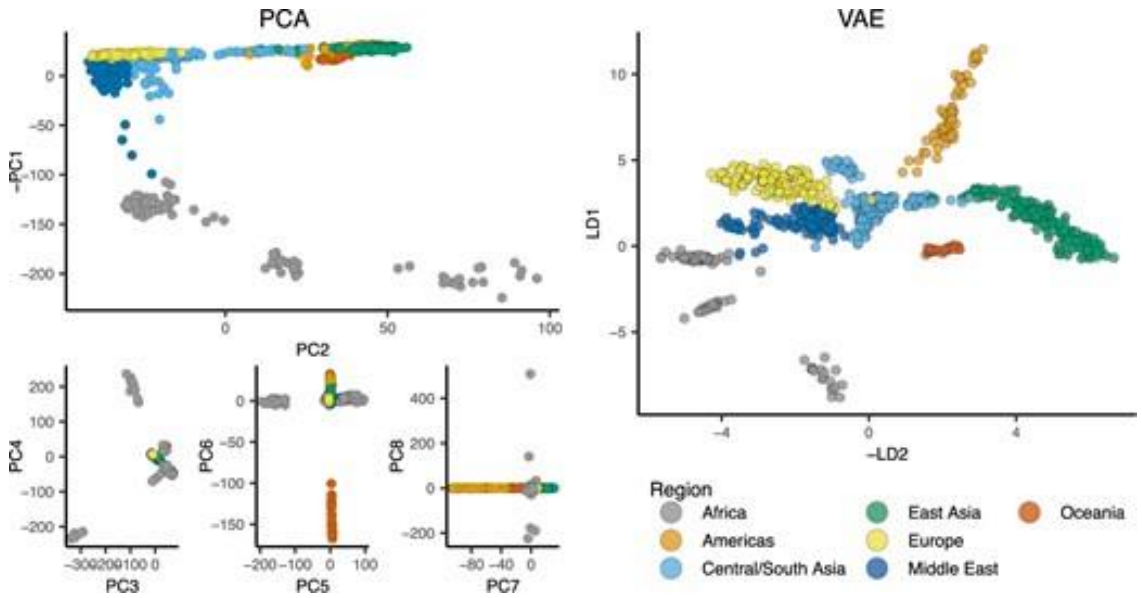
ex : pic of dog/person/car..., price of house, level of cholesterol

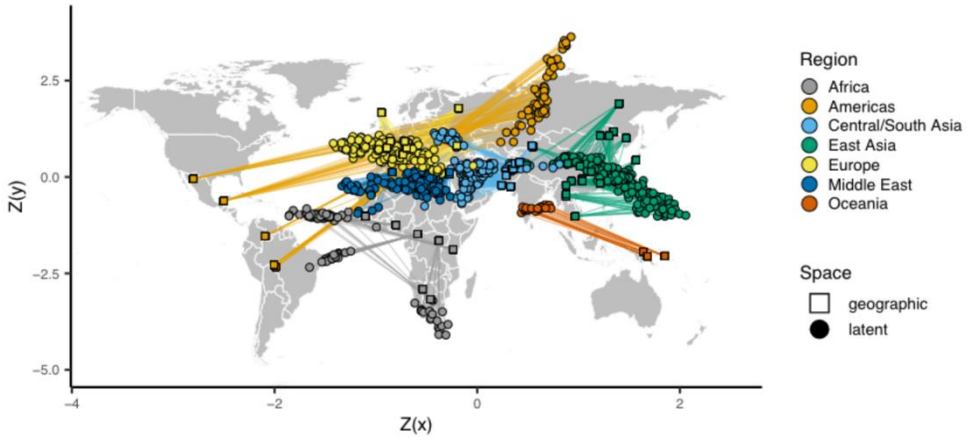
What is the model?

.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

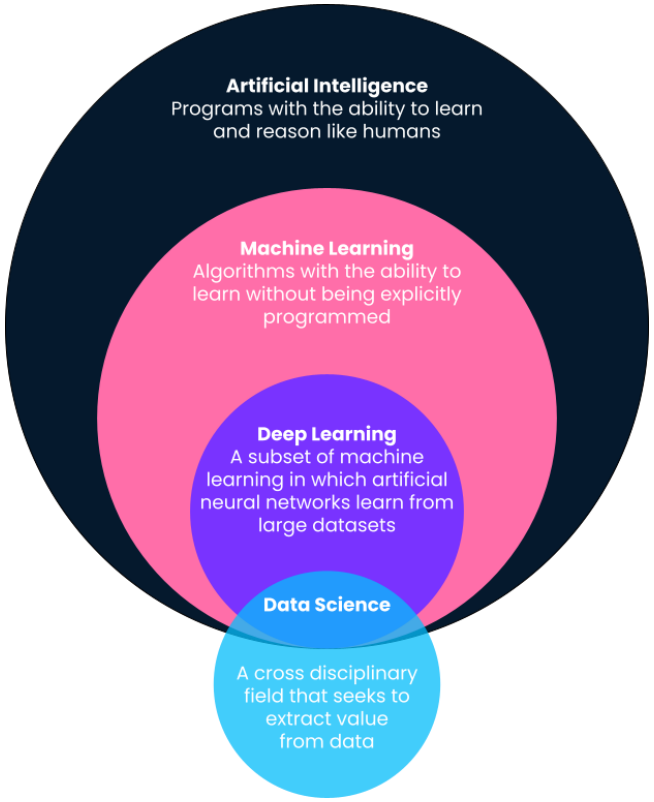
Classification (predict a class)

Regression (predict a variable)

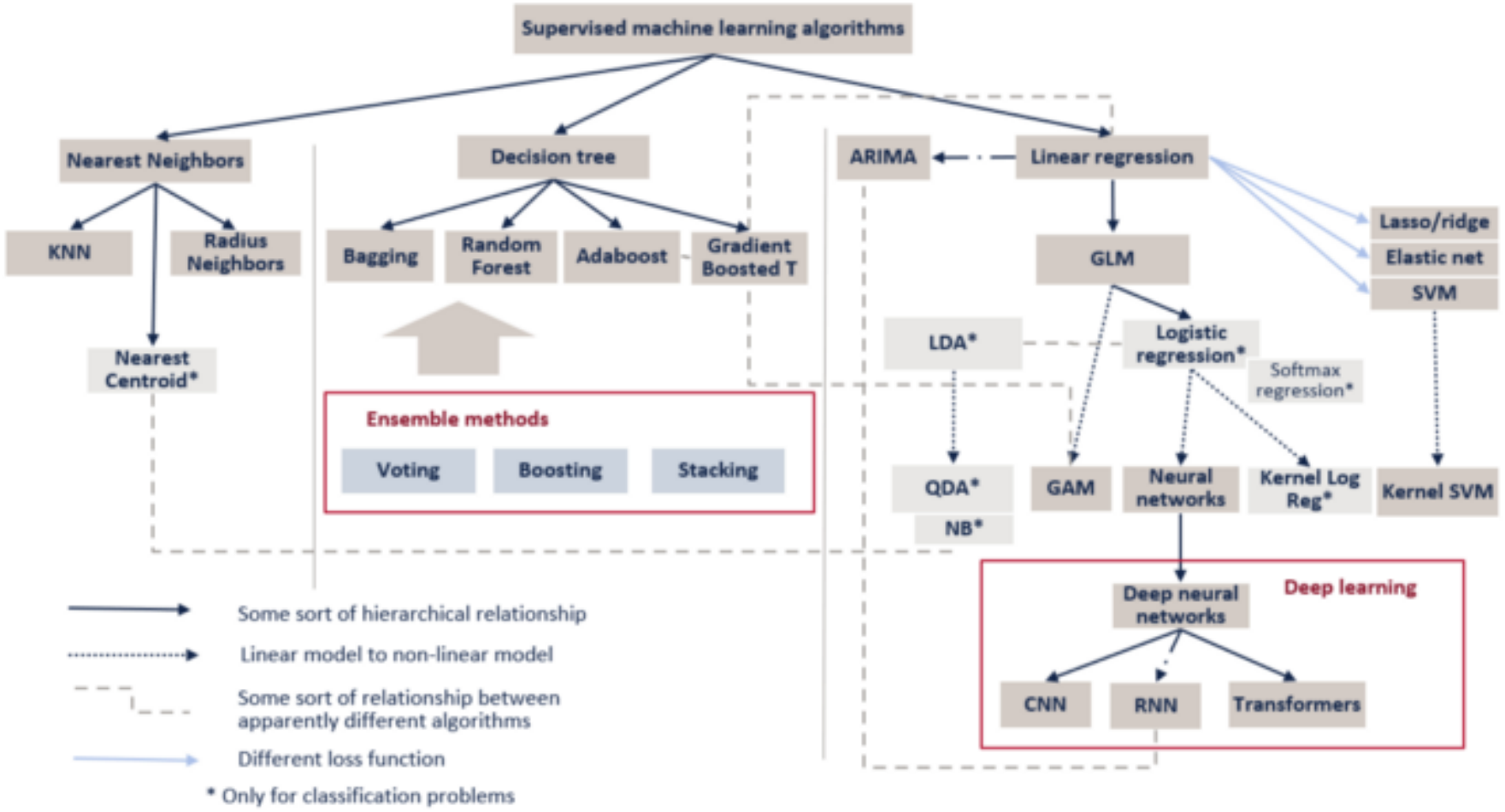
What for:
- Predict labels of new unlabeled samples (eg what's on an image?),
- Understand better the relationship between features and the label (eg understand which set of genes allow to predict a disease risk),
- ...

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

Deep Neural Networks

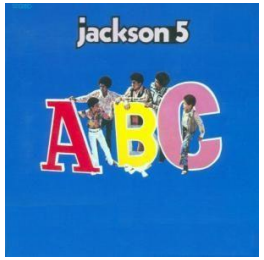


https://www.datacamp.com/blog/what-is-machine-learning



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

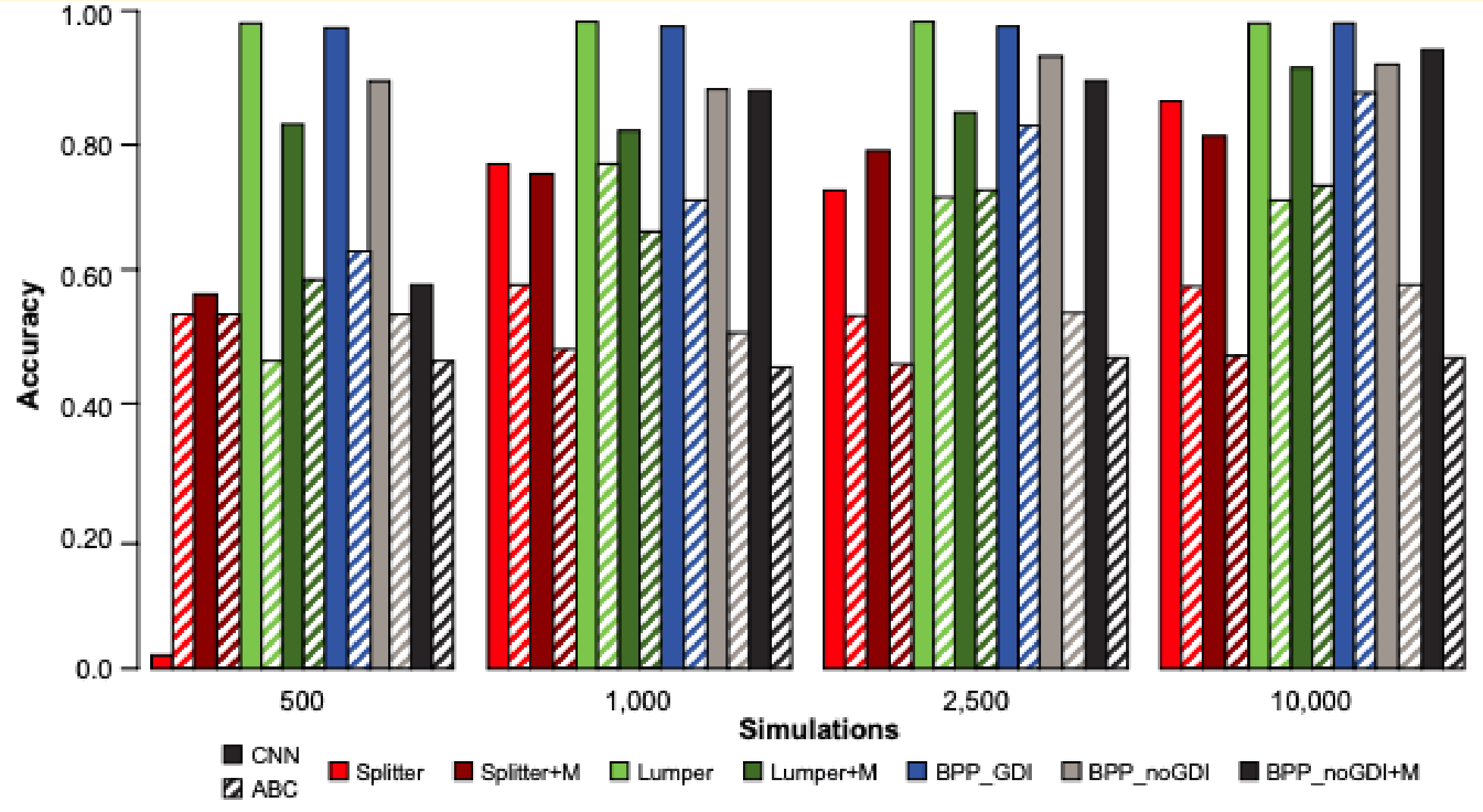
Why Deep Learning?



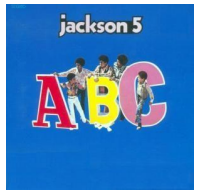
Deep Learning

CJ Battey
Twitter 2018

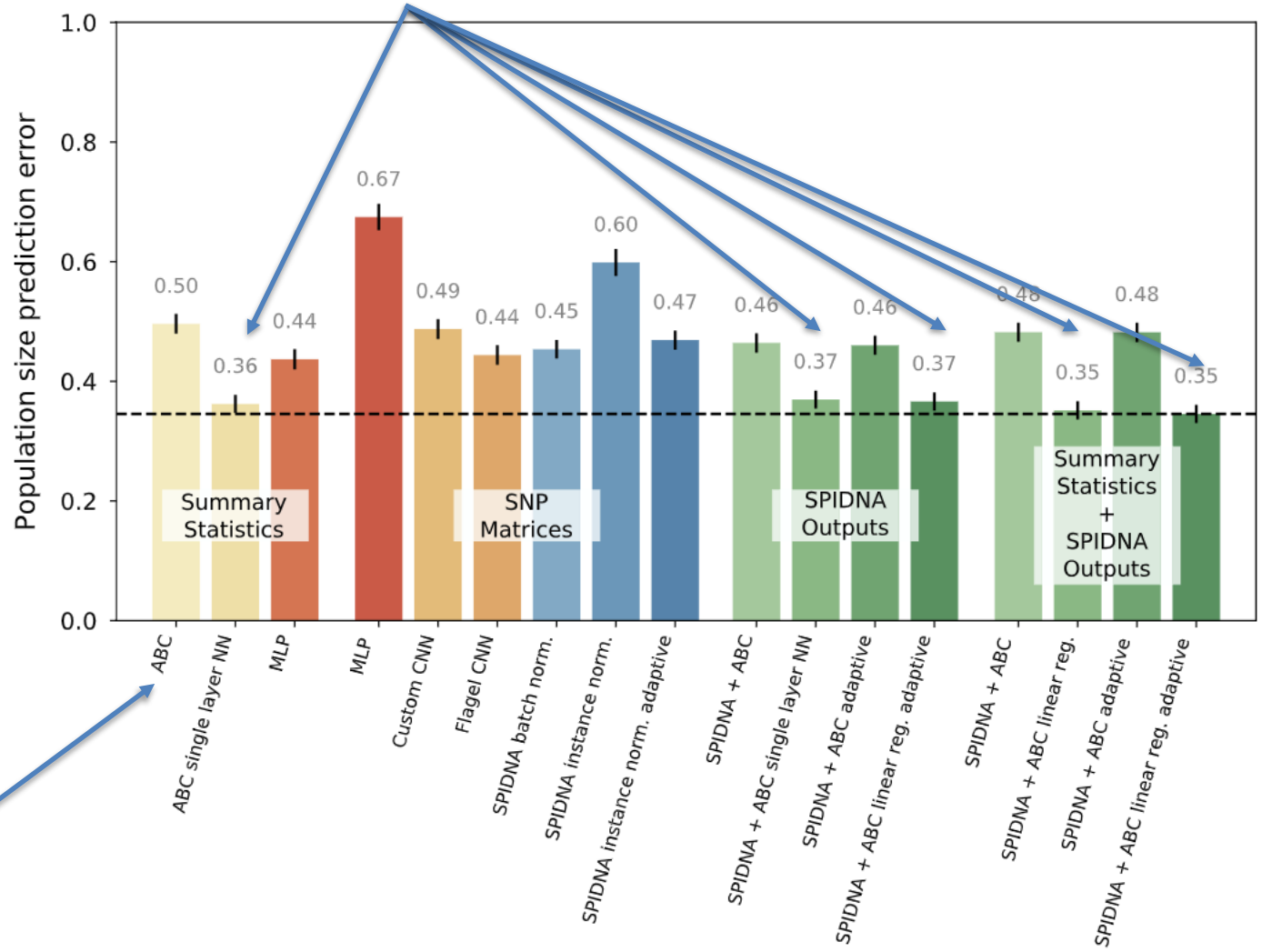
Why Deep Learning?

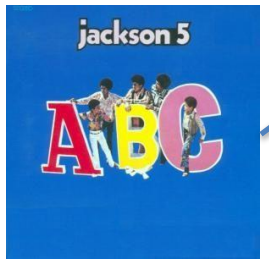


Perez et al. (2022) *Mol Ecol Res*



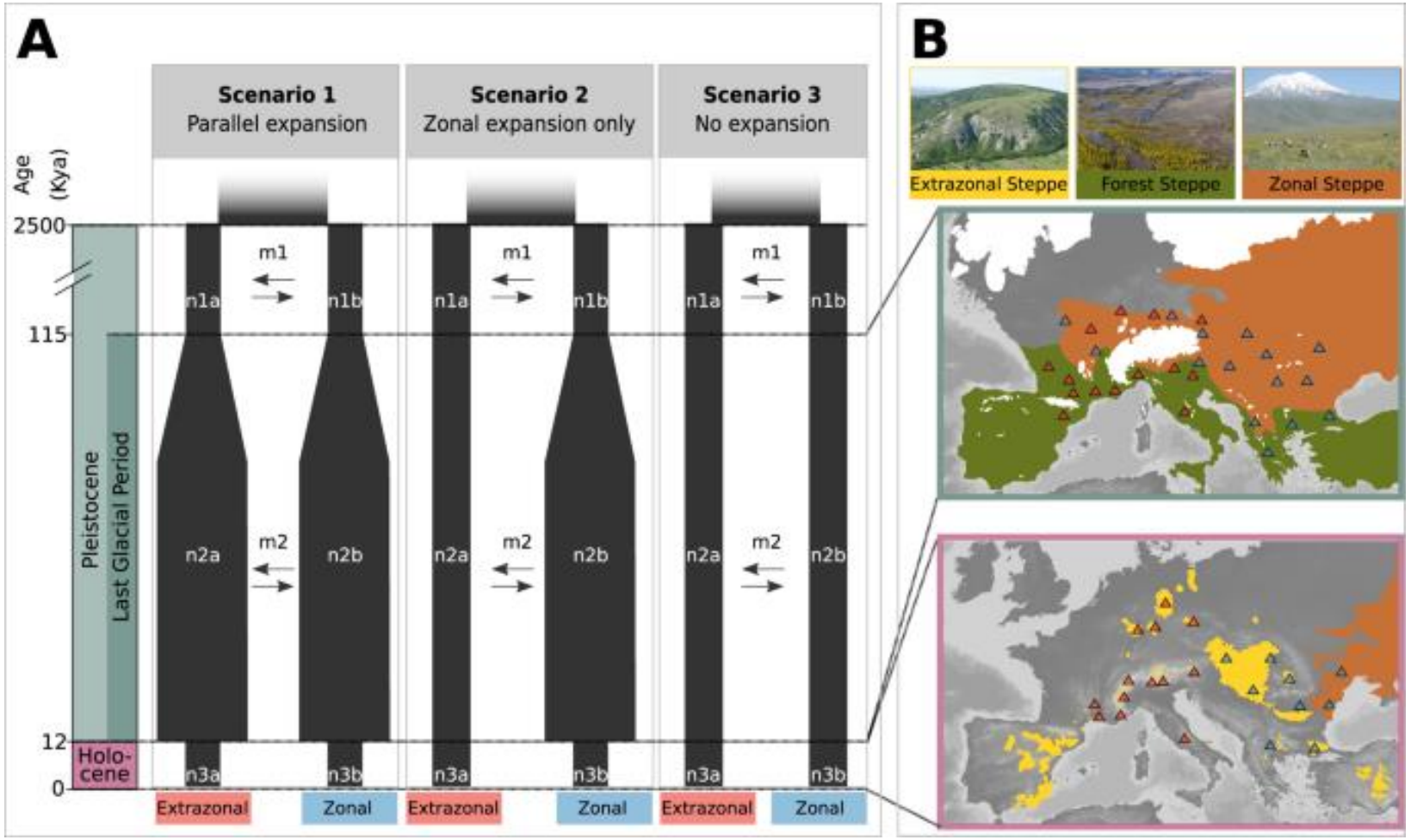
Why Deep Learning?





Sanchez et al. (2020) Mol Ecol Res

Supervised Deep Learning ~ ABC



Kirschner et al. (2022) *Nat Comm*

Simulate Genetic Data – ms (Hudson 2002)

BIOINFORMATICS **APPLICATIONS NOTE** *Vol. 18 no. 2 2002*
Pages 337–338

Generating samples under a Wright–Fisher neutral model of genetic variation

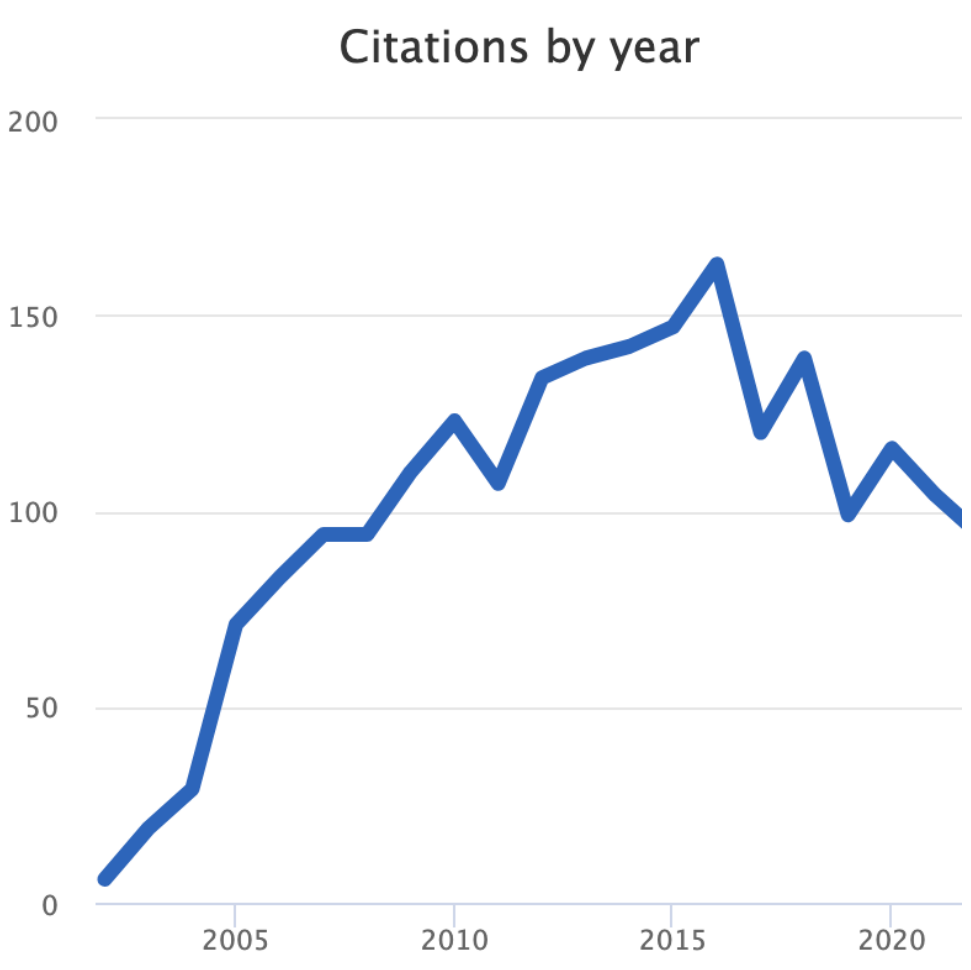
Richard R. Hudson

Department of Ecology and Evolution, University of Chicago, 1101 E. 57th Street, Chicago, IL 60637, USA

Received on August 8, 2001; revised and accepted on September 13, 2001

- Seminal simulator.
- Allows to fix the number of segregating sites.

2,142 citations



Simulate Genetic Data – other options

TABLE 6.1 Programs for simulating population samples of DNA sequences

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COALESCENT ("BACKWARD") SIMULATION SOFTWARE	
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SIMCOAL/SIMCOAL 2.0	Excoffier et al. 2000; Laval and Excoffier 2004
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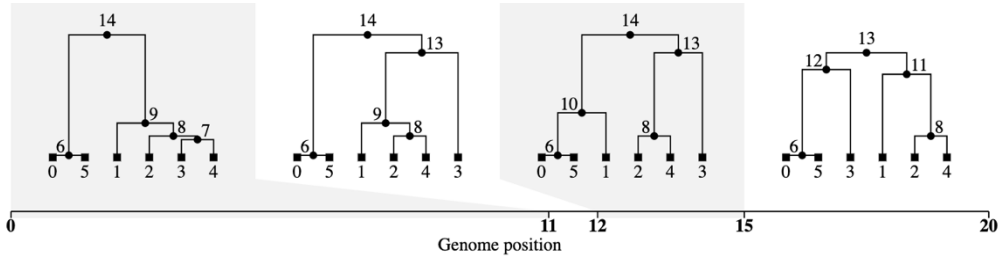
fwdpp	Thornton 2014
SLiM/SLiM 2	Messer 2013; Haller and Messer 2017
ARGON	Palamara 2016
APPROXIMATE COALESCENT ("SIDEWAYS") SIMULATION SOFTWARE	
FastCoal	McVean and Cardin 2005; Marjoram and Wall 2006
MaCS	Chen et al. 2009
fastsimcoal/fastsimcoal2	(Excoffier and Foll 2011; Excoffier et al. 2013)

ms prime



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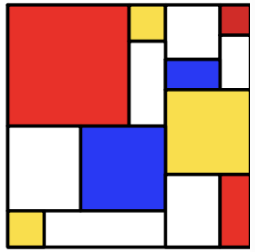
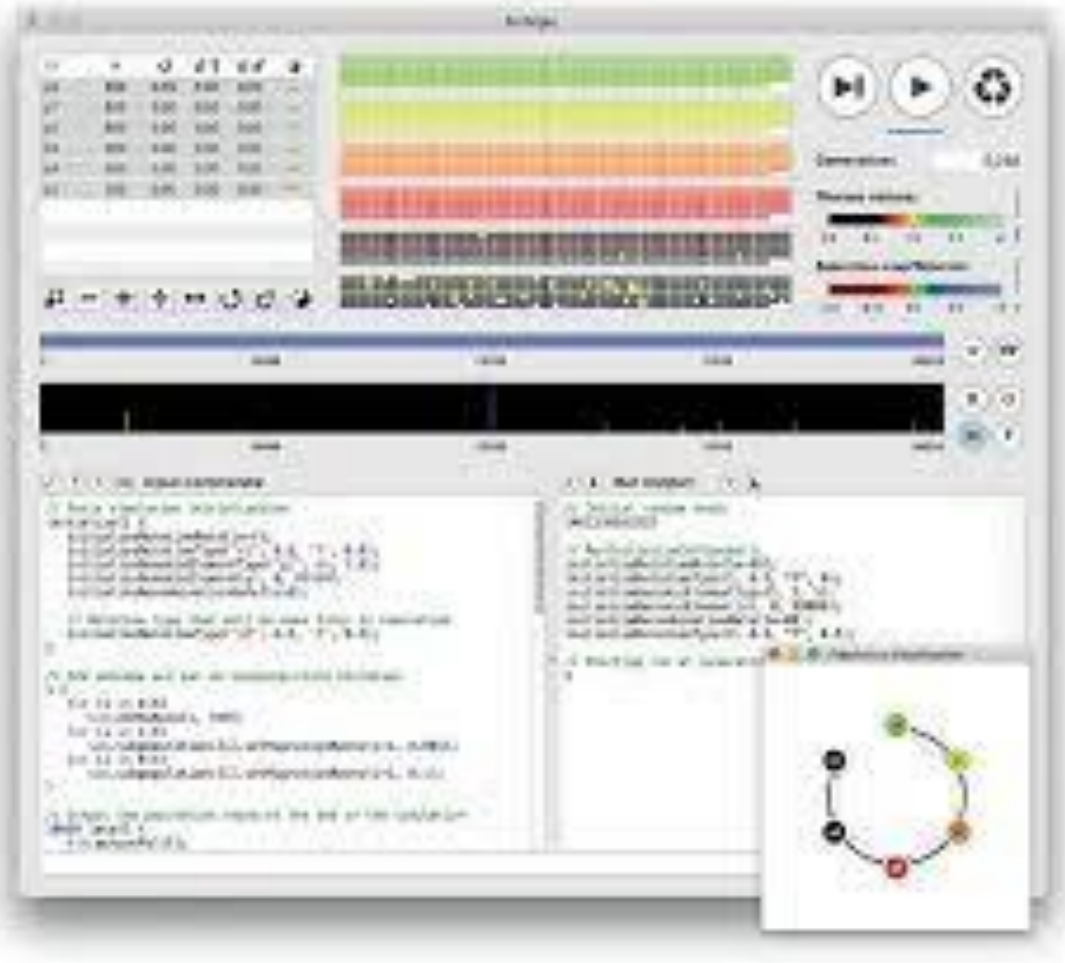
SLiM: An Evolutionary Simulation Framework

Benjamin C. Haller and Philipp W. Messer

Dept. of Computational Biology
Cornell University, Ithaca, NY 14853

Correspondence: bhaller@benhaller.co





Simulate Genetic Data – other options

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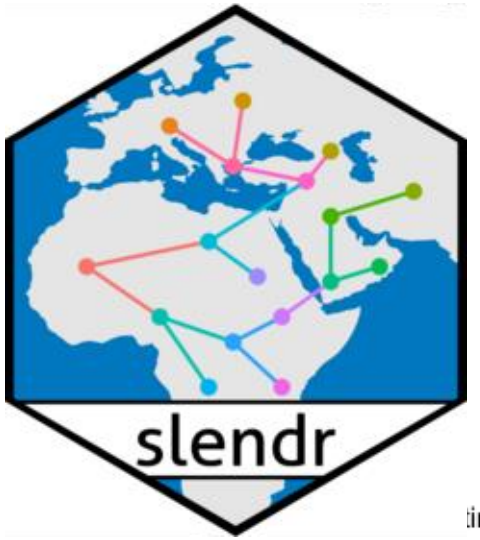
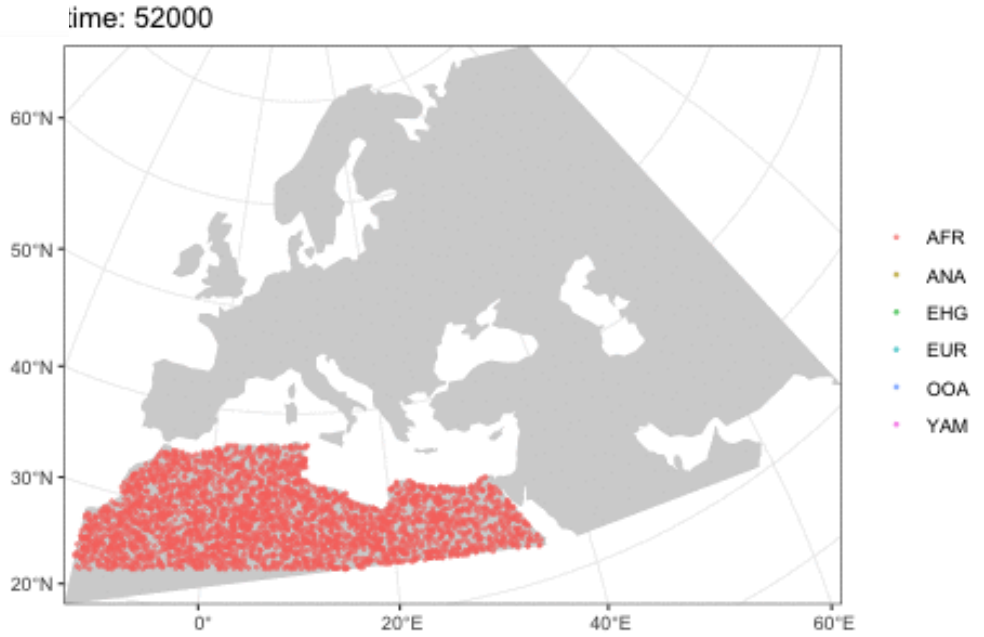




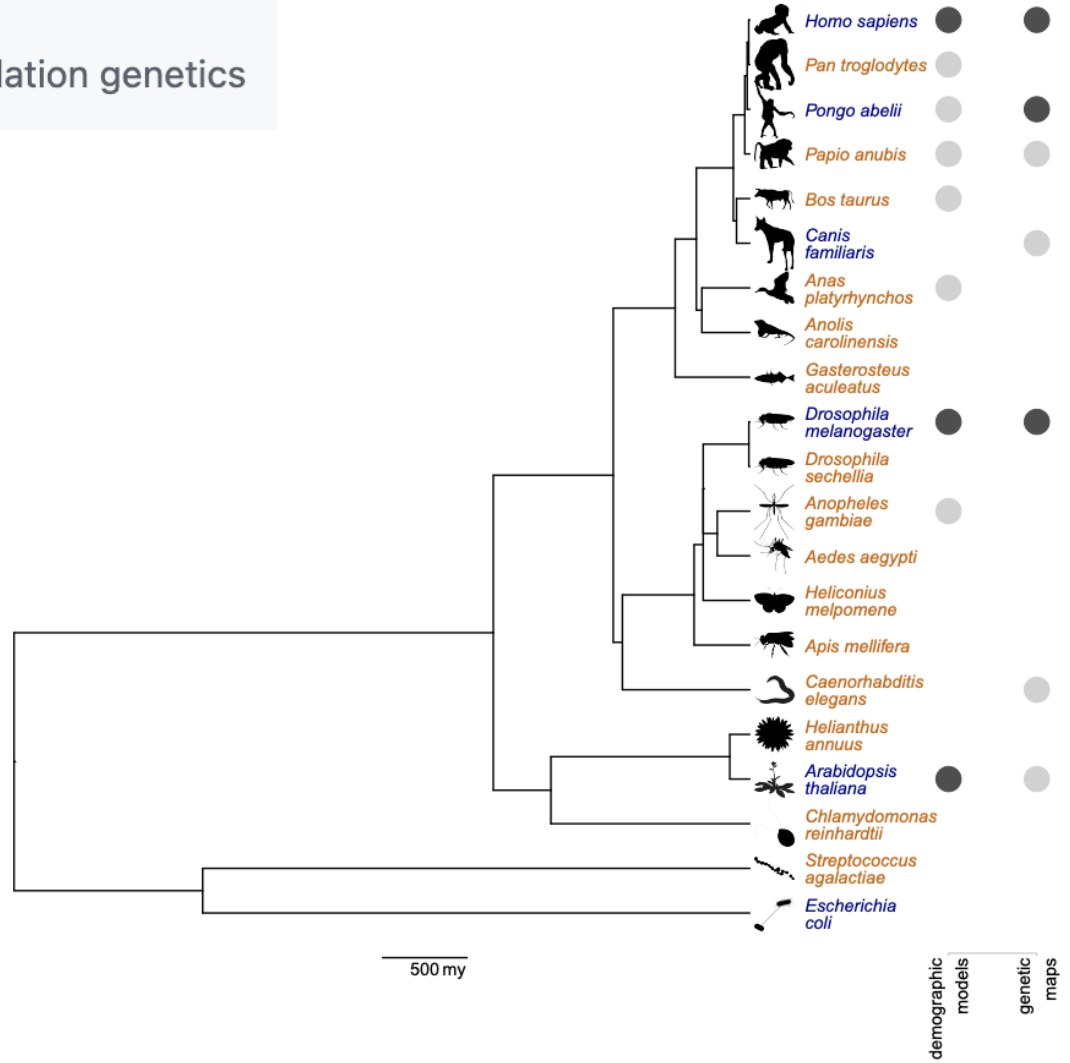
Simulate Genetic Data – other options

PopSim Consortium

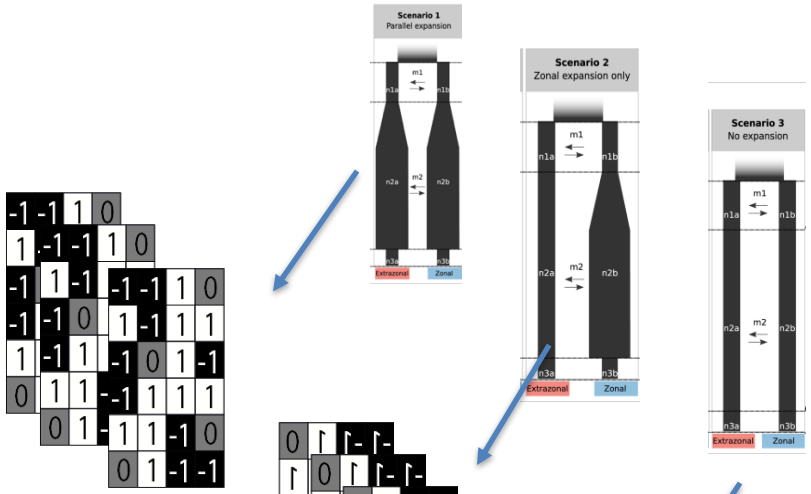
A community-driven effort to standardize population genetics

Expanding the **stdpopsim** species catalog, and lessons learned for realistic genome simulations

M. Elise Lauterbur[1,+], Maria Izabel A. Cavassim[2,*], Ariella L. Gladstein[3,*], Graham Gower[4,*], Nathaniel S. Pope[5*], Georgia Tsambos[6,*], Jeff Adrion[5,7], Saurabh Belsare[5], Arjun Biddanda[8], Victoria Caudill[5], Jean Cury[9], Ignacio Echevarria[10], Benjamin C. Haller[11], Ahmed R. Hasan[12,13], Xin Huang[14,15], Leonardo Nicola Martin Iasi[16], Ekaterina Noskova[17], Jana Obšteter[18], Vitor Antonio Corrêa Pavinato[19], Alice Pearson[20,21], David Peede[22,23], Manolo F. Perez[24], Murillo F. Rodrigues[5], Chris C. R. Smith[5], Jeffrey P. Spence[25], Anastasia Teterina[5], Silas Tittes[5], Per Unneberg[26], Juan Manuel Vazquez[27], Ryan K. Waples[28], Anthony Wilder Wohns[29], Yan Wong[30], Franz Baumdicker[31], Reed A. Cartwright[32], Gregor Gorjanc[33], Ryan N. Gutenkunst[34], Jerome Kelleher[30], Andrew D. Kern[5], Aaron P. Ragsdale[35], Peter L. Ralph[5,36], Daniel R. Schrider[37], and Ilan Gronau[38,+]



Supervised Deep learning ~ ABC



Scenario 1

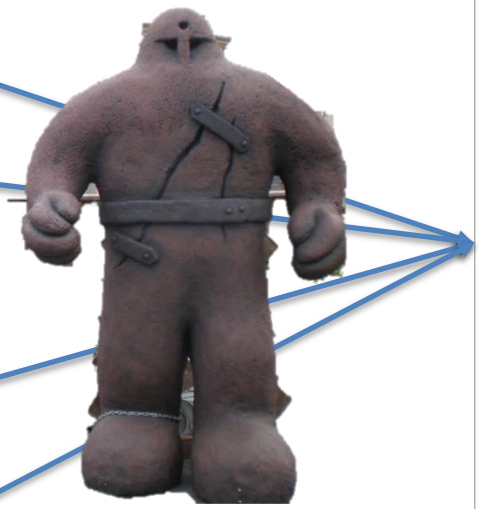
Scenario 2

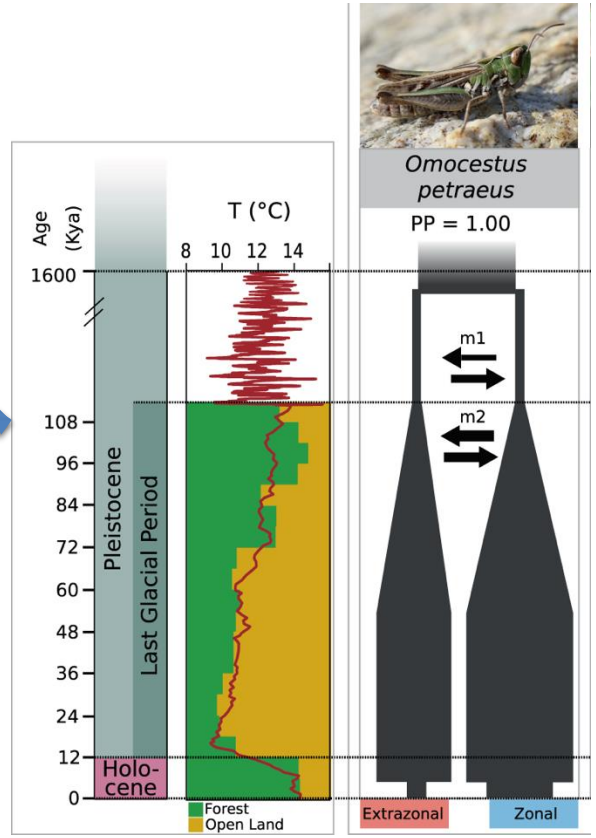
Scenario 3

Data is labeled

Parameters

	θ	T1	T2	T3	Ne
Sim1					
Sim2					
Sim3					
Sim4					





1. Define Models

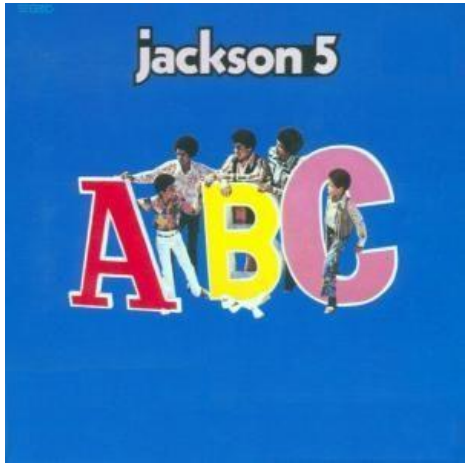
2. Sample parameters from a given distributions (prior)

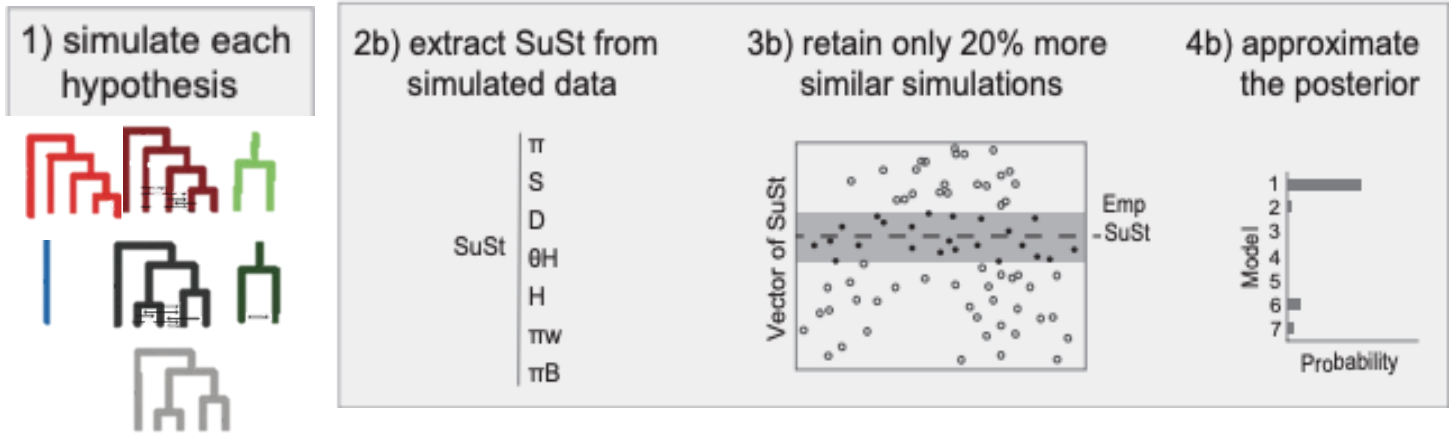
3. Simulate data for each model using the sampled parameter values

4. Calculate Summary Statistics (SuSt) from simulations and from the empirical data

5. Compare simulated and empirical data retaining only simulations that are more similar.

ABC





Modified from
Perez et al. (2022) *Mol Ecol Res*

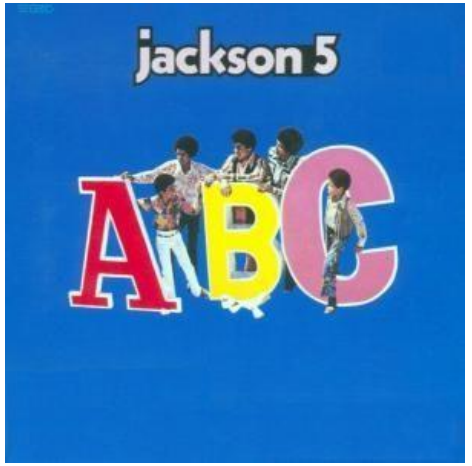
ABC

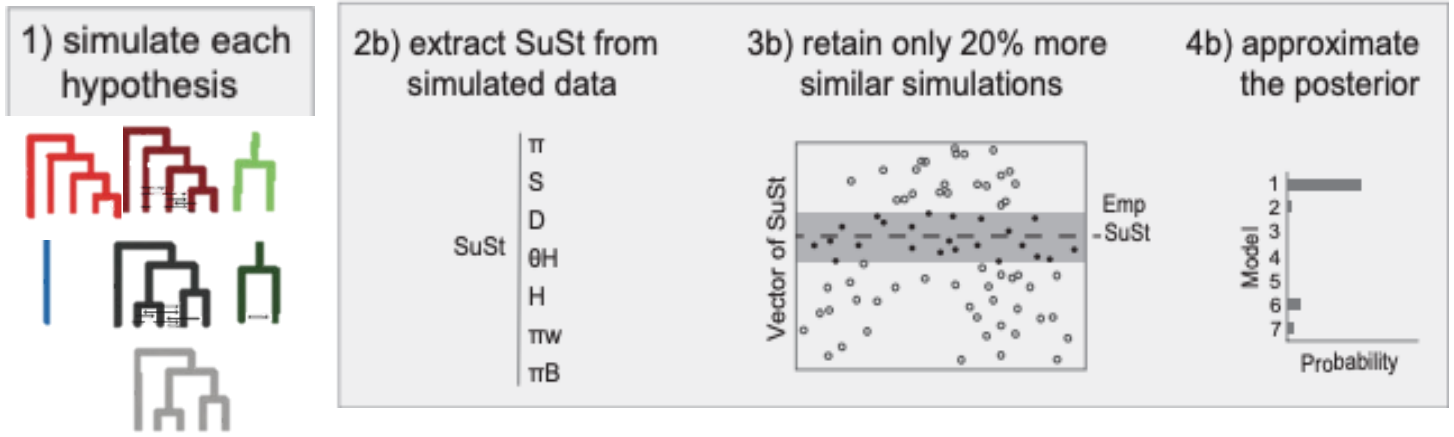
ABC implies 3 **approximations**:

1. finite # simulations

2. informativeness of S

3. S don't match S* exactly





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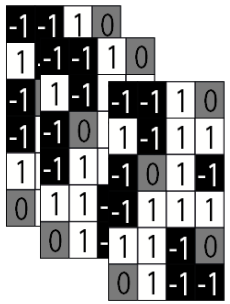
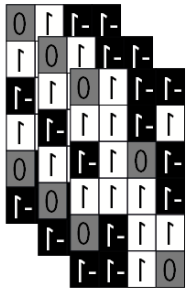
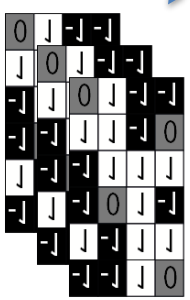
Supervised Deep Learning ~ ABC



Scenario 1

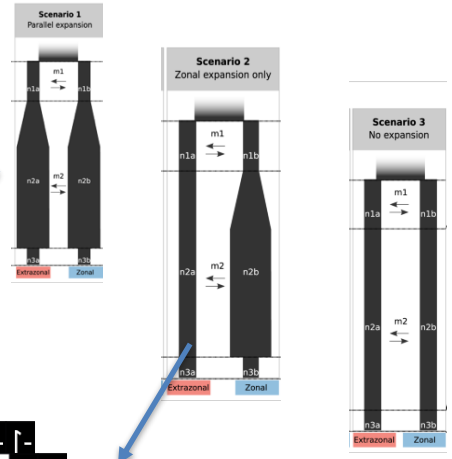


Scenario 2



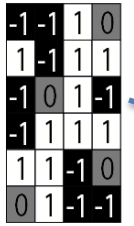
Scenario 3

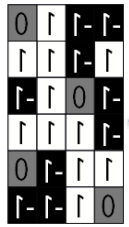
Data is labeled

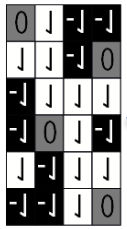


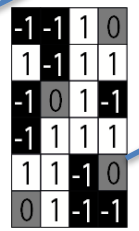
Parameters

	θ	T1	T2	T3	Ne
Sim1					
Sim2					
Sim3					
Sim4					









DL witchcraft

Cuca – Brazilian Legend

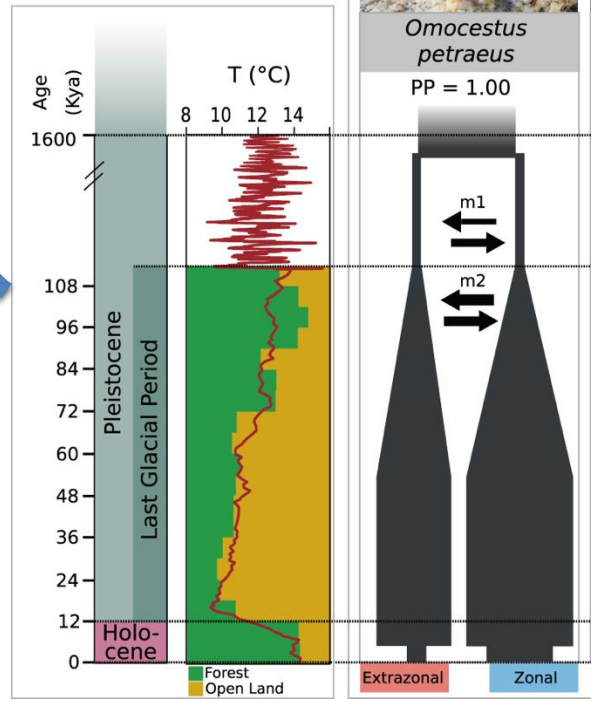
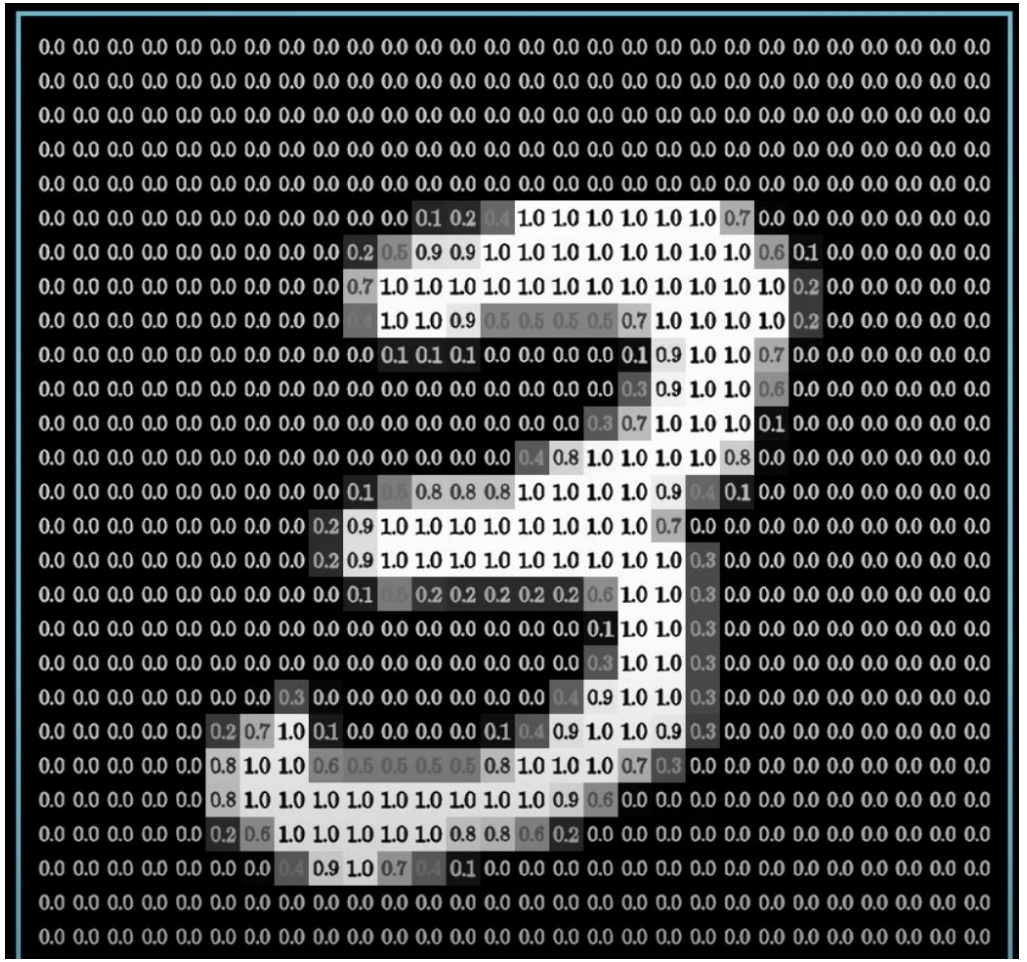


Image recognition

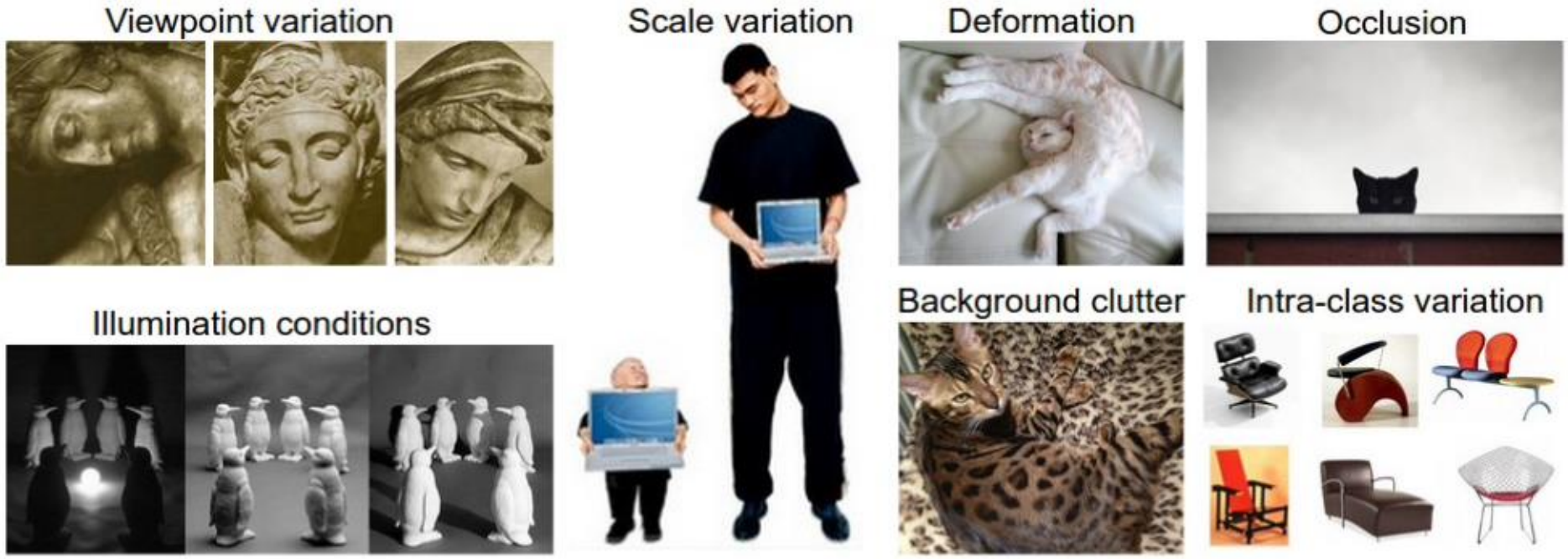
What do you see?

What the computer sees?



https://www.3blue1brown.com/lessons/neural-networks

Challenges



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

Image recognition

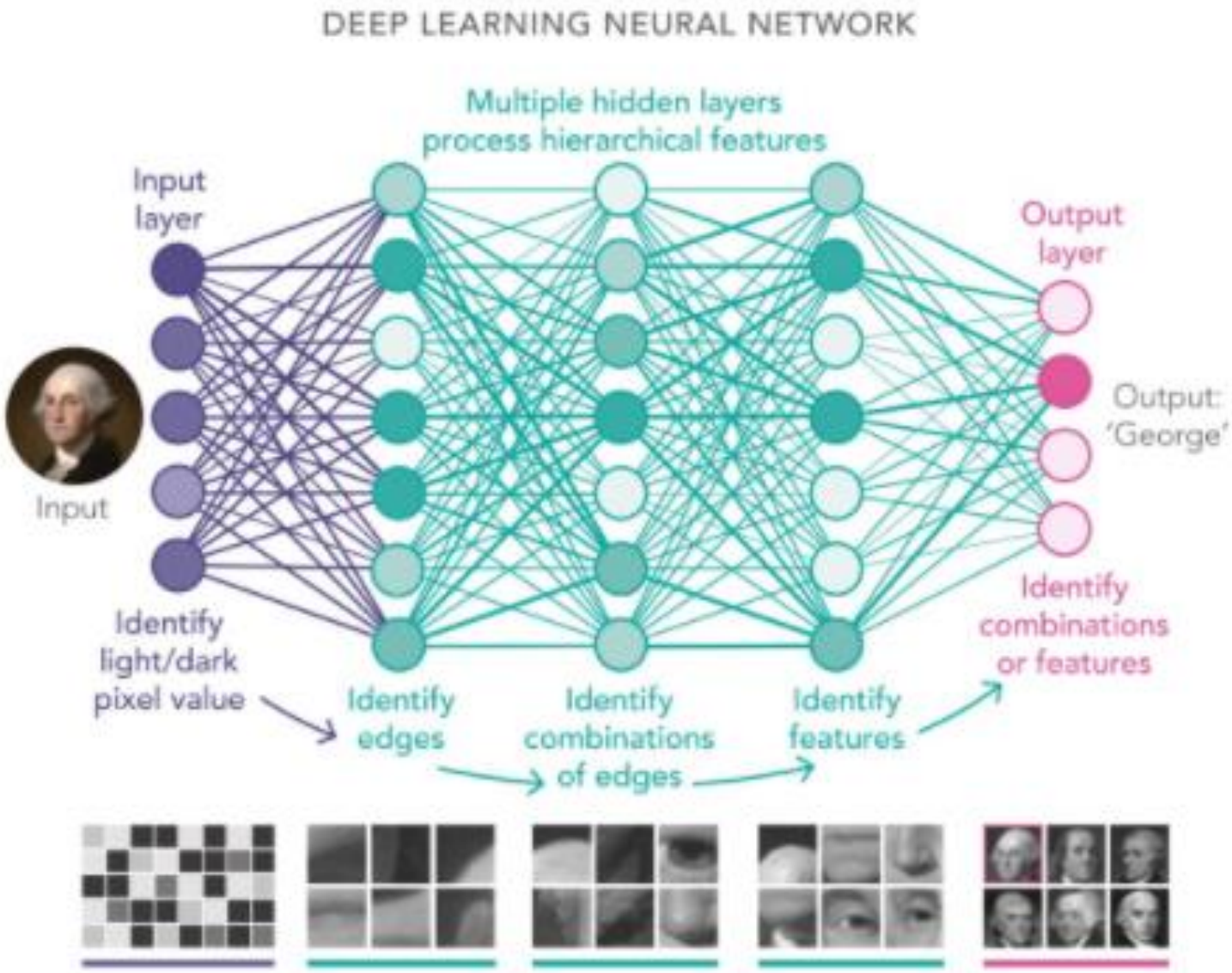
Data-Driven approach (need a large training set)

The MNIST dataset (70,000 hanwritten numbers)

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

Deep Neural Networks

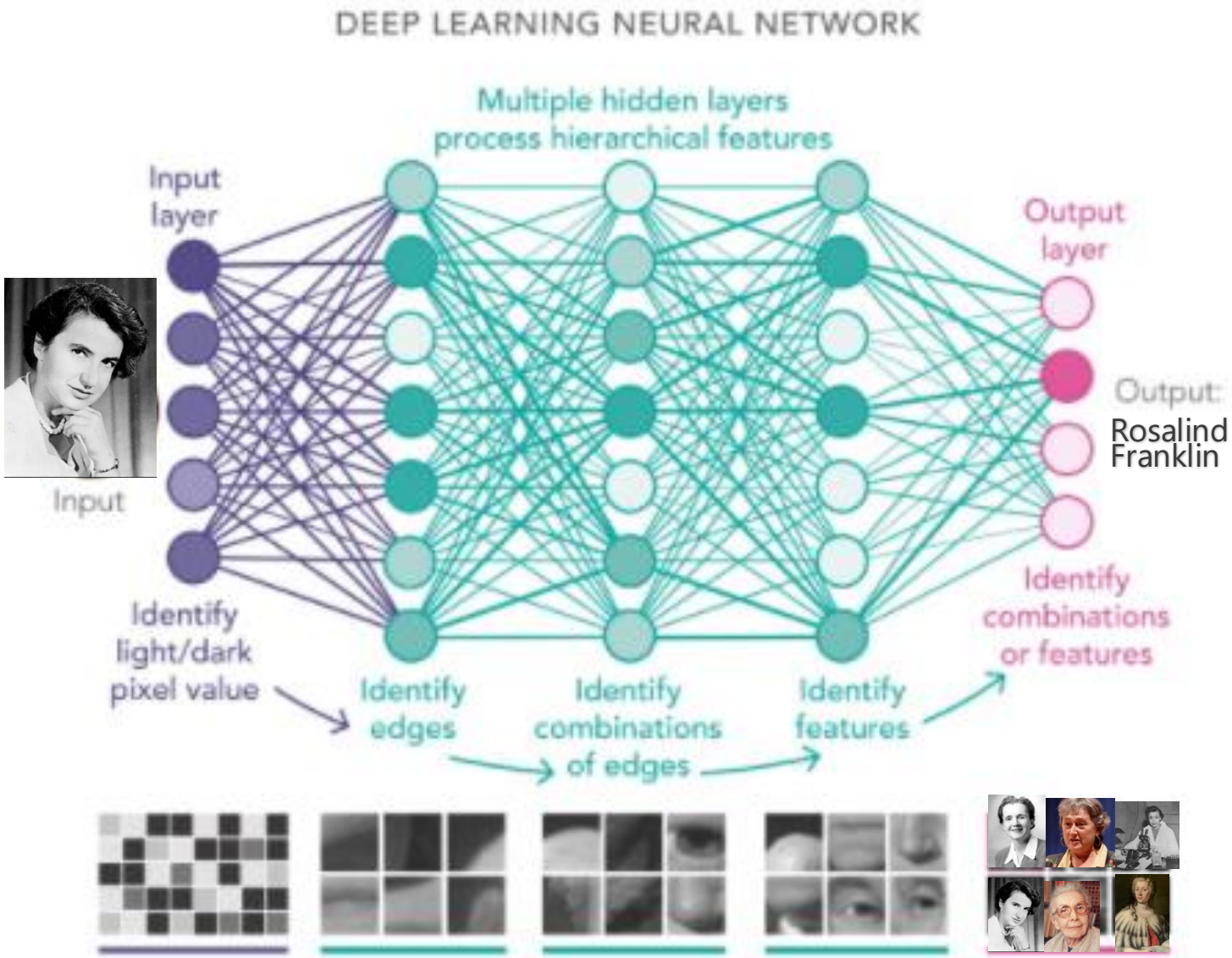
Multi-Layer Perceptron (MLP)



Waldrop (2019) *PNAS*

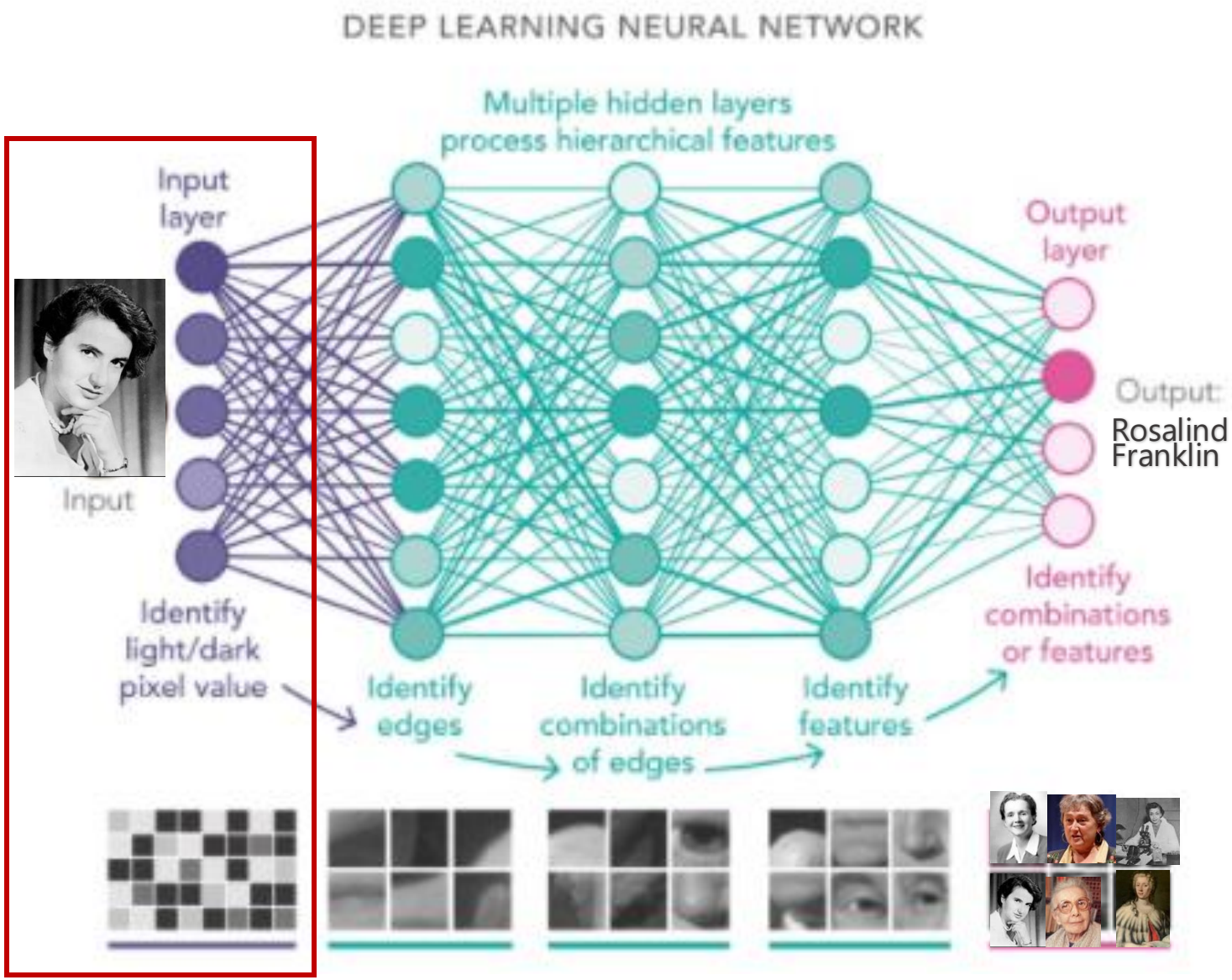
Deep Neural Networks

Multi-Layer Perceptron (MLP)



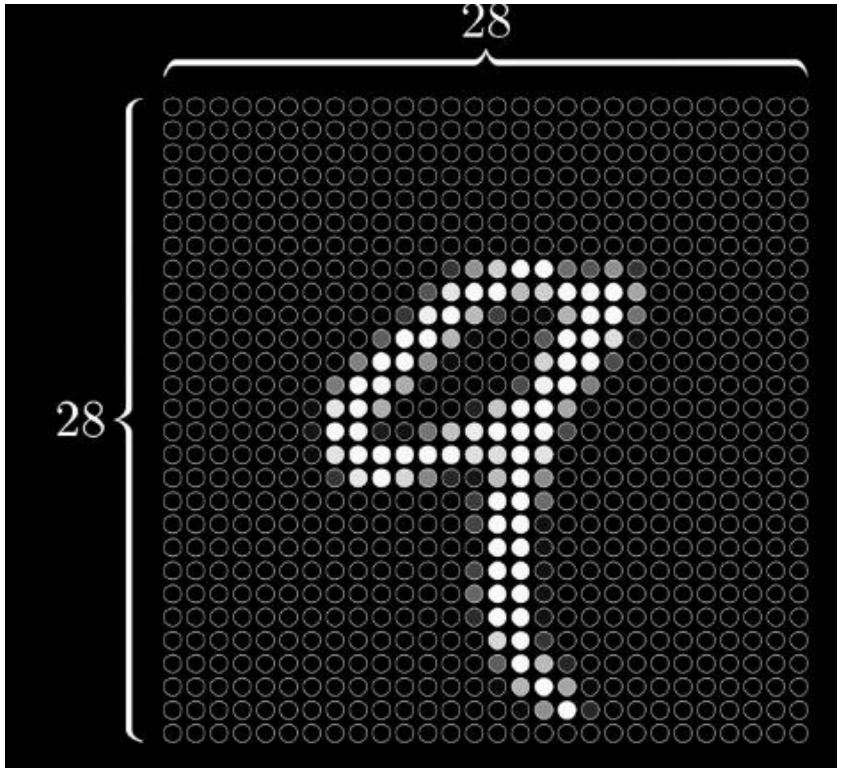
Adapted from Waldrop (2019)
PNAS

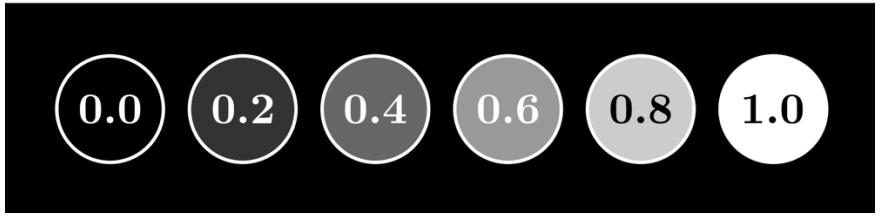
Deep Neural Networks

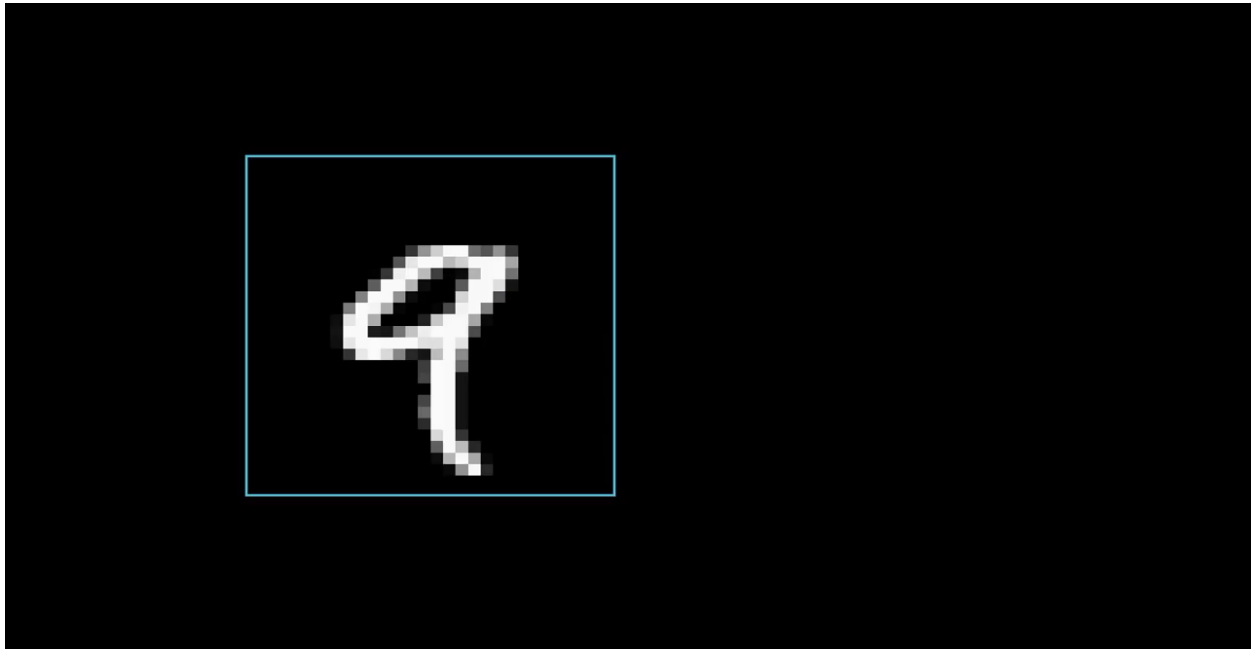


Adapted from Waldrop (2019)
PNAS

Input Layer

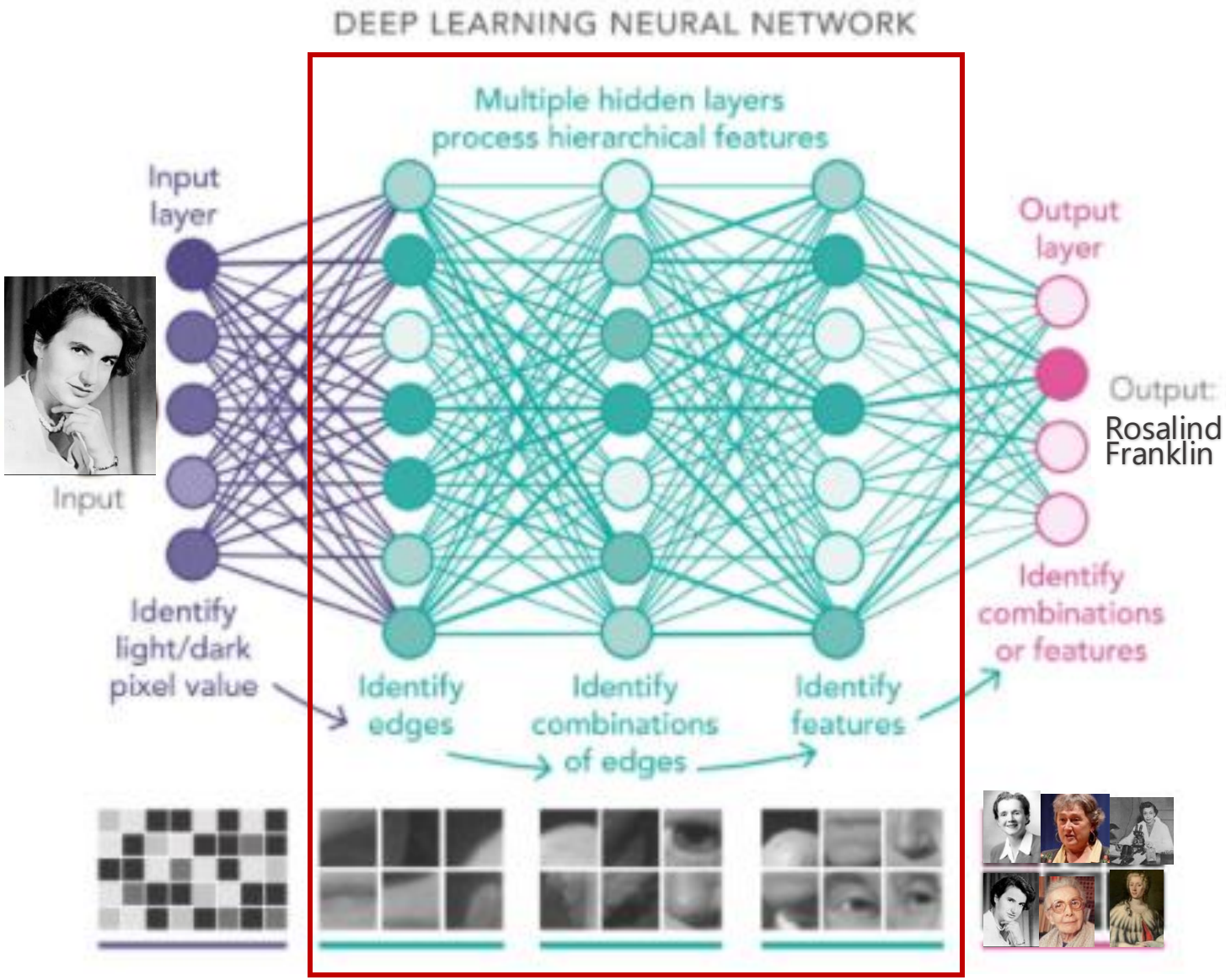






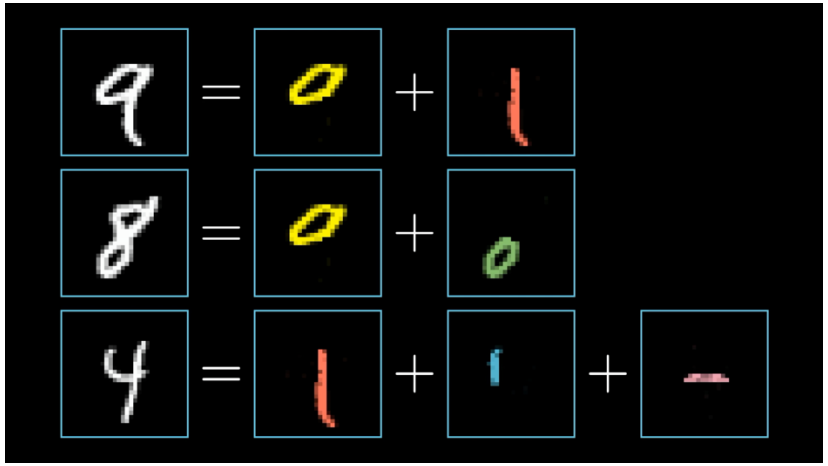
https://www.3blue1brown.com/lessons/neural-networks

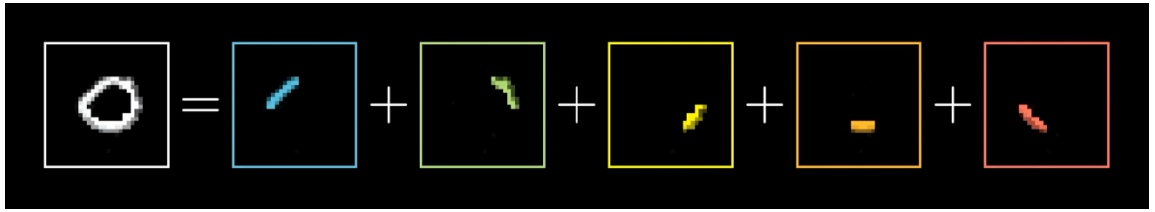
Deep Neural Networks

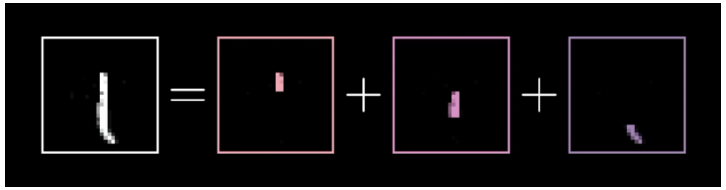


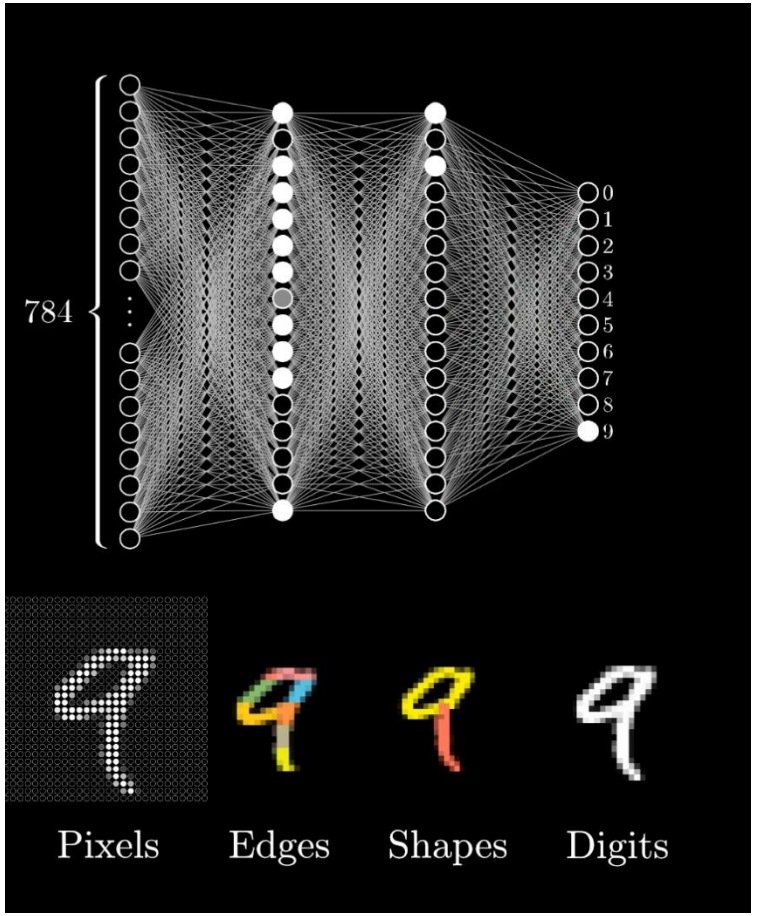
Adapted from Waldrop (2019)
PNAS

Hidden Layers process hierarchical features



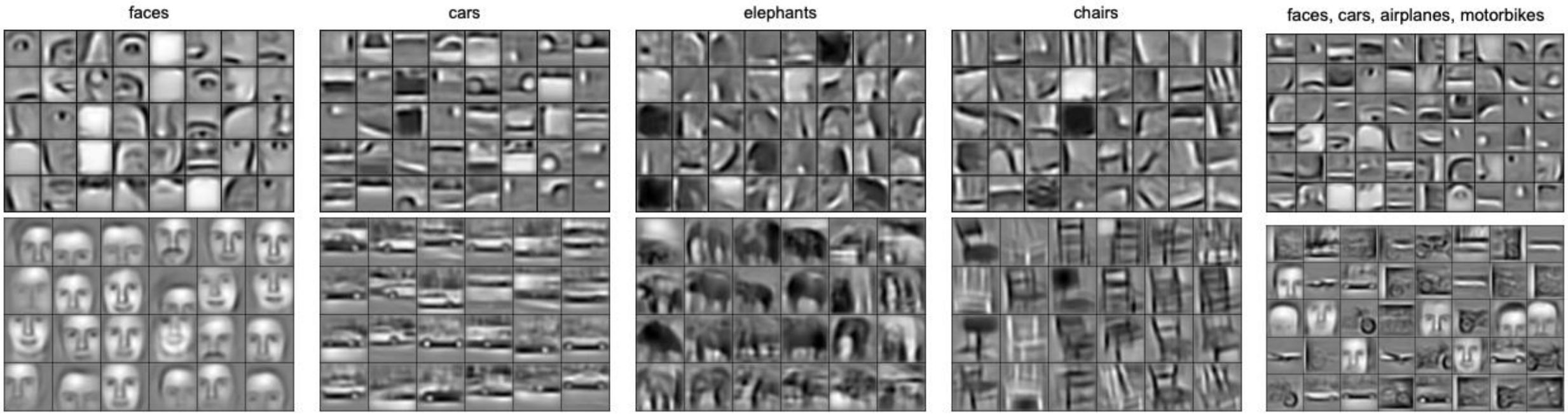






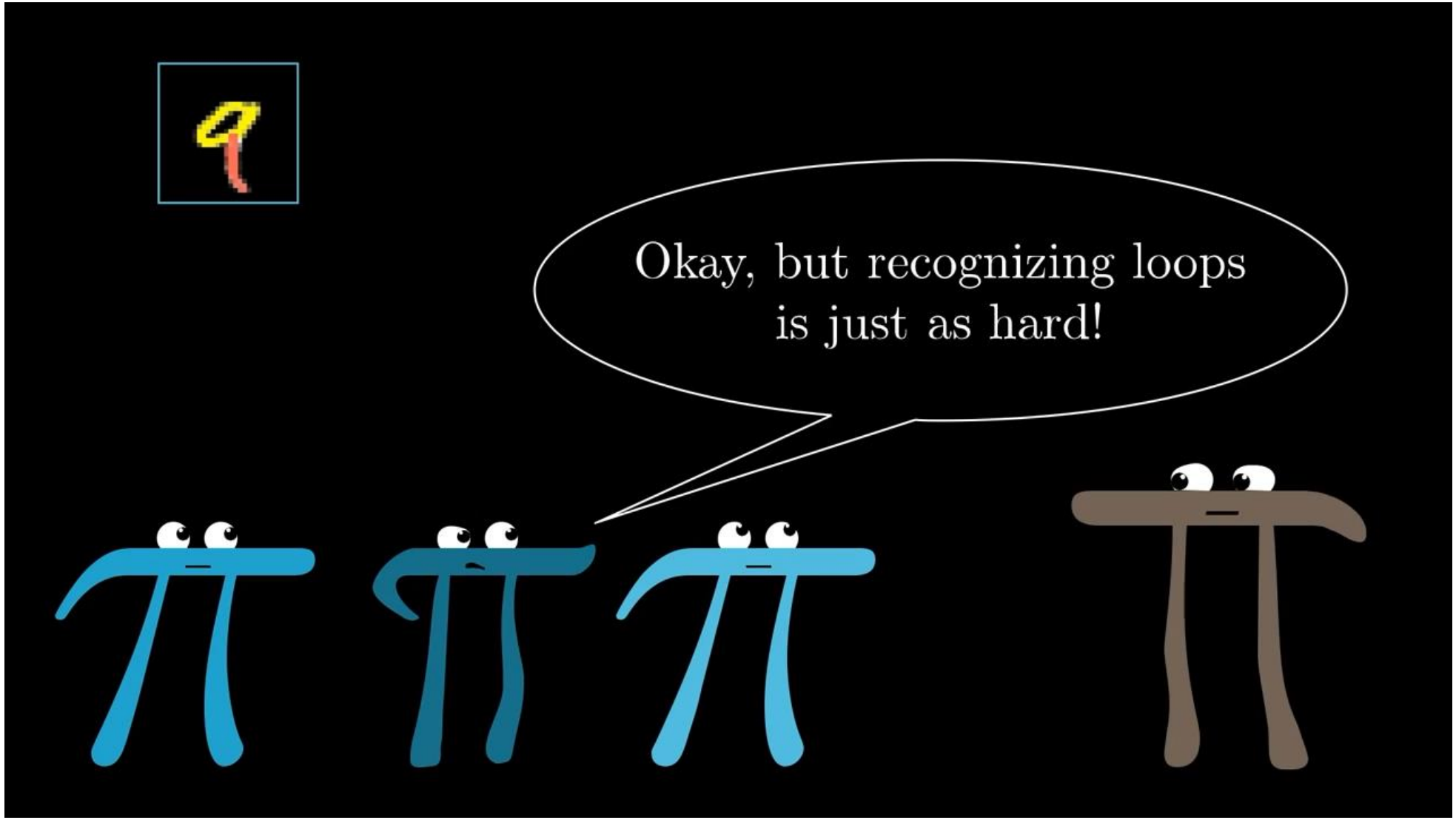
https://www.3blue1brown.com/lessons/neural-networks

Hidden Layers process hierarchical features



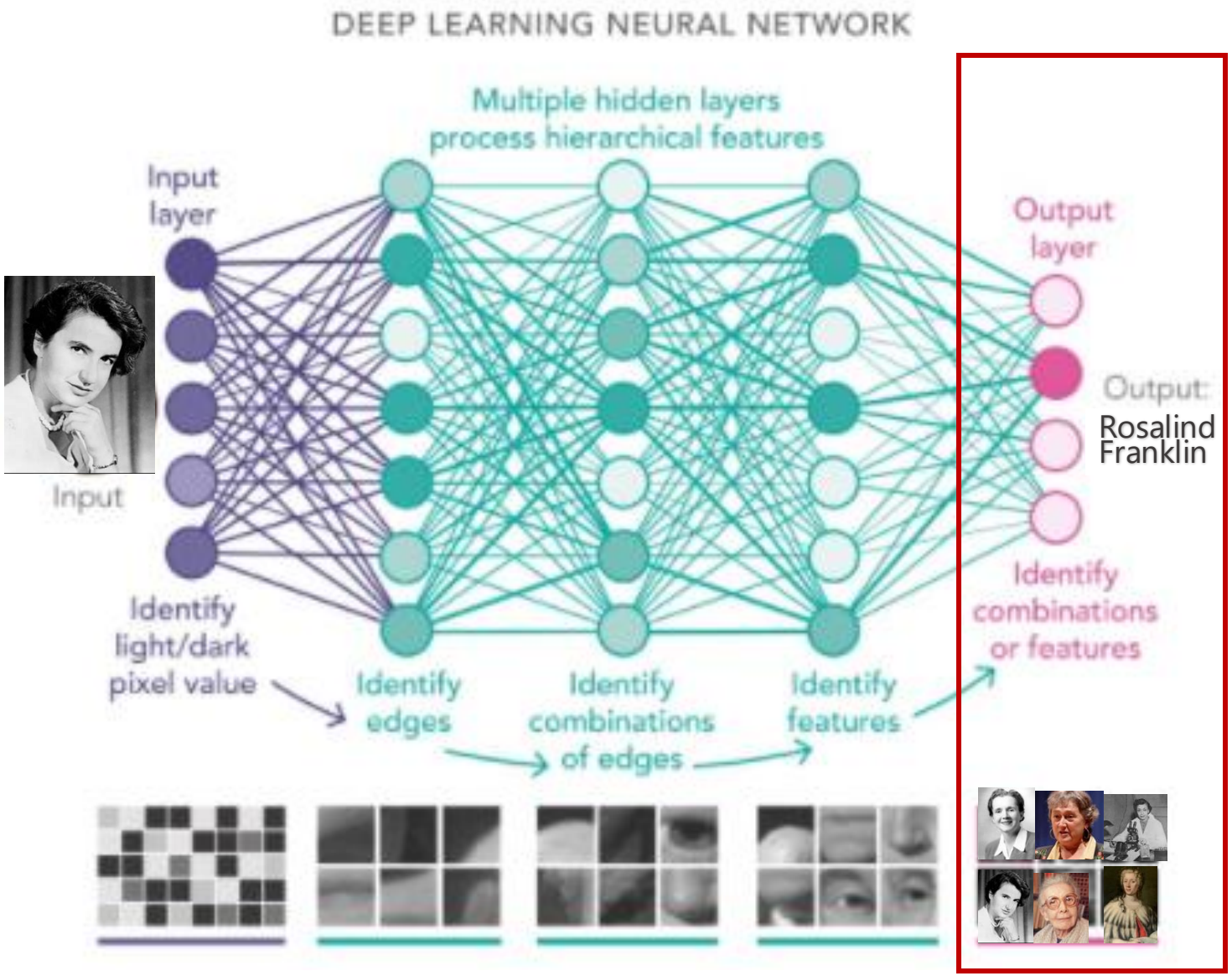
Lee et al. 2009

Hidden Layers process hierarchical features



https://www.3blue1brown.com/lessons/neural-networks

Deep Neural Networks

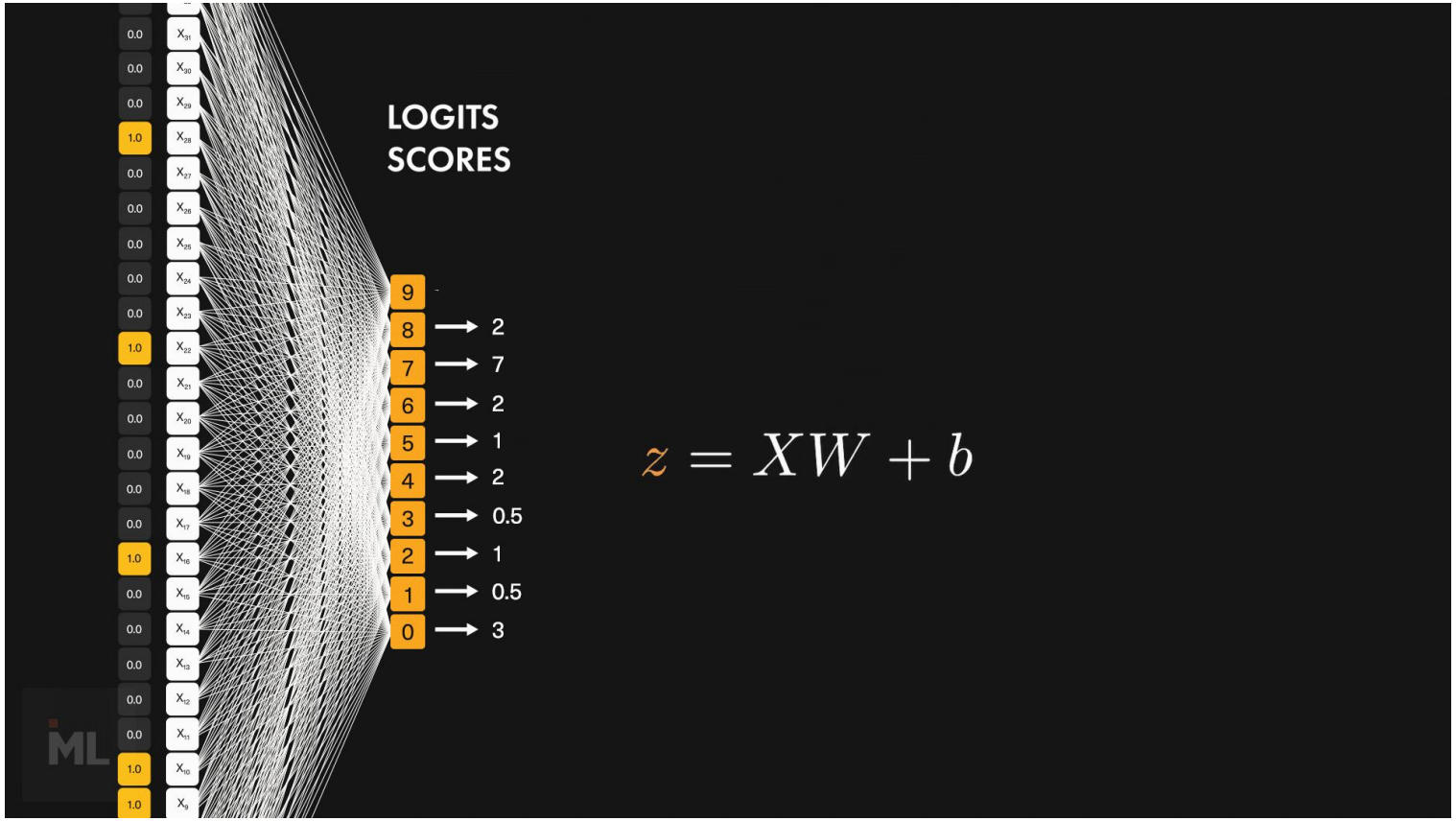


Adapted from Waldrop (2019)
PNAS

Output activation function

Softmax for classification tasks

- Outputs the “probability” of each class

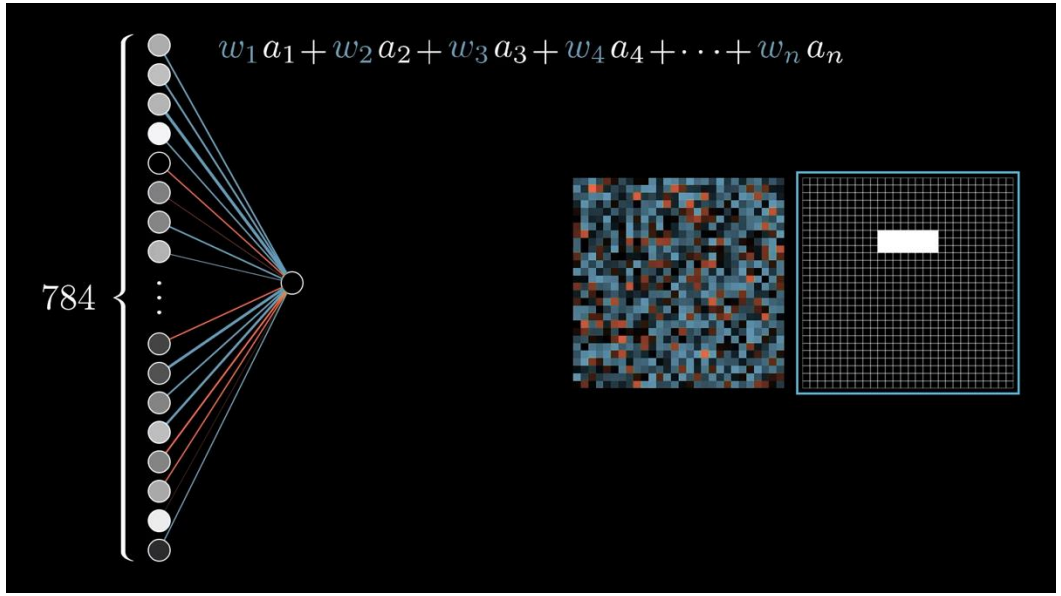


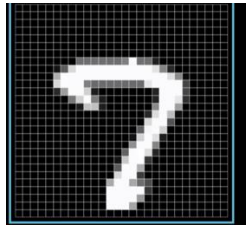
- **Practical Exercise 1:**

- Access https://www.3blue1brown.com/lessons/neural-networks

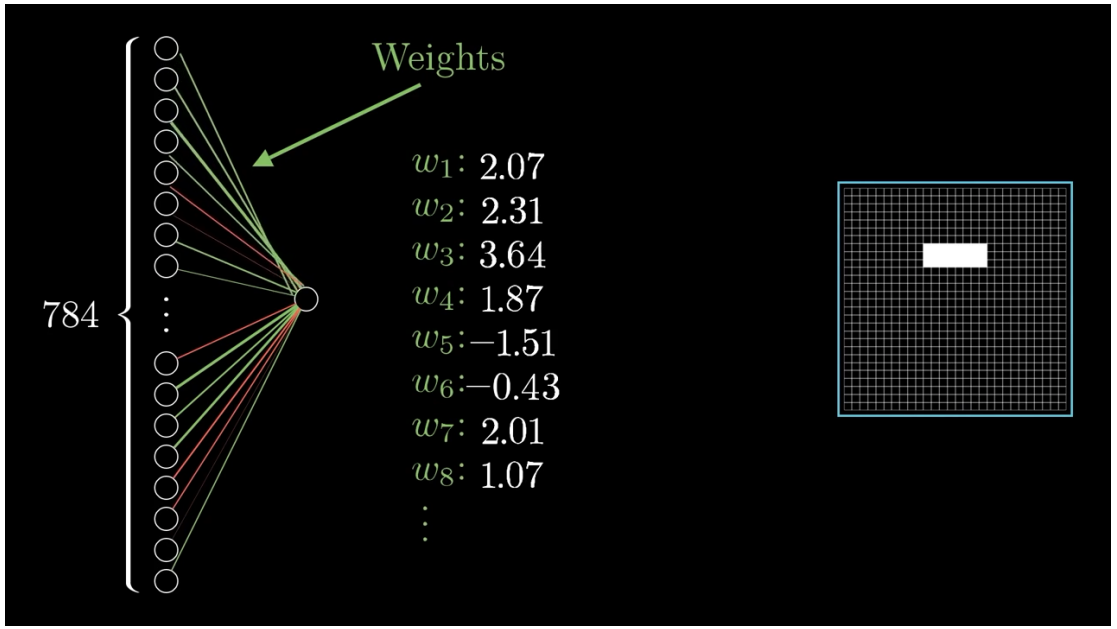
- Draw different number in the first interative exercise and look at how the hidden layers and the output layers get activated.

Network Weights



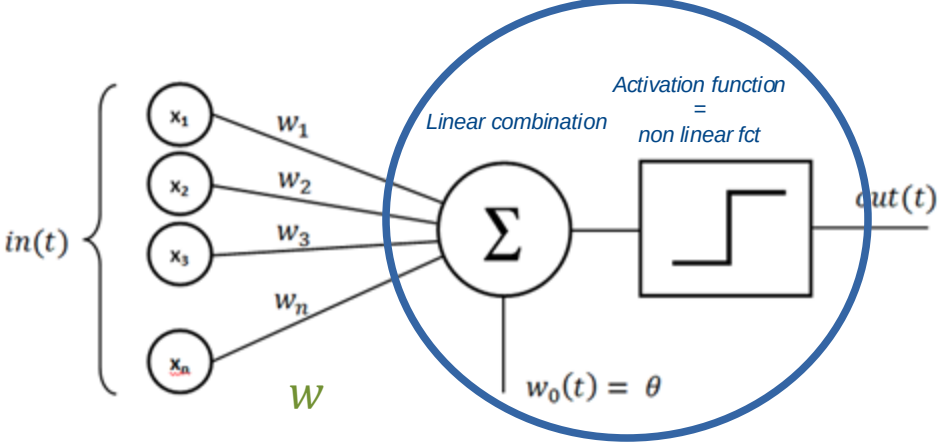


Neuron in the second layer to check whether the image contains this one, specific edge.



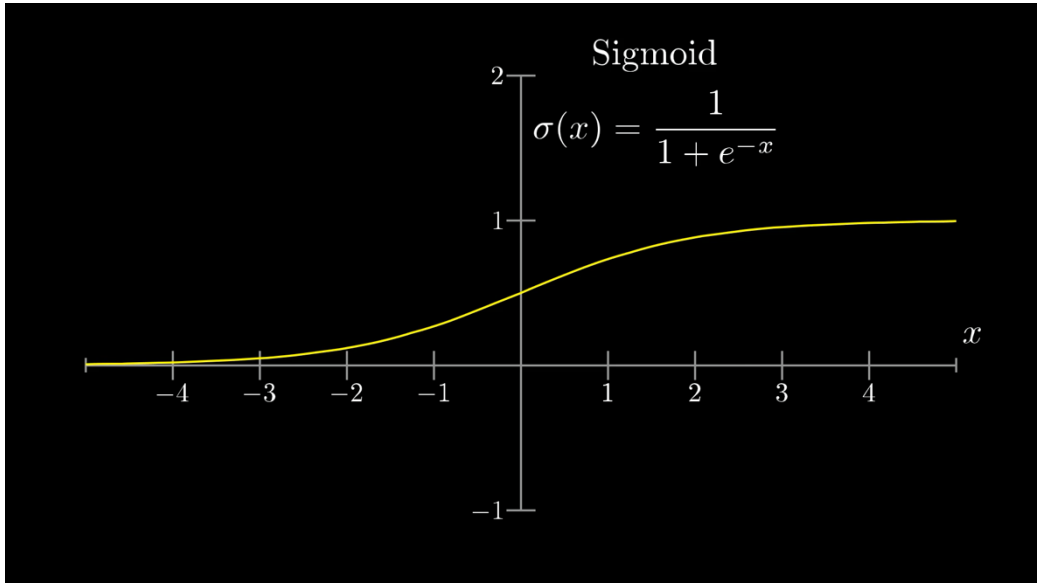
https://www.3blue1brown.com/lessons/neural-networks

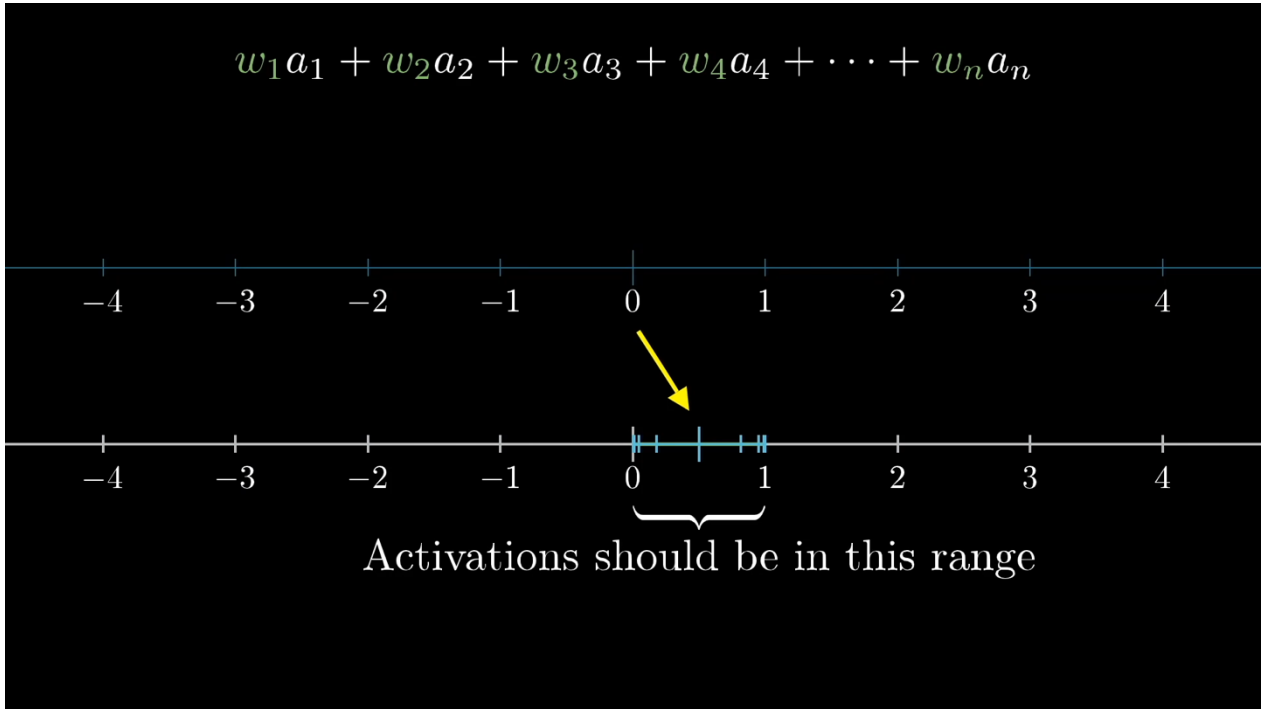
Network Weights



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

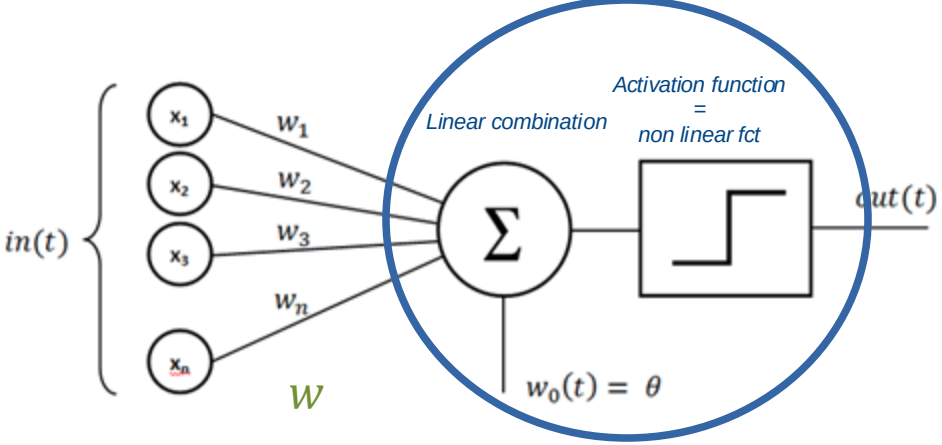
1 neuron = f (∑)
Linear comb. + Non Linear activation function f()





https://www.3blue1brown.com/lessons/neural-networks

Network Weights



1 neuron = f (∑)
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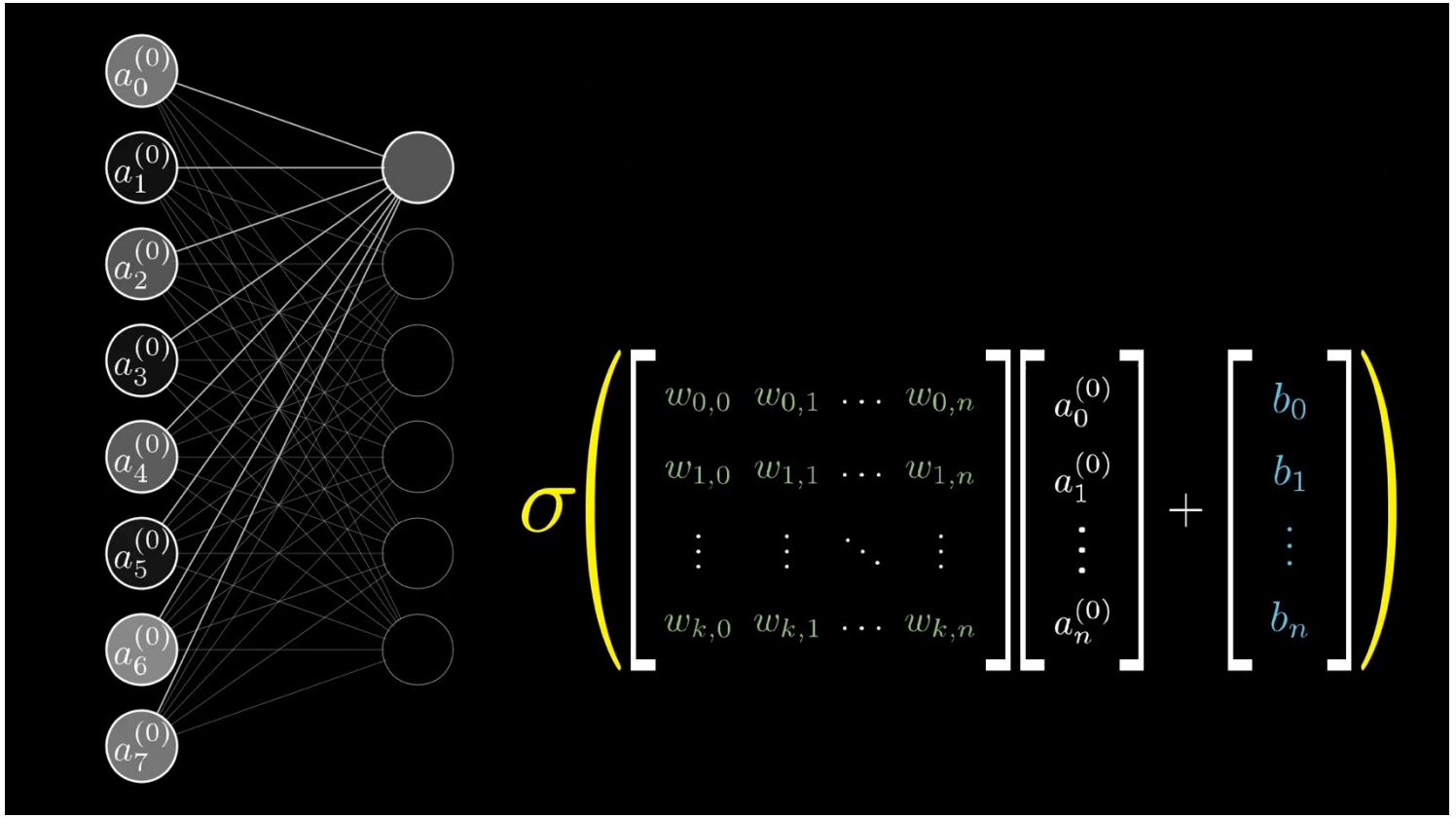
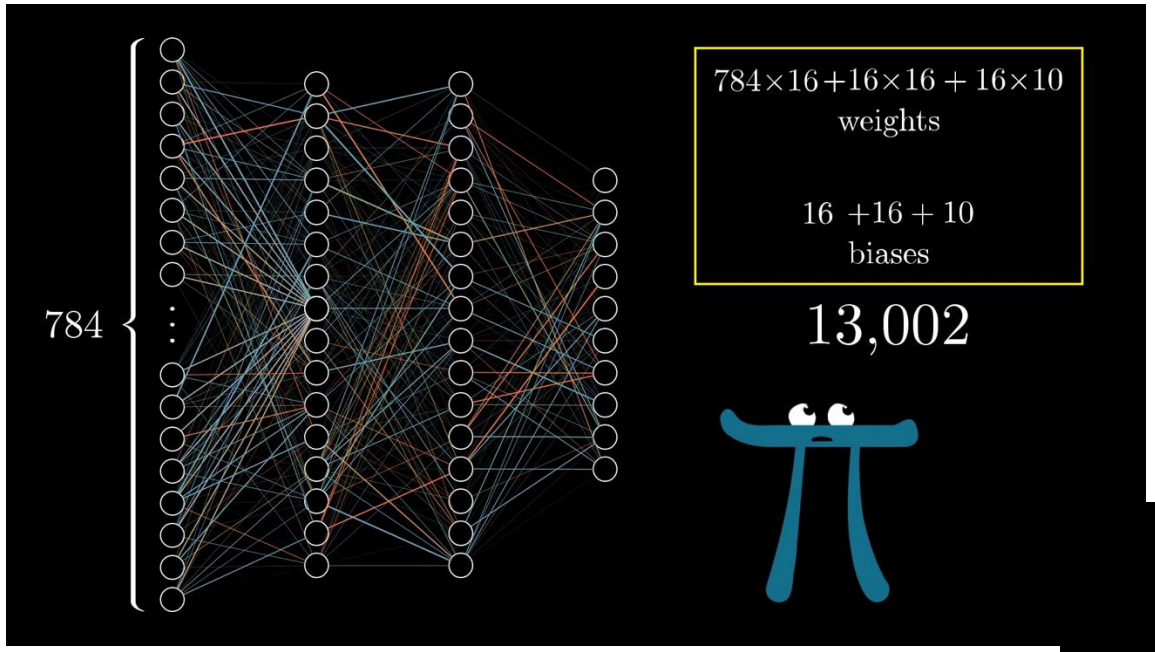
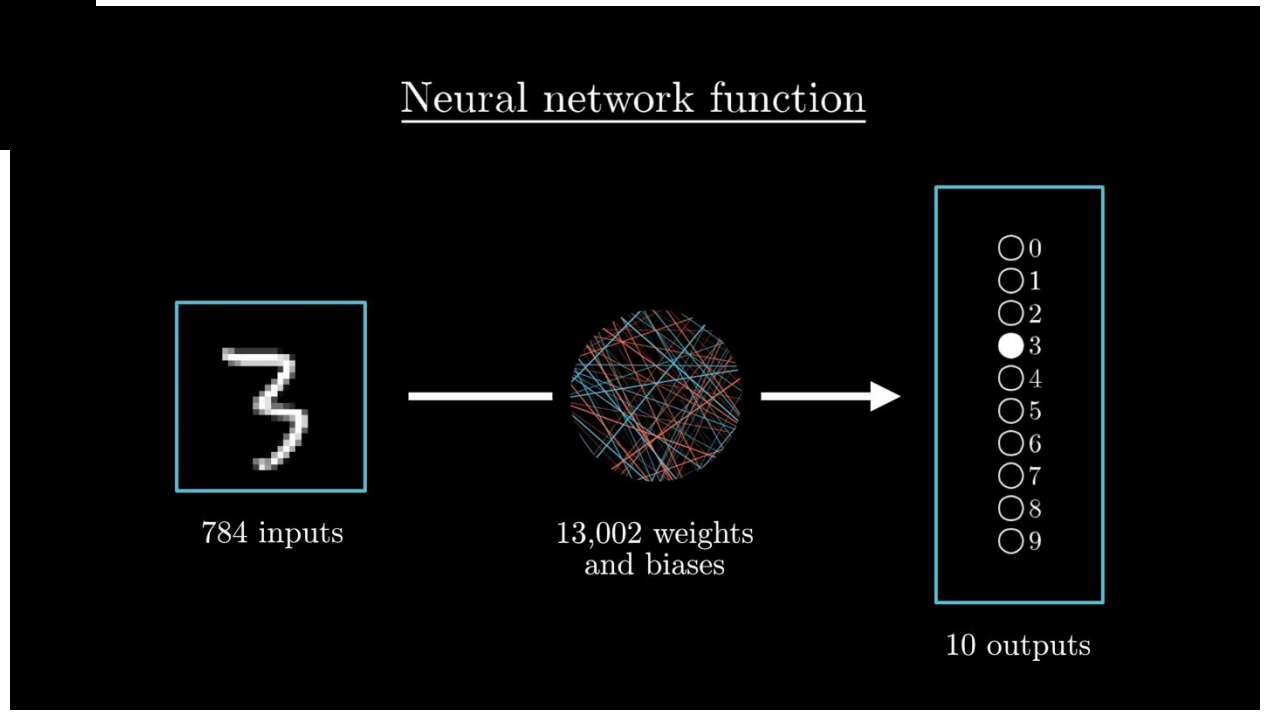


https://www.3blue1brown.com/lessons/neural-networks

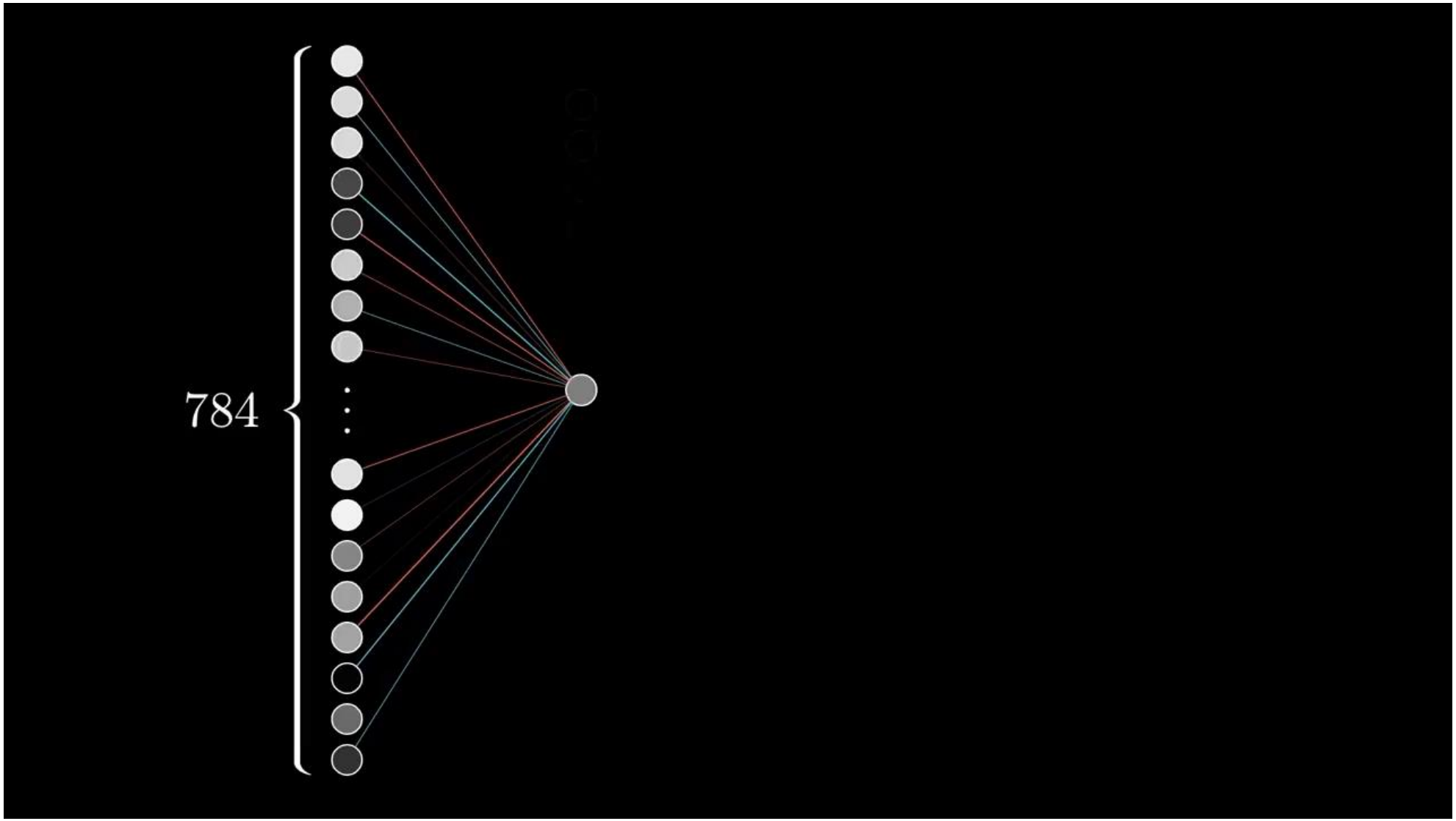
Score function





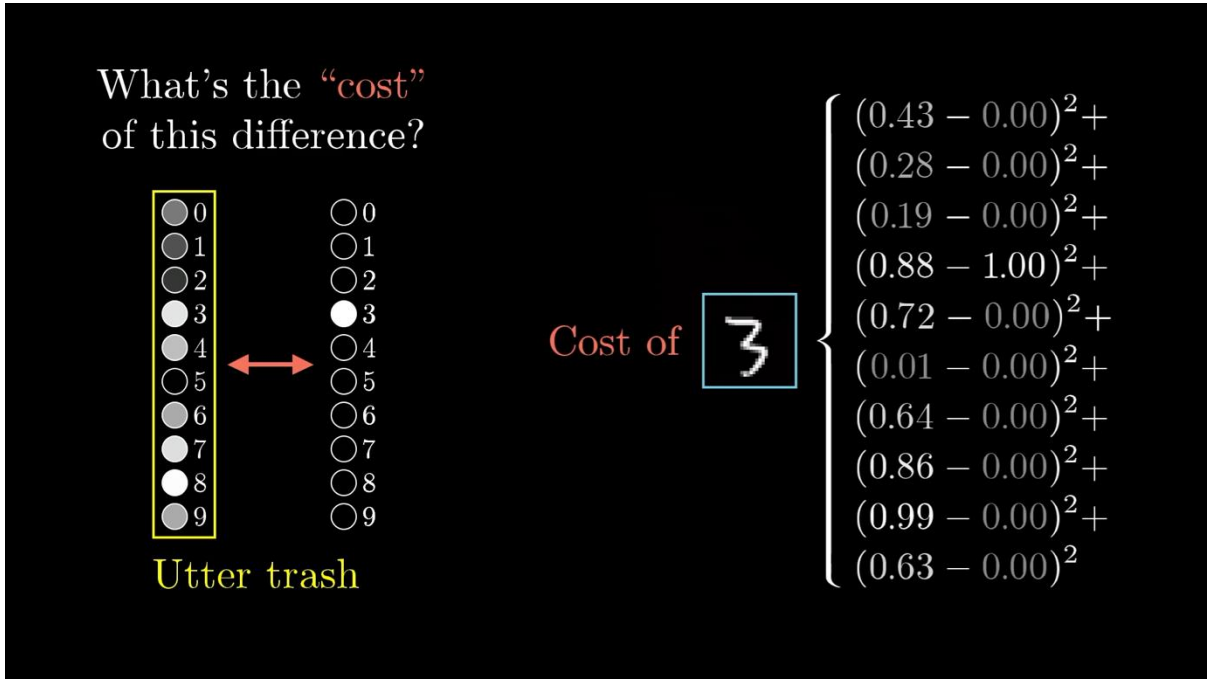
https://www.3blue1brown.com/lessons/neural-networks

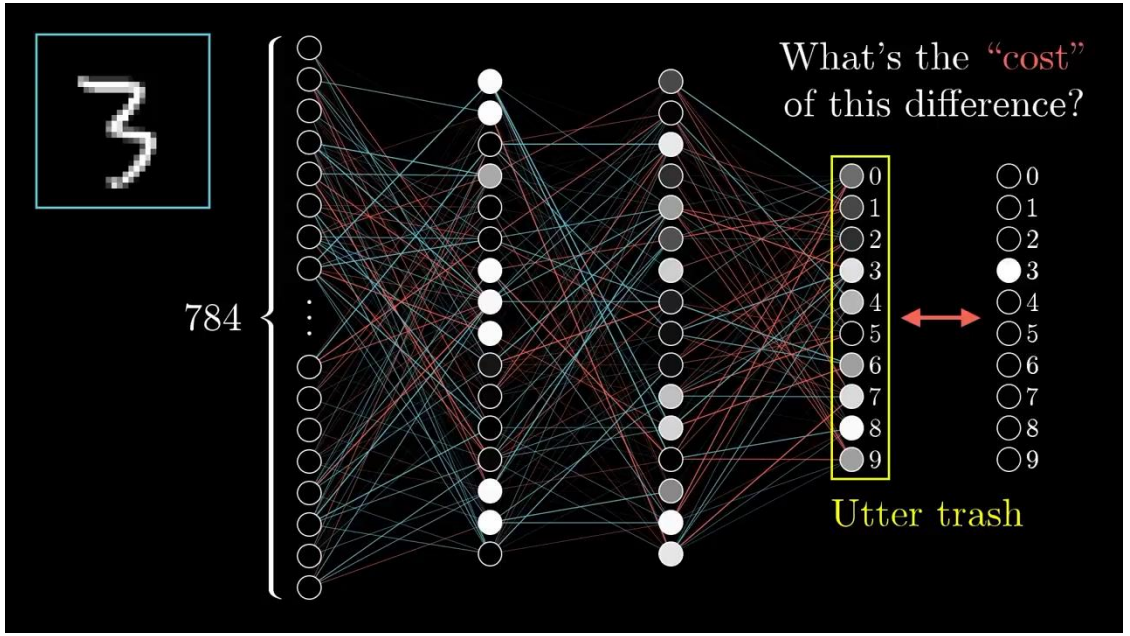
How the network learns? Cost function



https://www.3blue1brown.com/lessons/gradient-descent

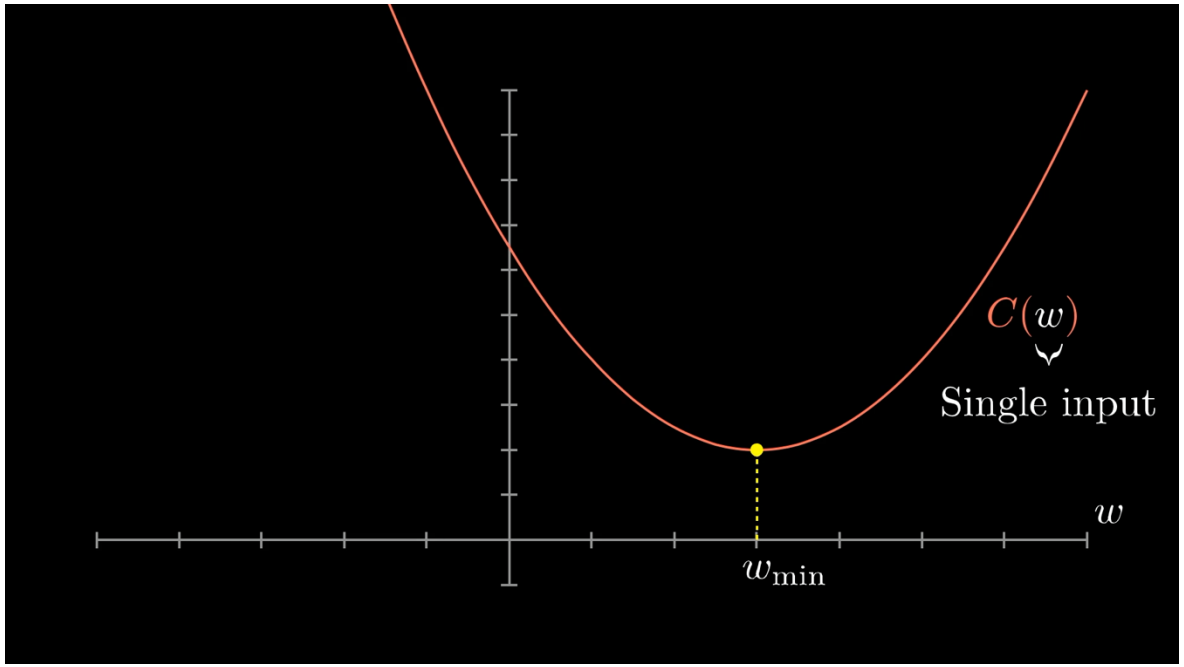
Cost Function

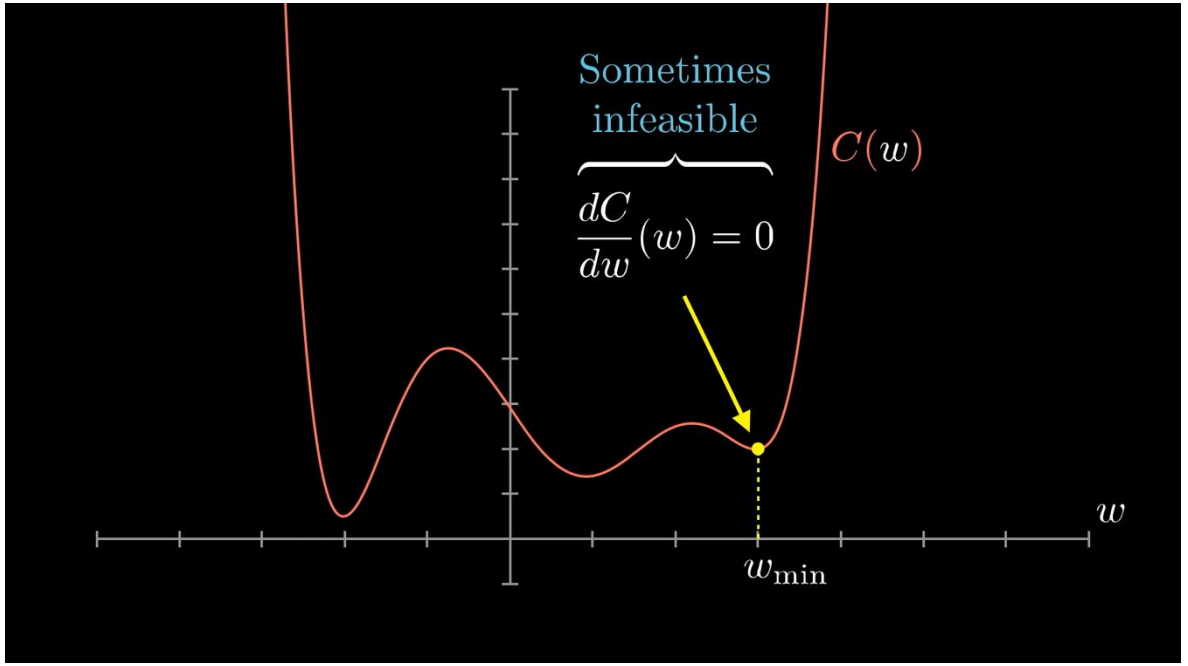




https://www.3blue1brown.com/lessons/gradient-descent

Cost Function

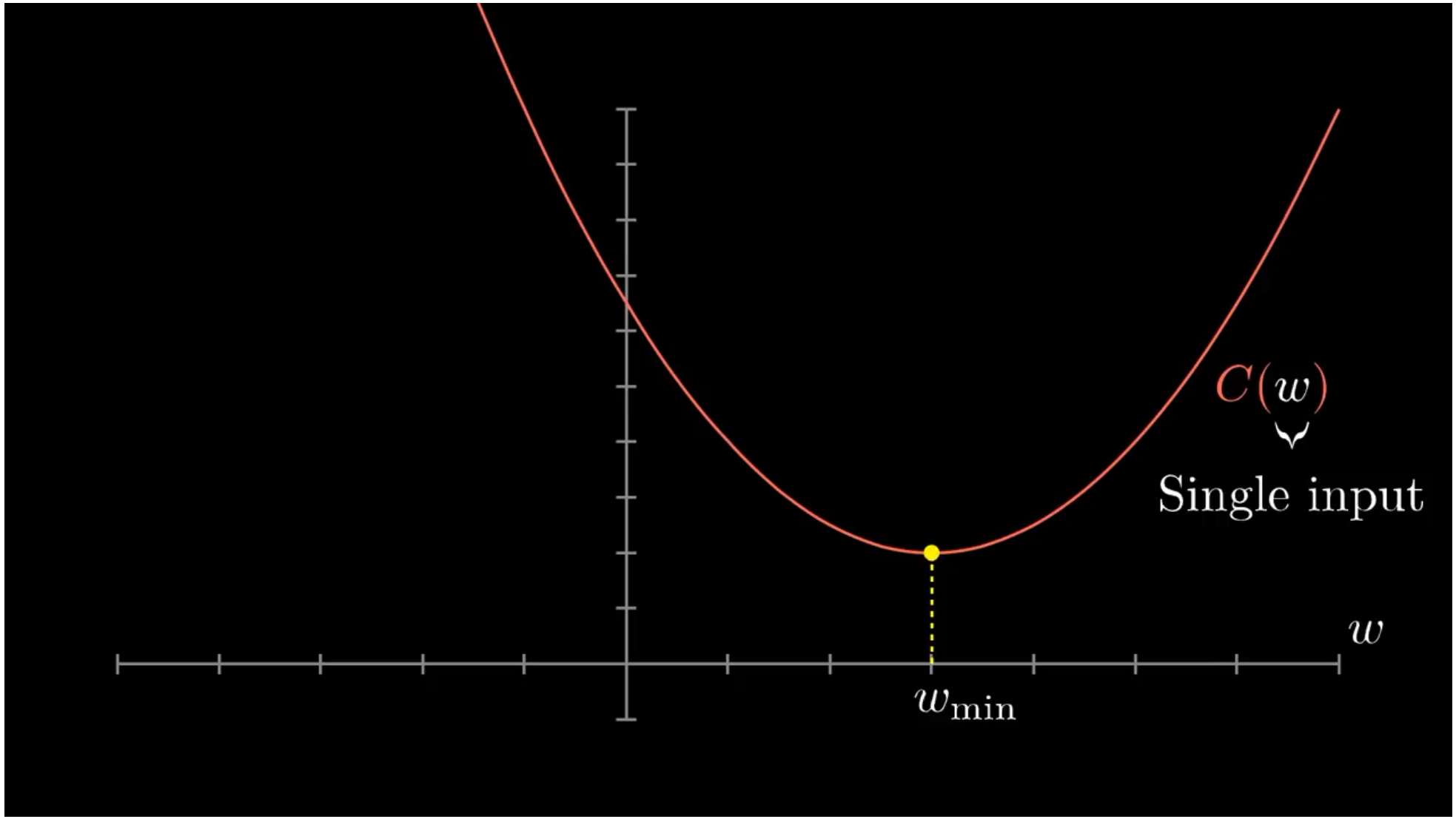




https://www.3blue1brown.com/lessons/gradient-descent

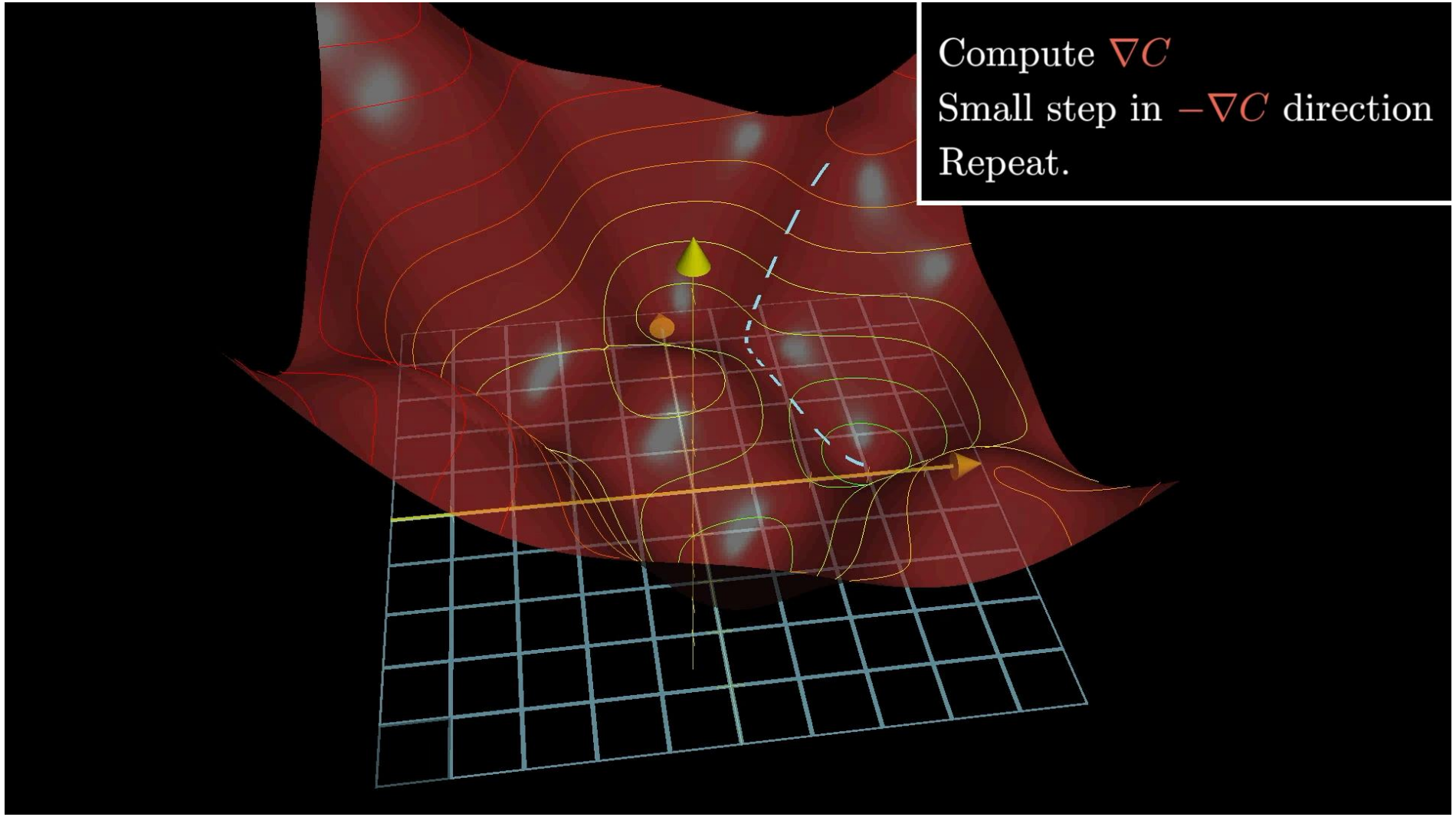
Optimization

Gradient Descent



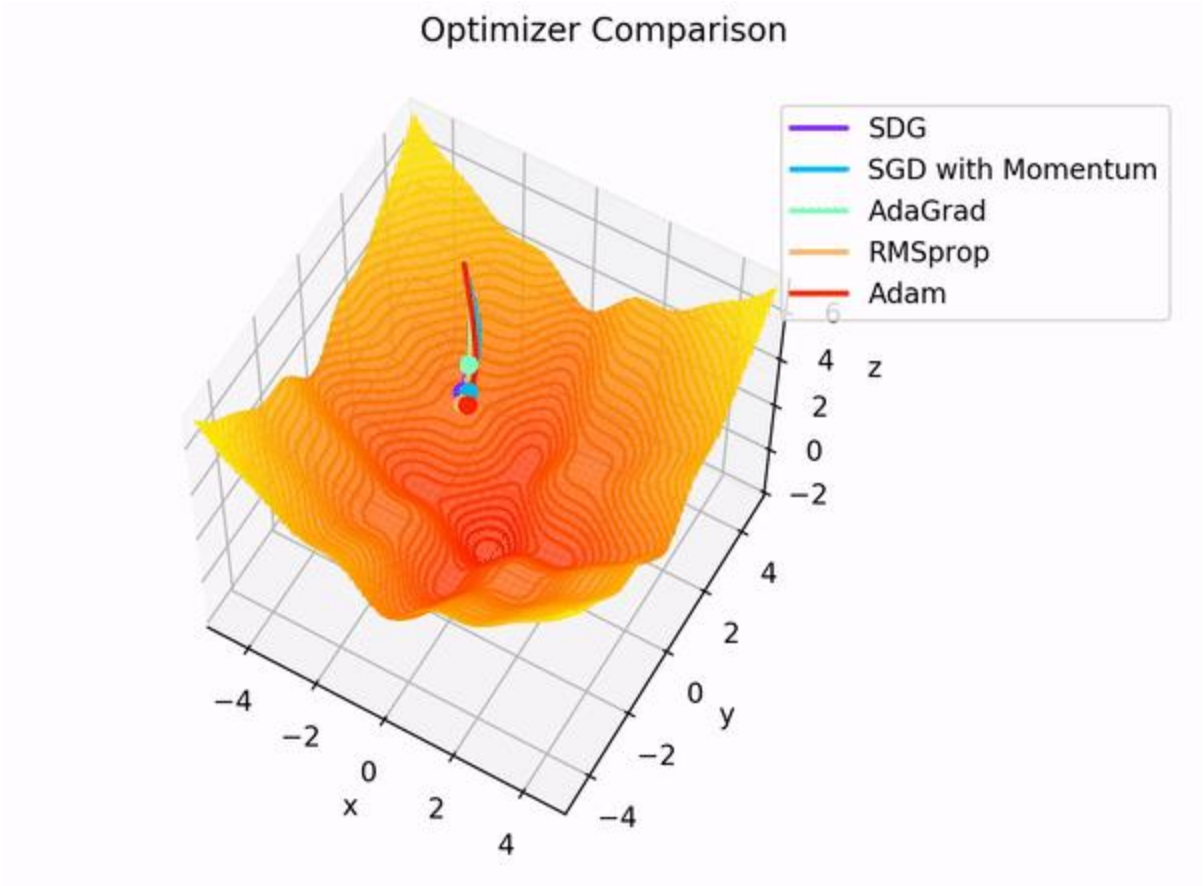
https://www.3blue1brown.com/lessons/gradient-descent

Gradient Descent



https://www.3blue1brown.com/lessons/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

https://www.3blue1brown.com/lessons/gradient-descent

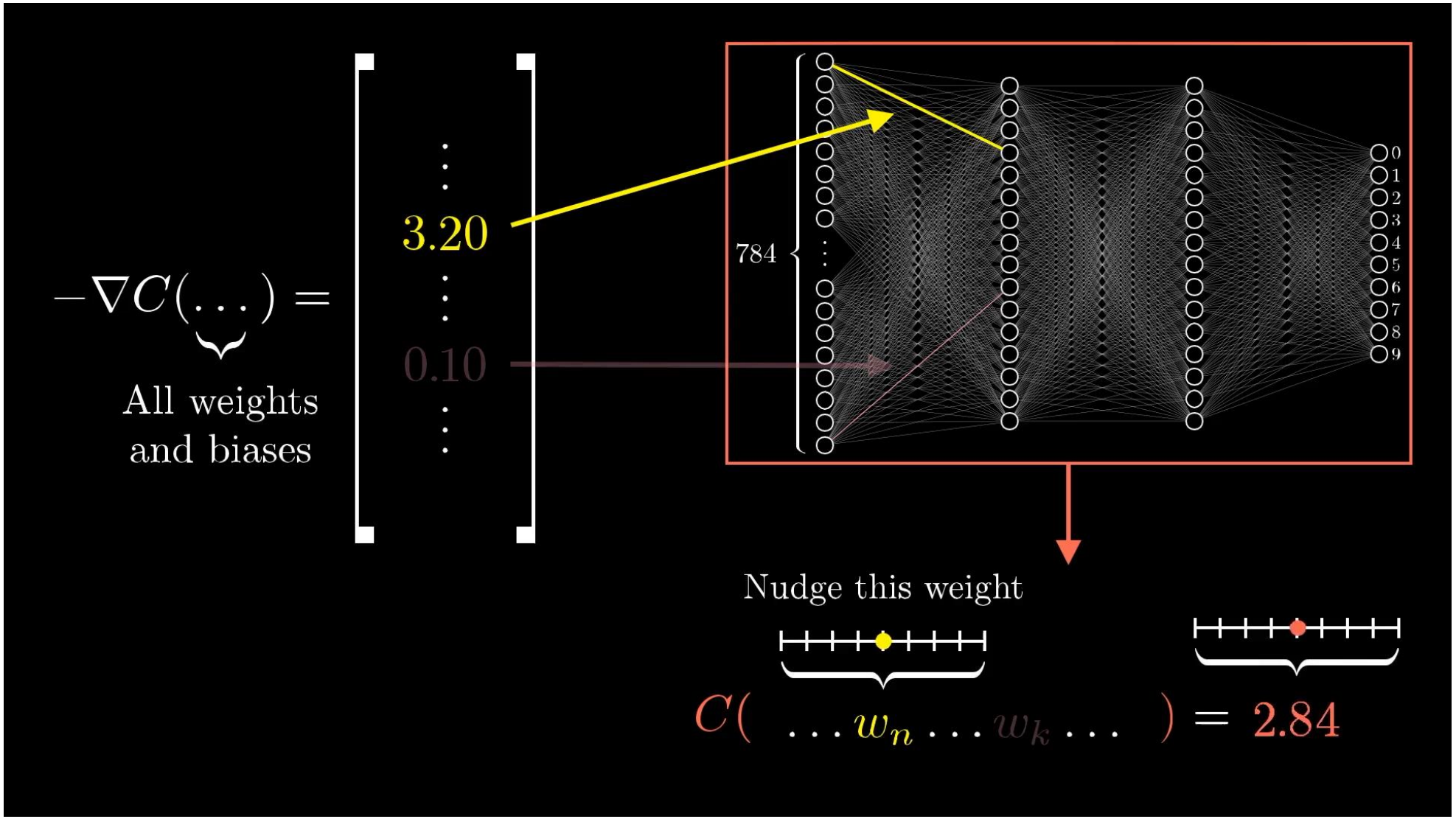
Gradient Descent

$$\vec{\mathbf{W}} = \begin{bmatrix} w_0 \\ w_1 \\ w_2 \\ \vdots \\ w_{13,000} \\ w_{13,001} \\ w_{13,002} \end{bmatrix}$$

$$-\nabla C(\vec{\mathbf{W}}) = \left.\begin{bmatrix} 0.31 \\ 0.03 \\ -1.25 \\ \vdots \\ 0.78 \\ -0.37 \\ 0.16 \end{bmatrix}\right\} \text{Example gradient}$$

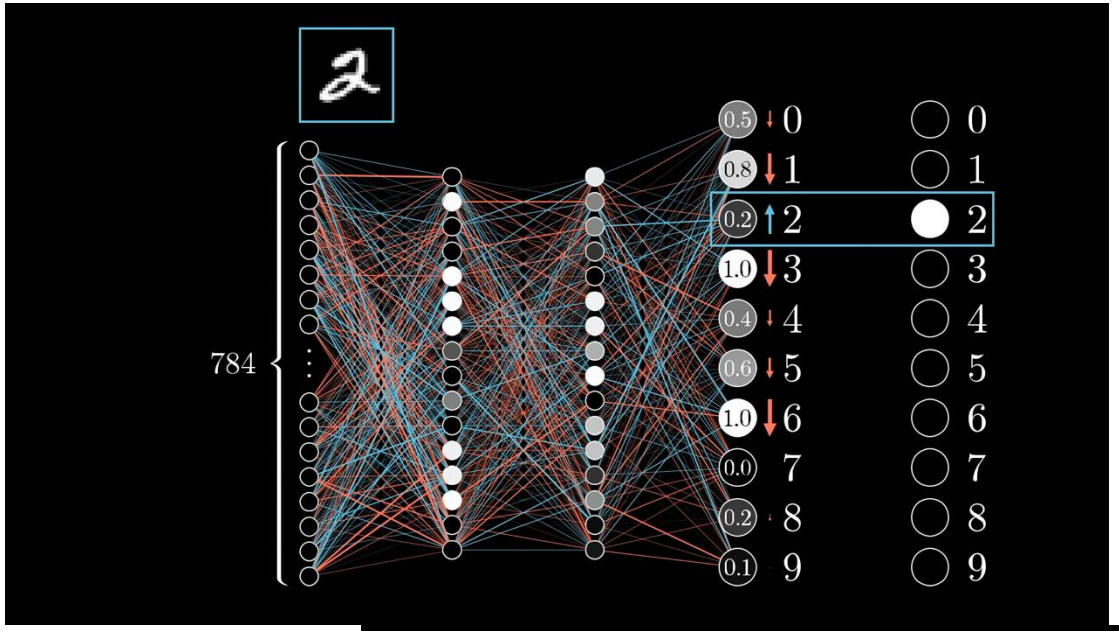
https://www.3blue1brown.com/lessons/gradient-descent

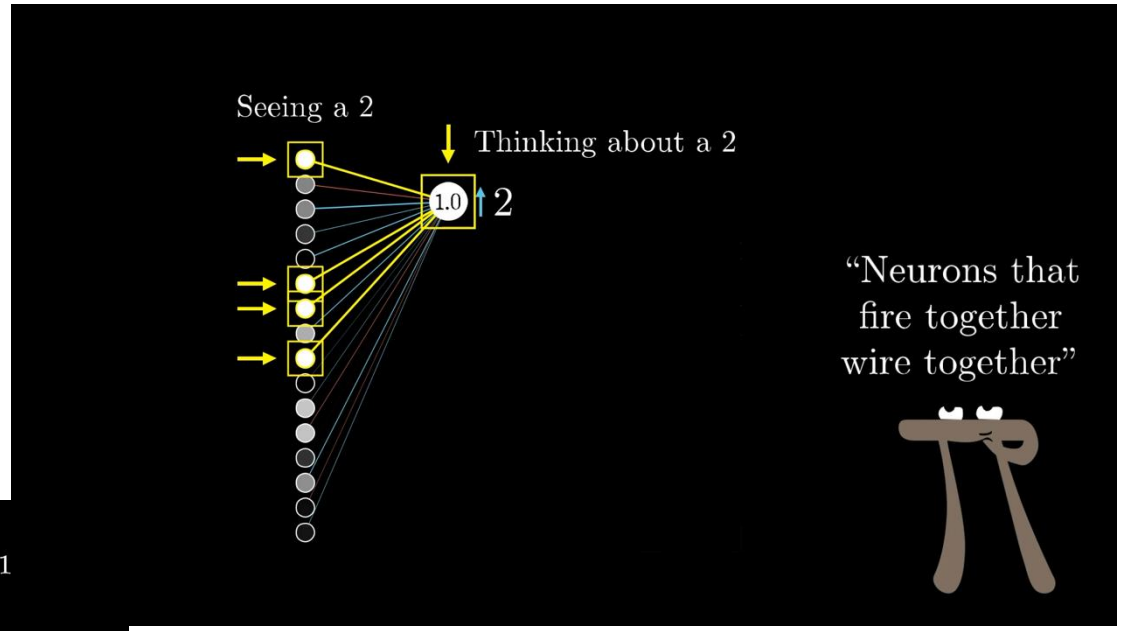
Gradient Descent

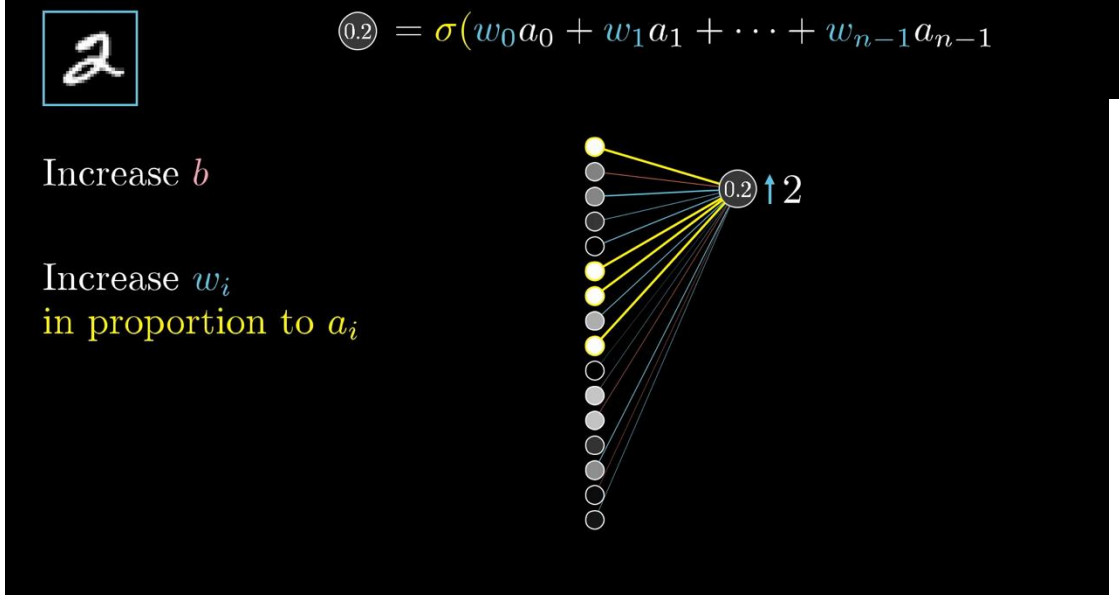


https://www.3blue1brown.com/lessons/backpropagation

Backpropagation

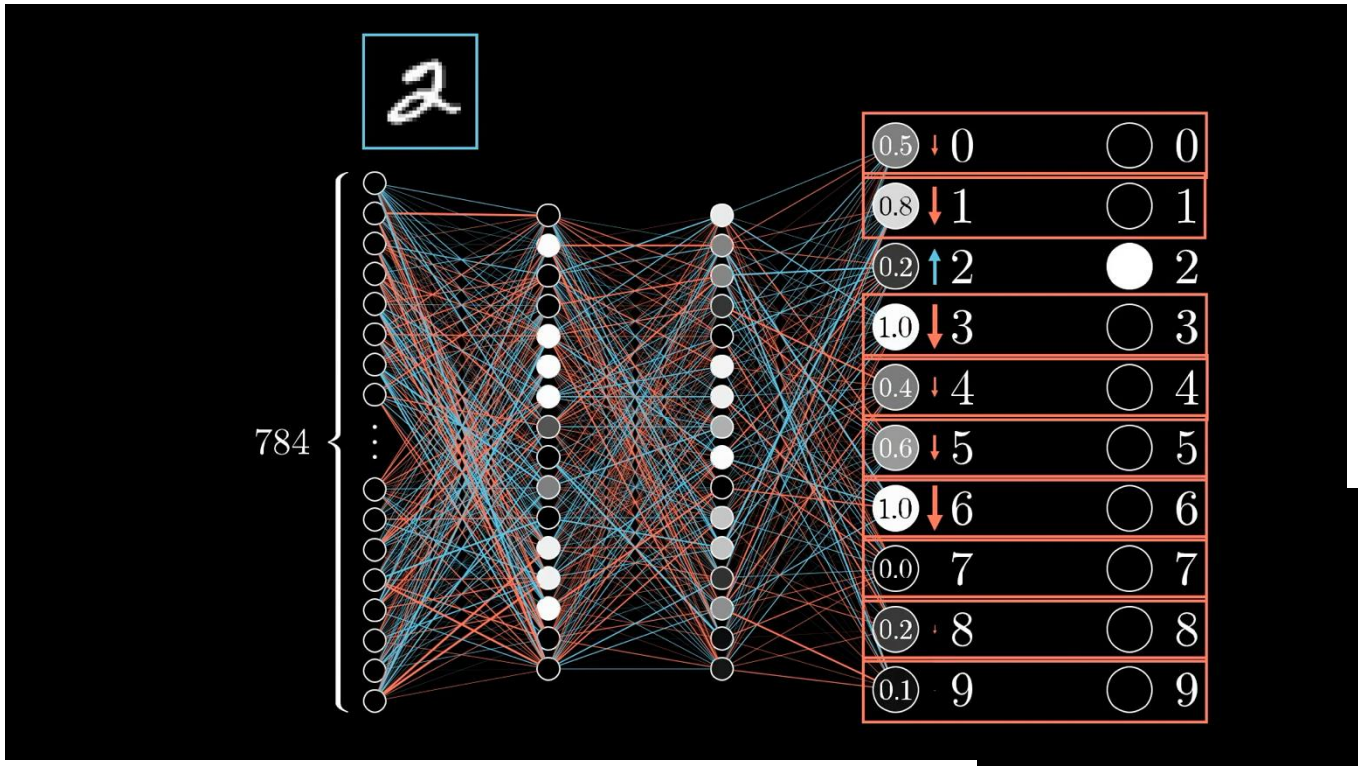


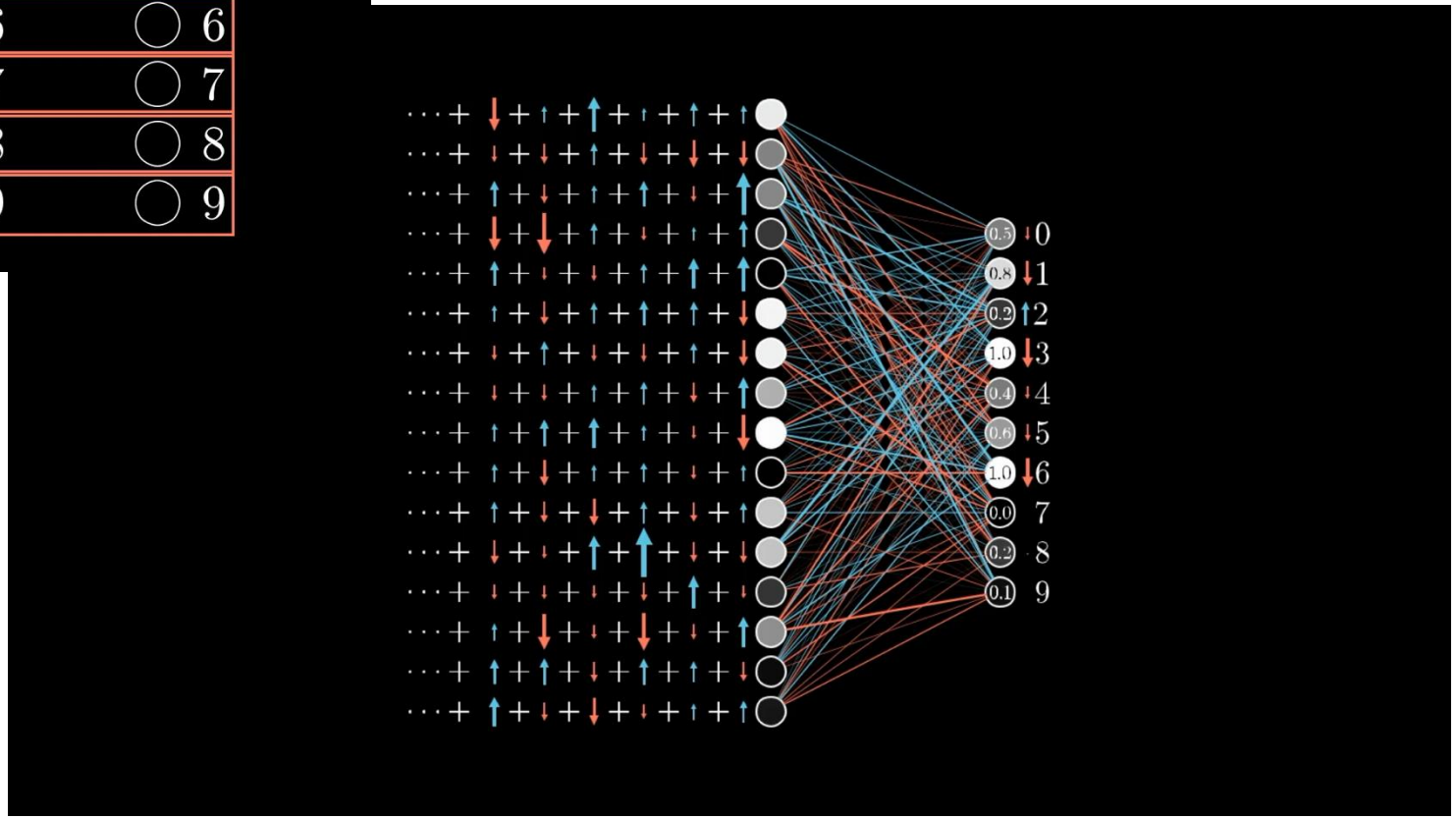




https://www.3blue1brown.com/lessons/backpropagation

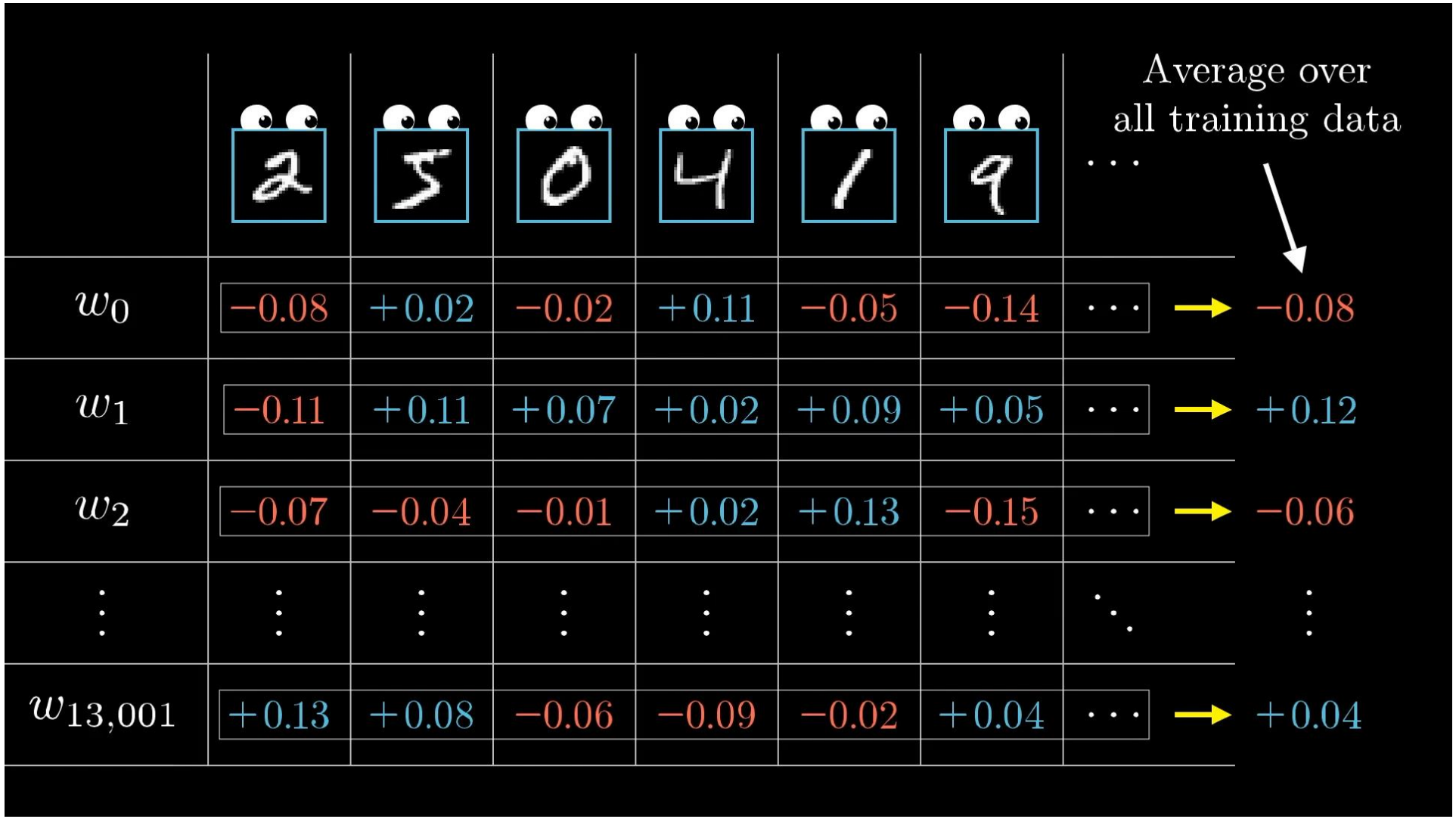
Backpropagation





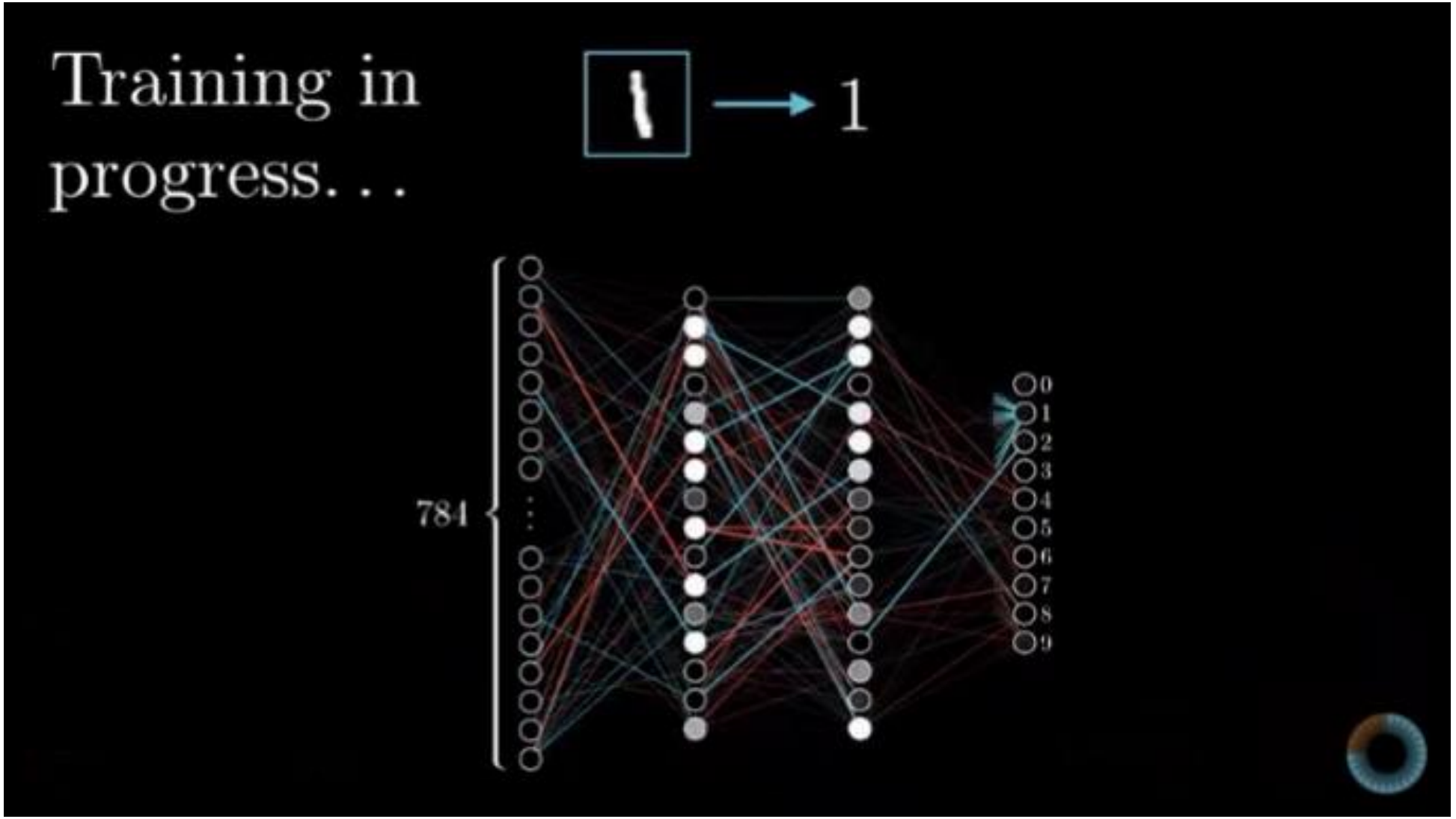
https://www.3blue1brown.com/lessons/backpropagation

Backpropagation



https://www.3blue1brown.com/lessons/backpropagation

Backpropagation



https://www.3blue1brown.com/lessons/backpropagation

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)

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

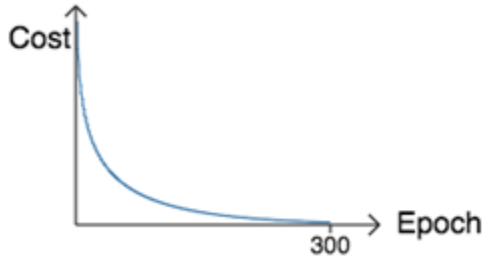
- Training algorithm :

- Step 1 Initialize randomly the weights

For each epoch :

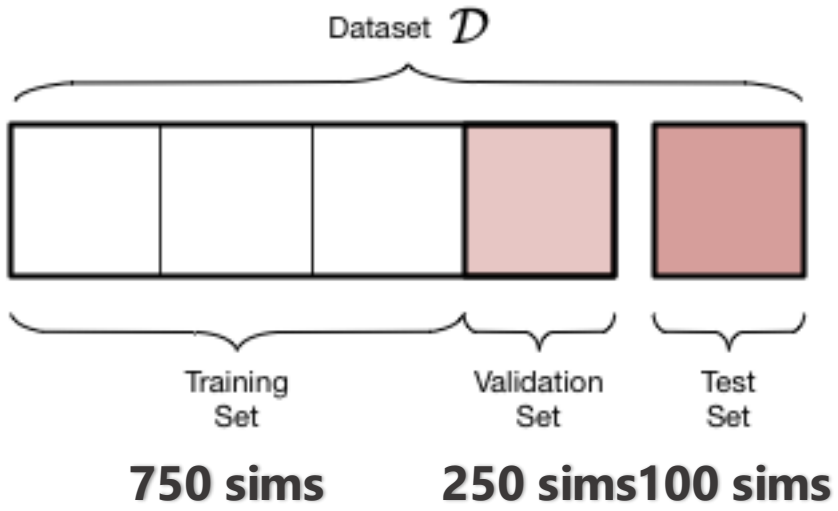
Step 2 Forward pass your examples (eg labeled images of cats and birds) through nnet to compute predicted values (as previously explained)
Step 3 Compute loss
Step 4 Backward propagation
Step 5 Update weights (gradient descent algorithm)

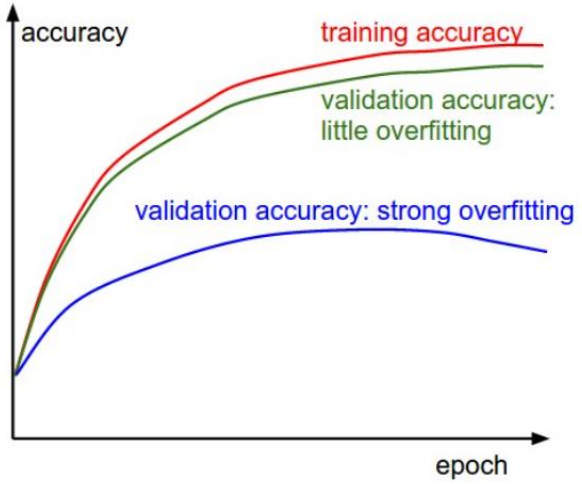
Repeat from step 2 until a plateau is reached

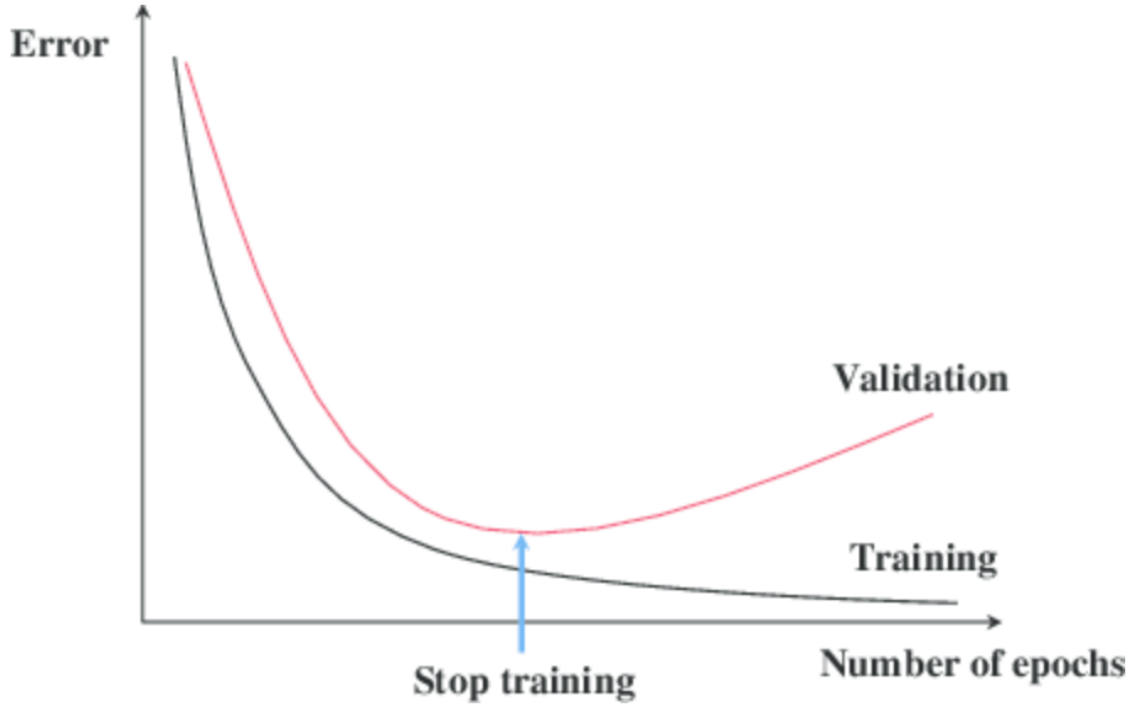


Early Stop to avoid overfitting

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







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

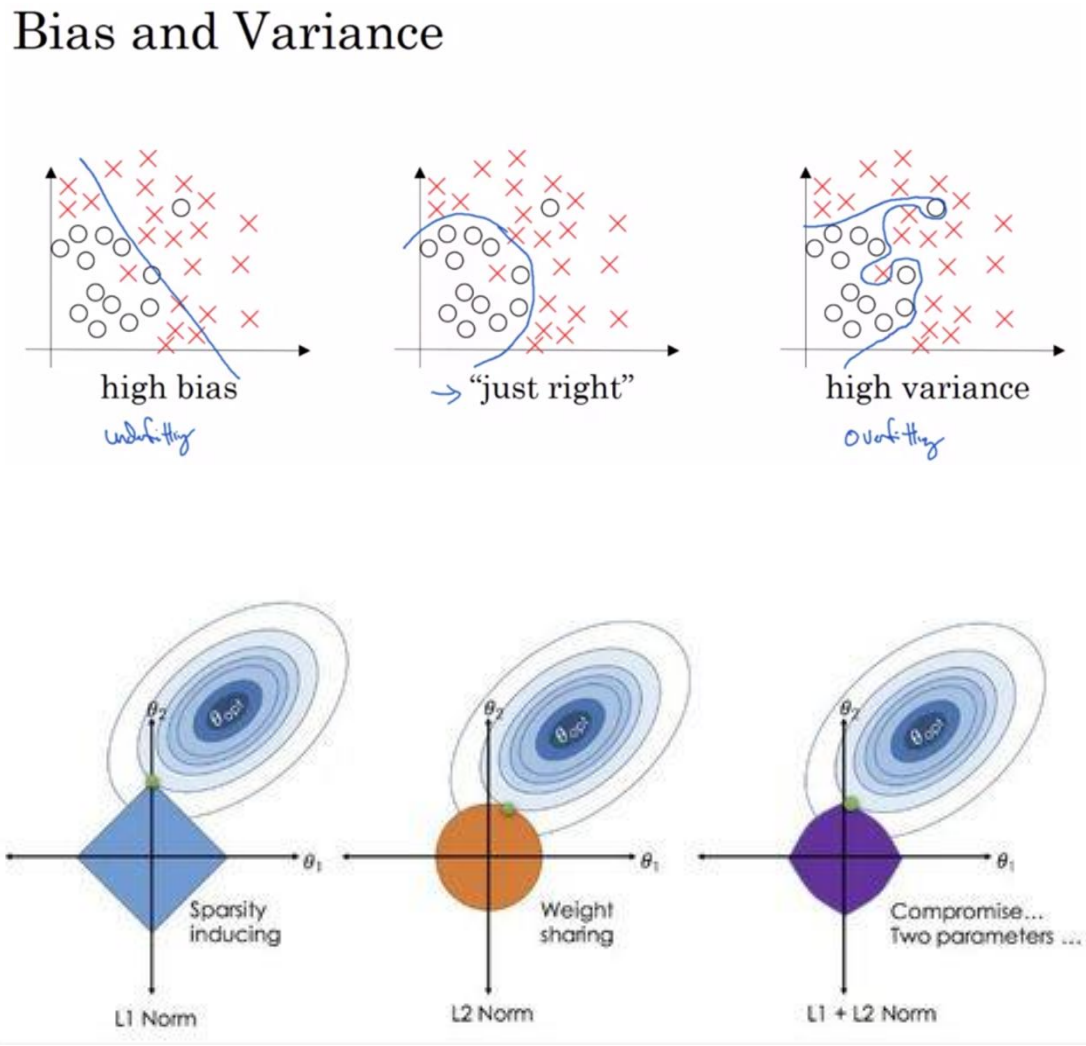
- **Practical Exercise 2:**

- 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.

Regularization to avoid overfitting



Regularization Type	Advantages	Disadvantages
L1	1. Performs feature selection by shrinking less important feature weights to zero.	1. Not effective for datasets with many important features.
	2. Can be used for high-dimensional datasets with many irrelevant features.	2. The solution may not be unique, which can lead to instability in the model.
L2	1. Provides a smooth solution and improves the generalization performance of the model.	1. May not perform well for datasets with many irrelevant features.
	2. Can handle datasets with many important features.	2. Does not perform feature selection, and all features are included in the model with non-zero weights.

https://medium.com/codex/understanding-l1-and-l2-regularization-the-guardians-against-overfitting-175fa69263dd

- **Practical Exercise 3:**

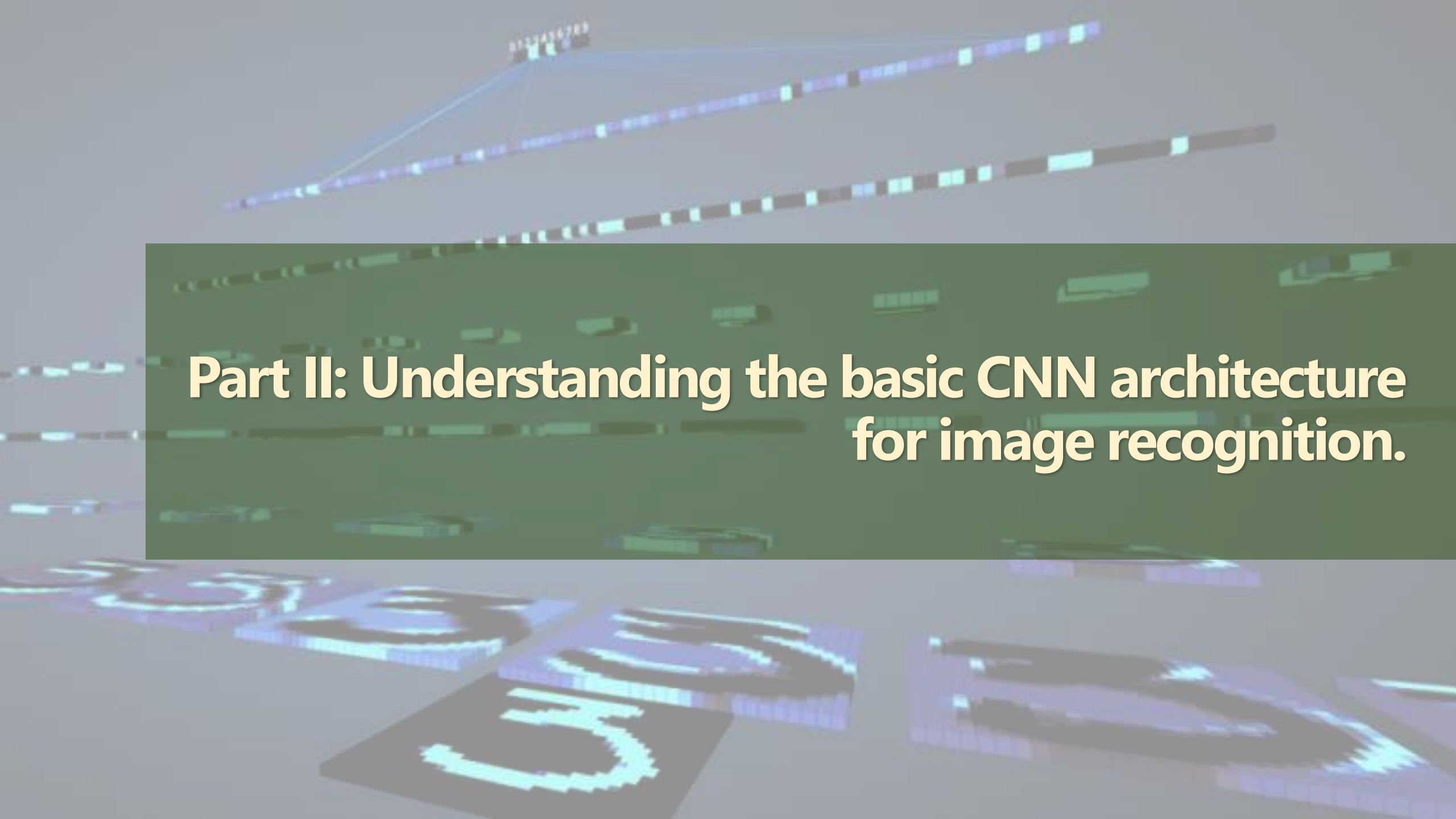
- Access the notebook at https://drive.google.com/file/d/1JjHU4MMbJc5NMLr7IJykW8sNqmABr1M5/view?usp=sharing. It is also on the Github page.

Goals

- Conceive and simulate genetic data under competing demographic scenarios 

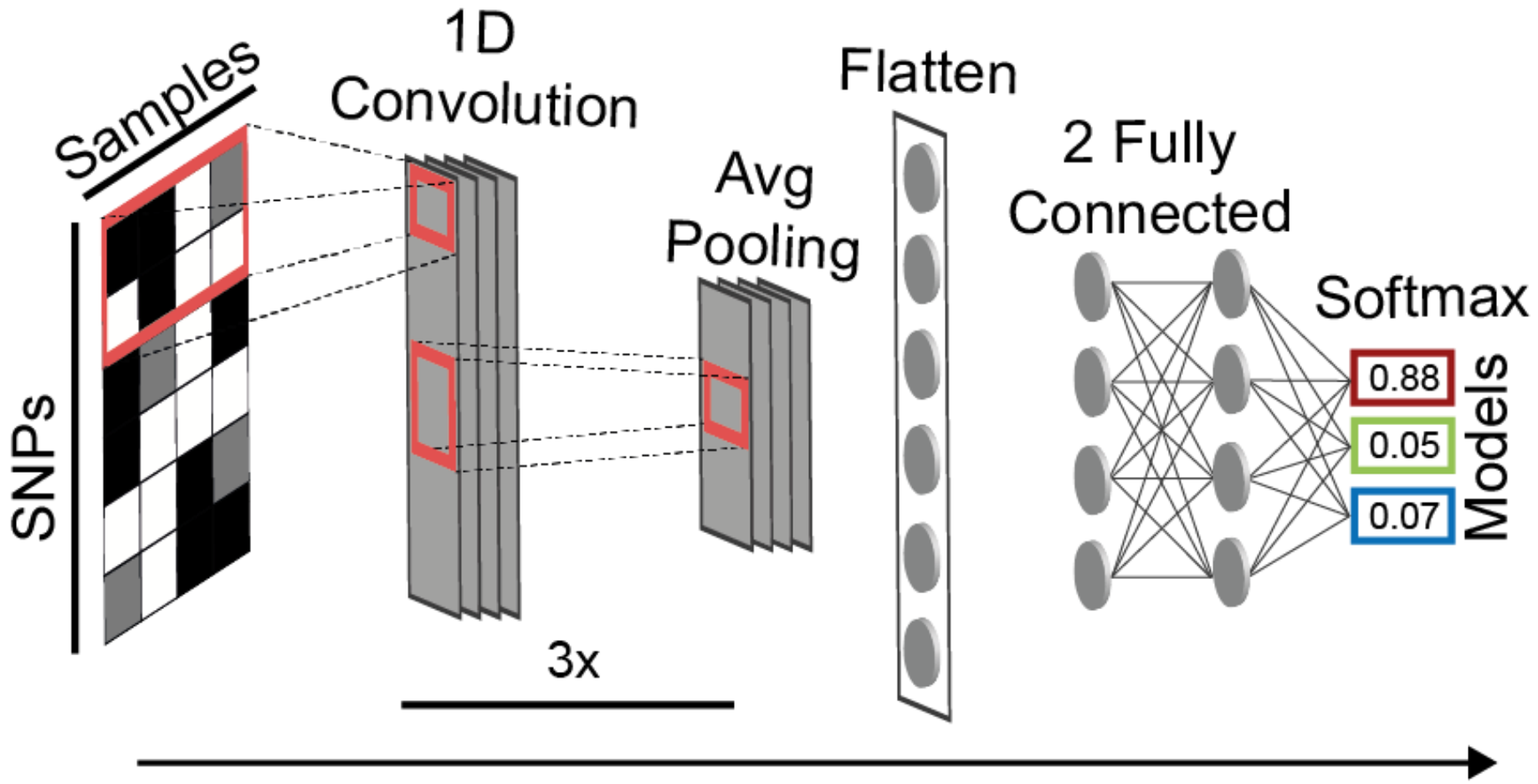
- Understand deep learning background and how a CNN works 

- How to use deep learning to compare demographic scenarios



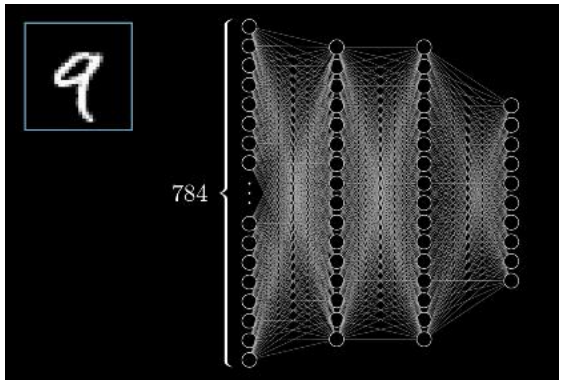
Part II: Understanding the basic CNN architecture for image recognition.

CNN architecture



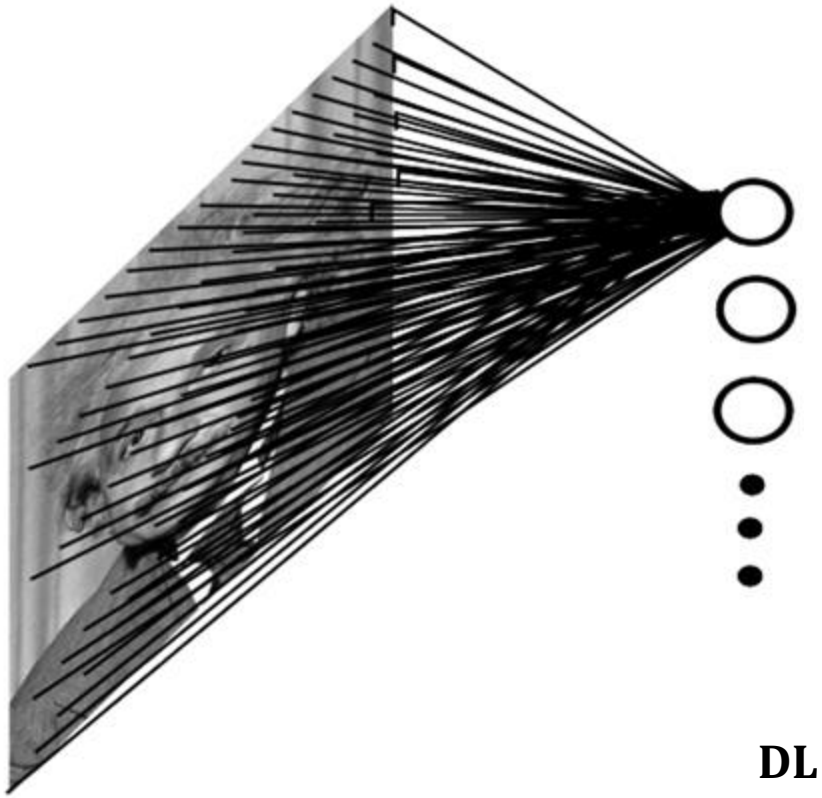
Kirschner et al. (2022) *Nat Comm*

Convolutional Neural Networks (CNNs)

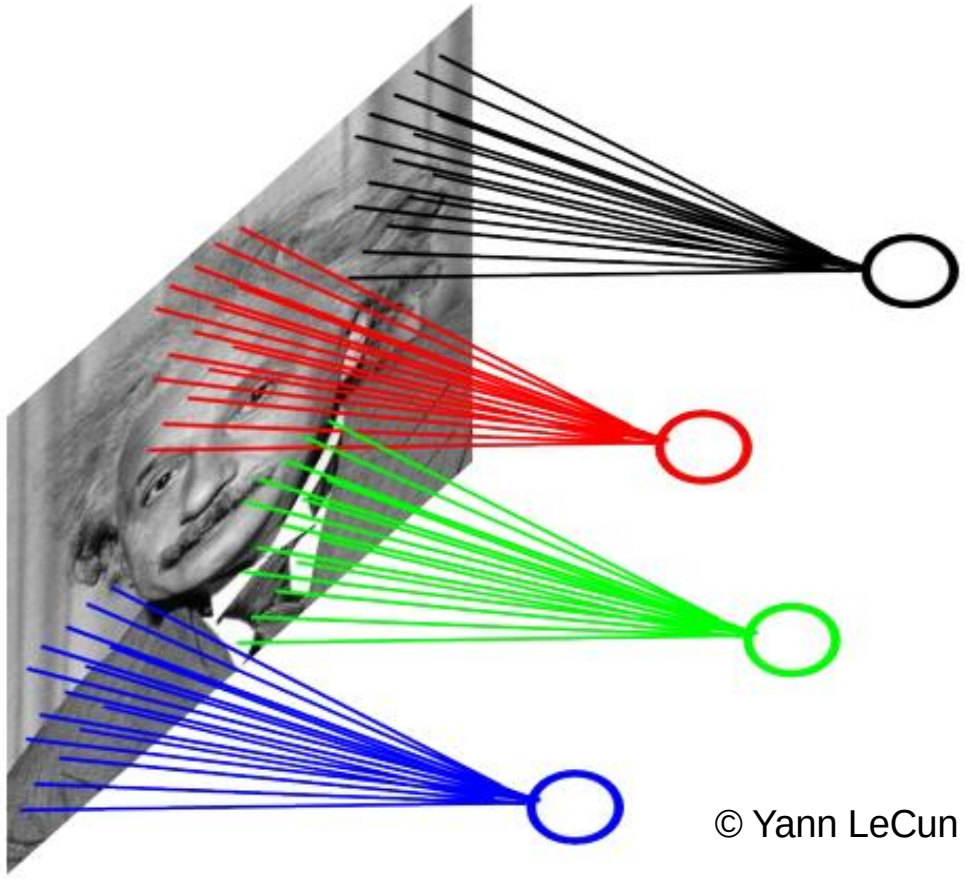


MLP
Fully connected

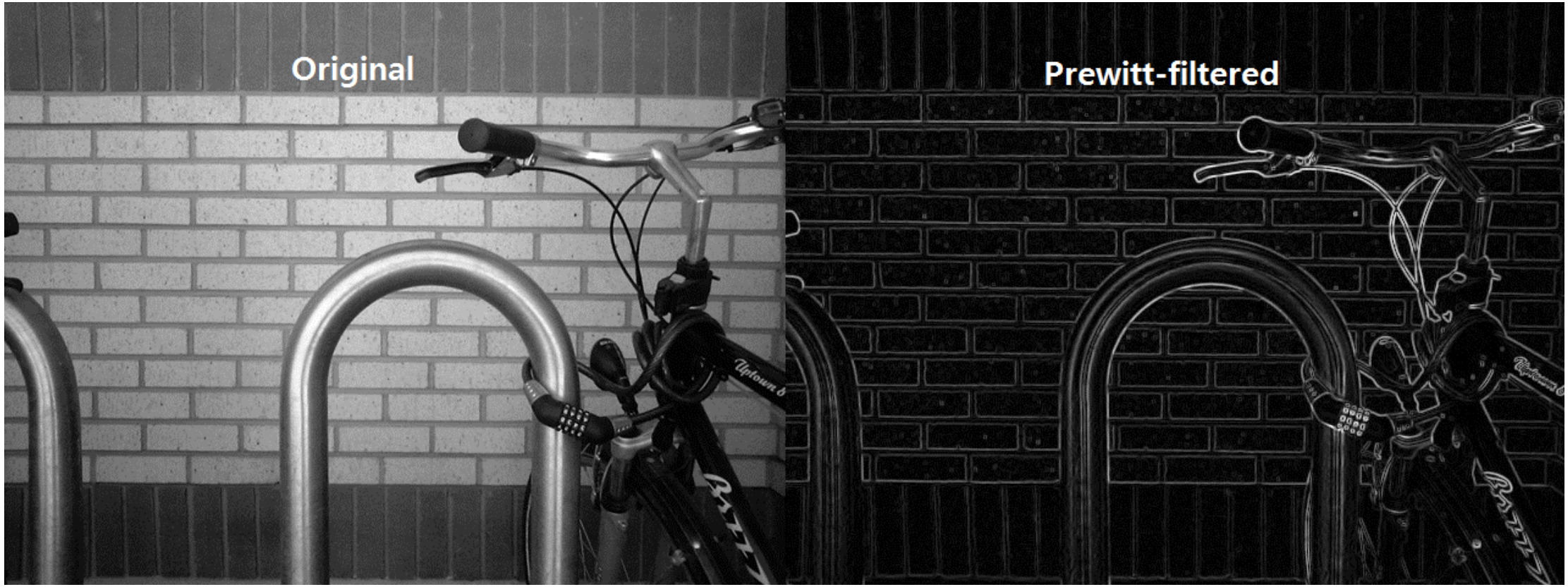
Convnet
locally connected
→ smaller number of parameters to learn



DL witchcraft

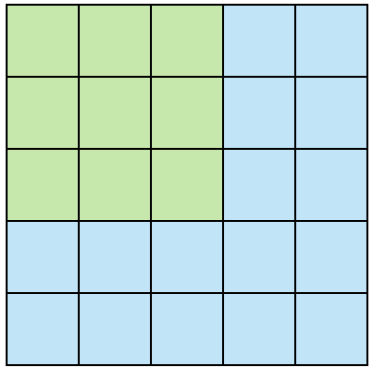


Convolutional Layers

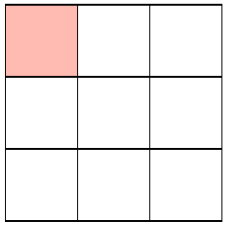


https://towardsdatascience.com/covolutional-neural-network-cb0883dd6529

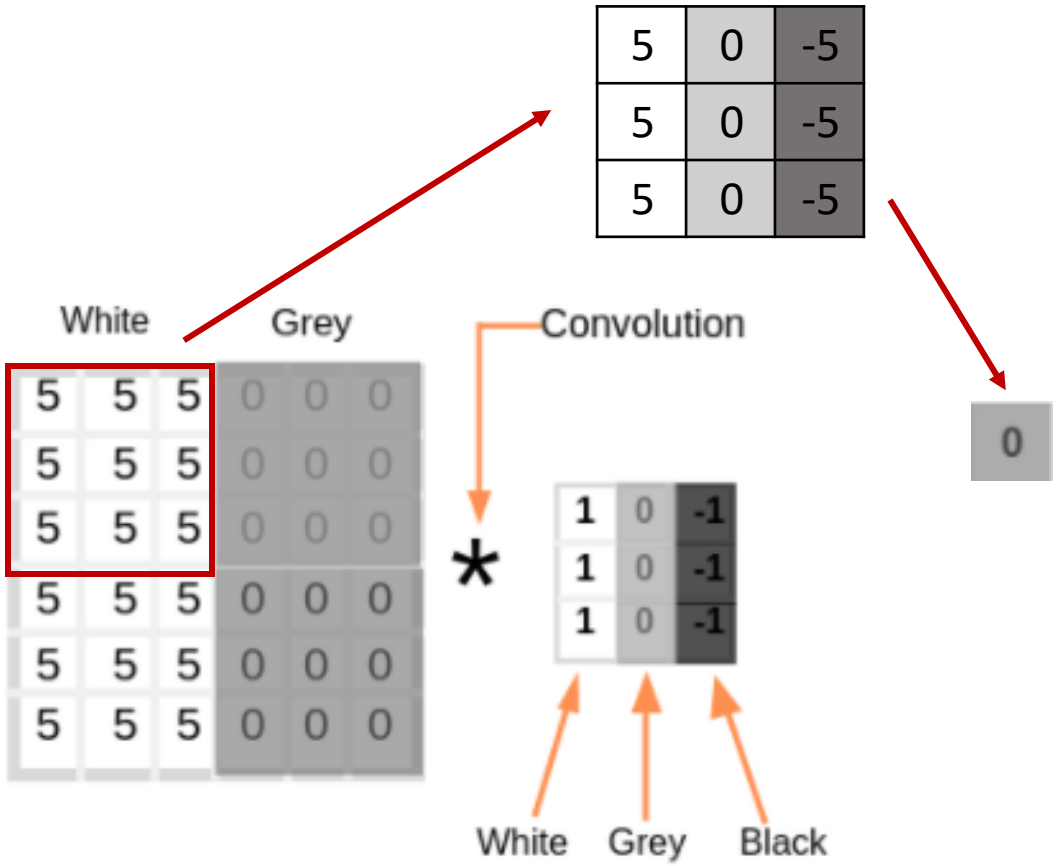
Convolutional Layers



Stride 1

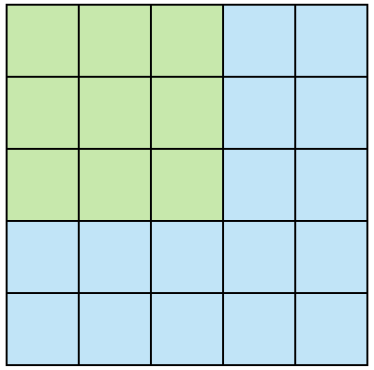


Feature Map

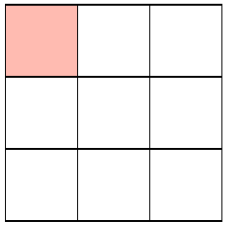


https://towardsdatascience.com/covolutional-neural-network-cb0883dd6529

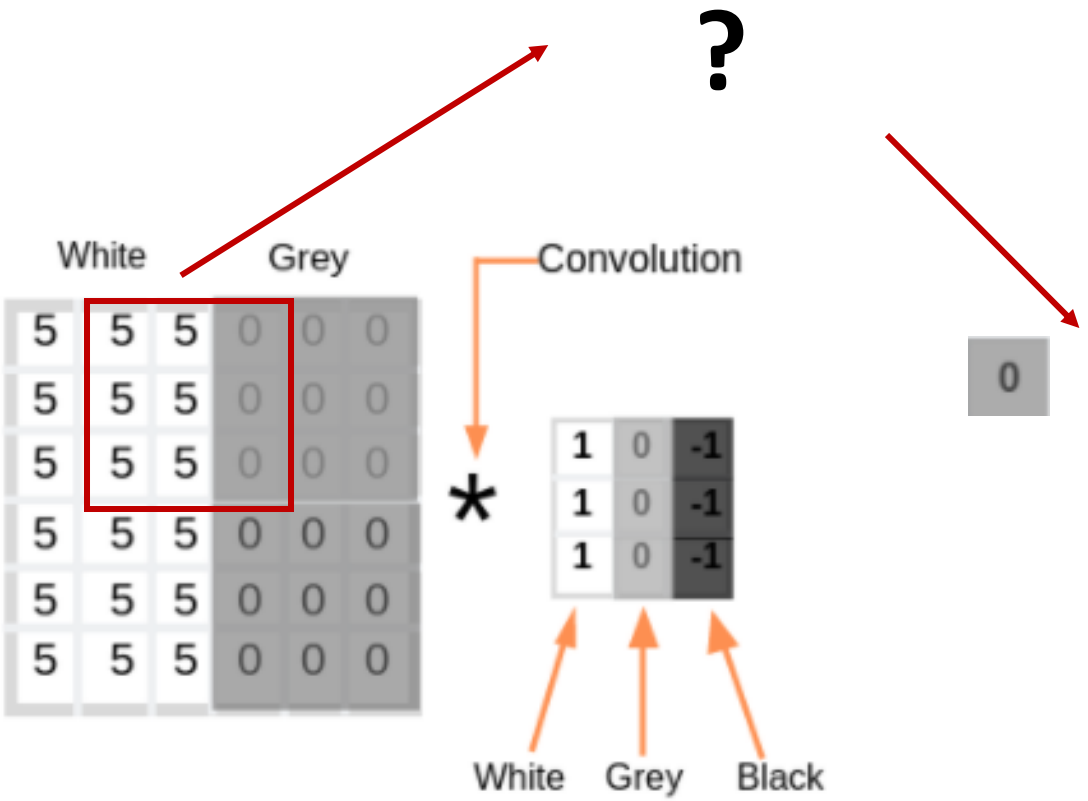
Convolutional Layers



Stride 1



Feature Map



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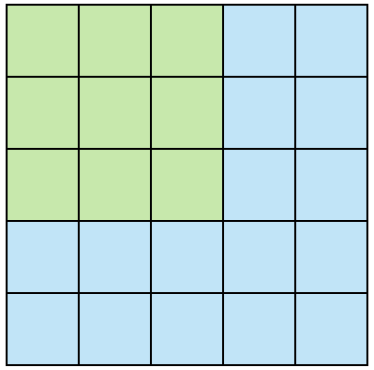
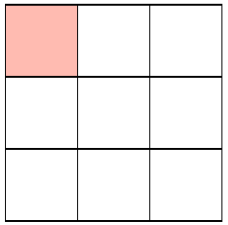
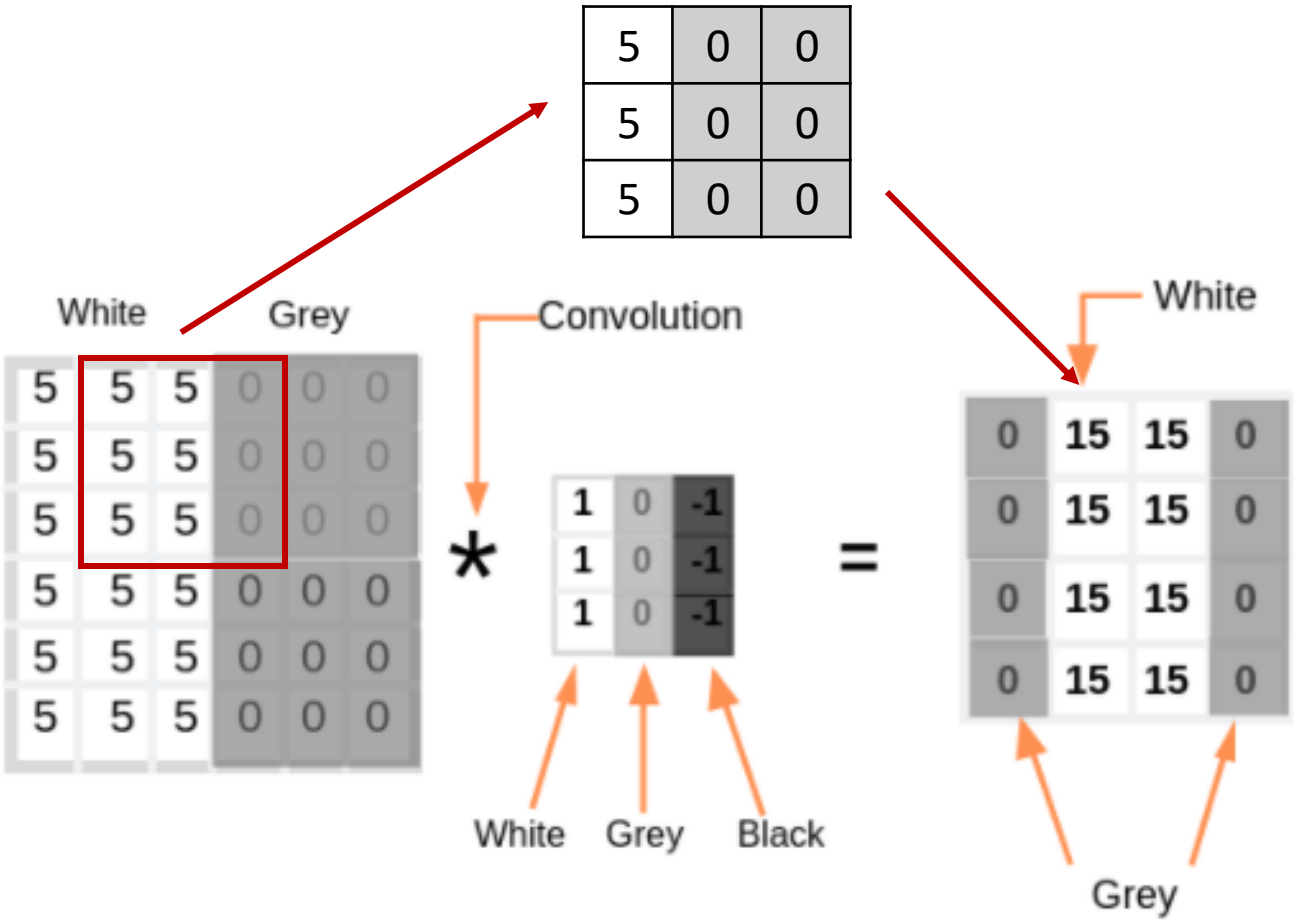
Convolutional Layers



Stride 1



Feature Map



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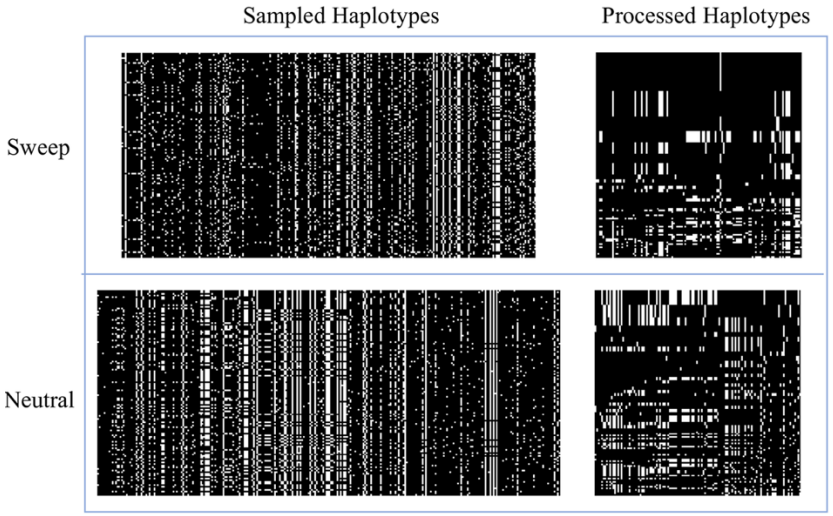
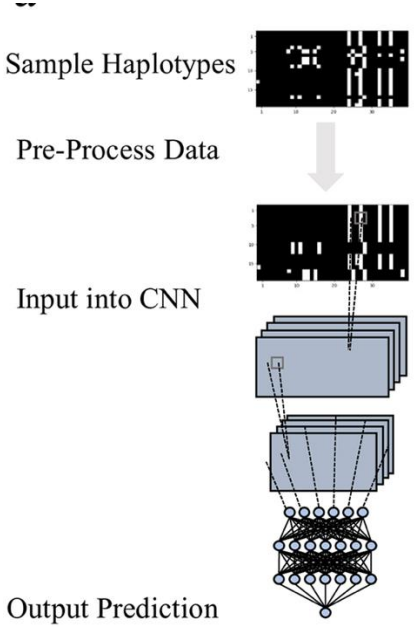
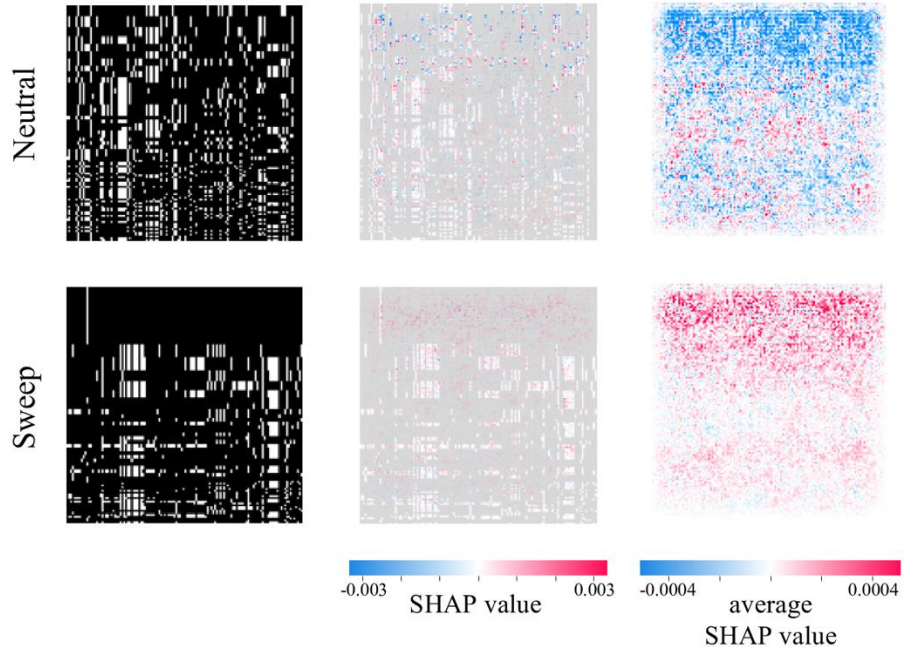
Neural Network for Genomic data

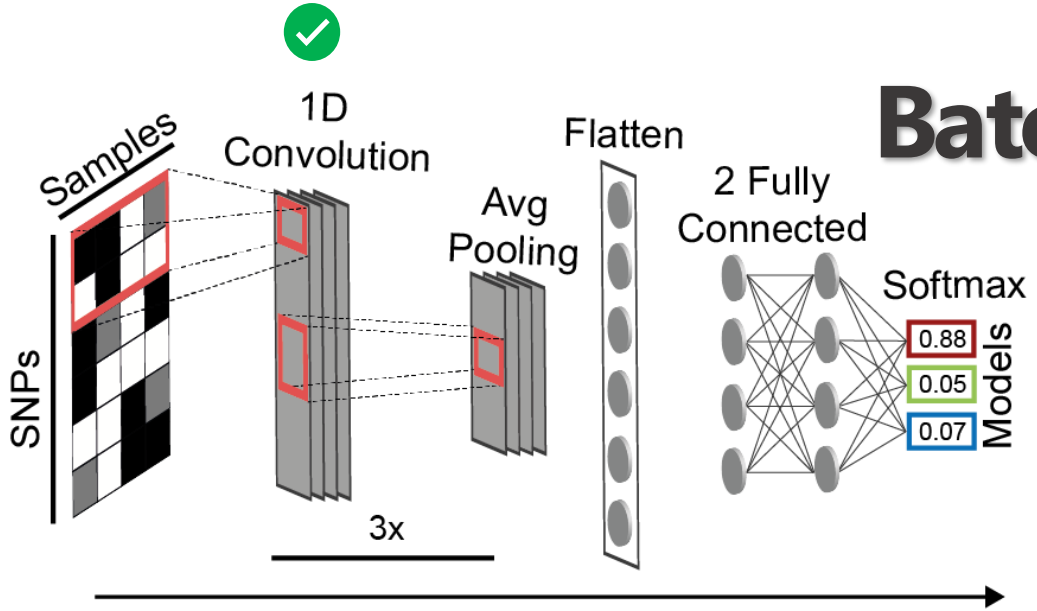




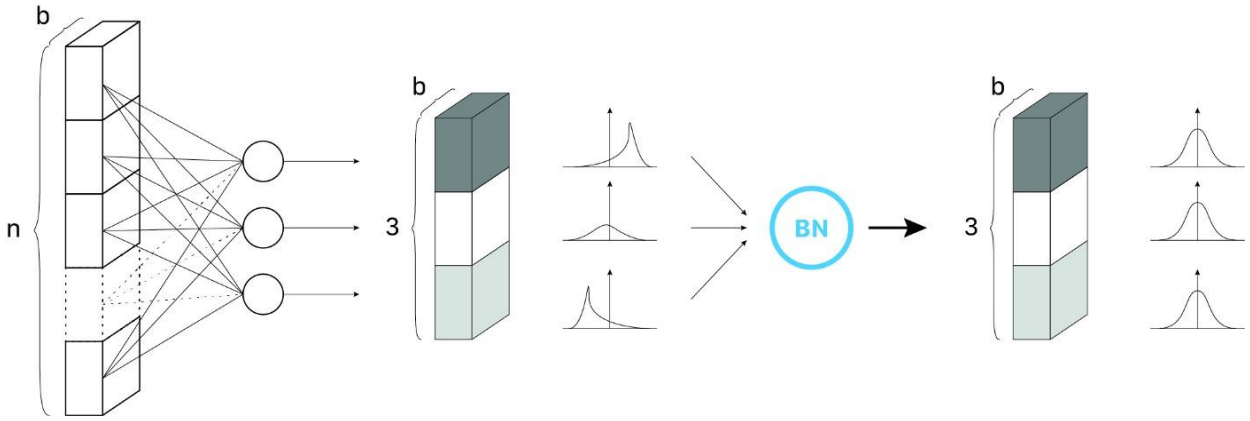


Cecil & Sudgen (2023) *PLoS Comp Biol*

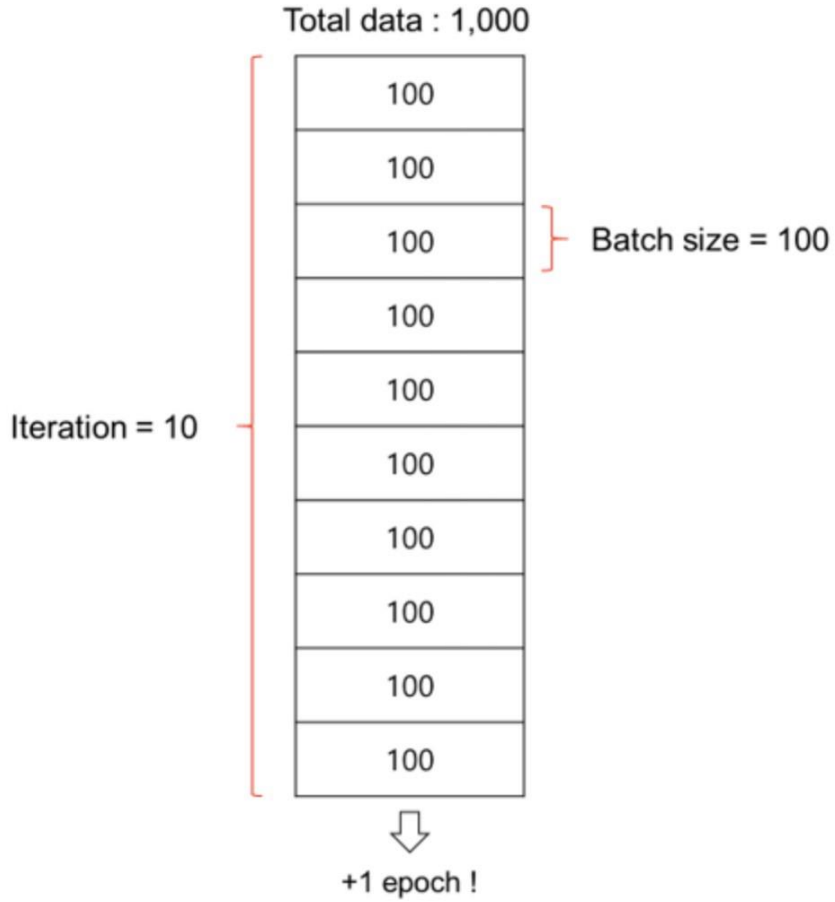
Batches and Batch Normalization



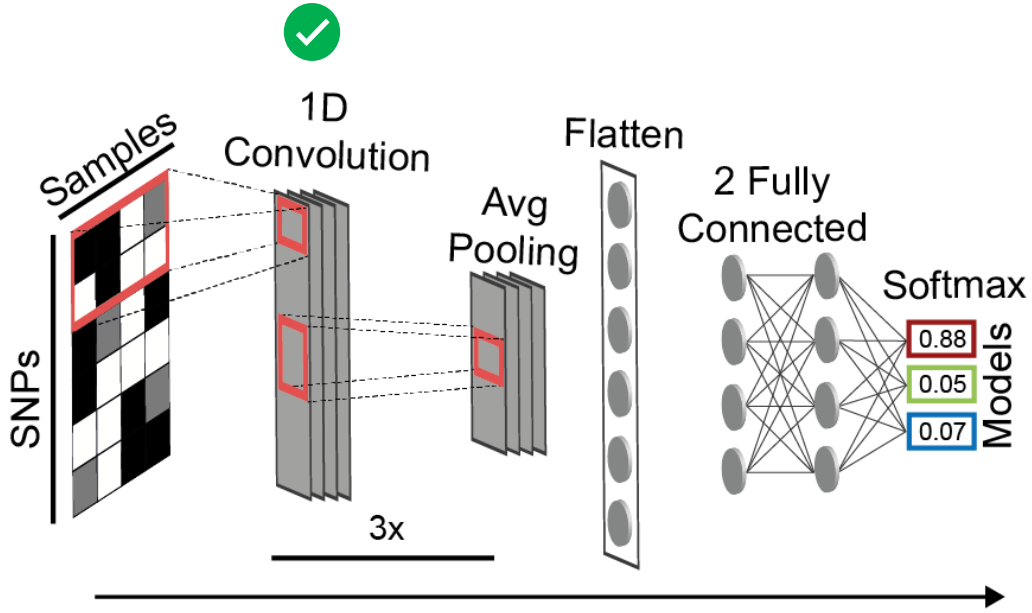
Kirschner et al. (2022) *Nat Comm*



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



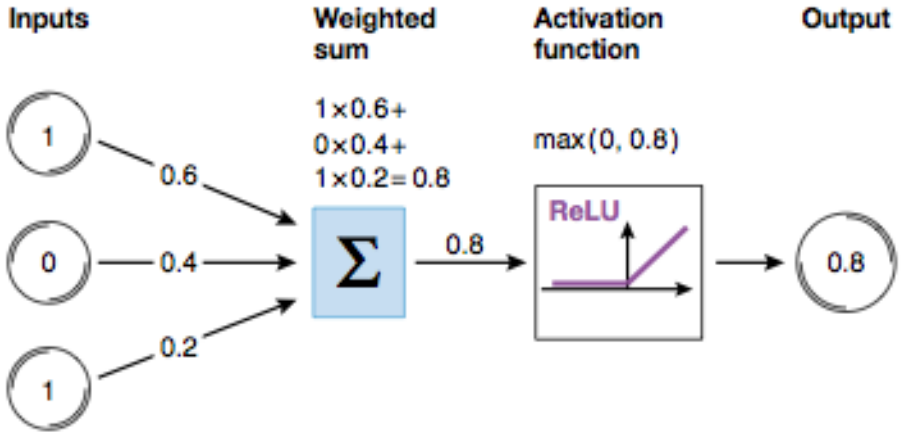
https://jerryan.medium.com/batch-size-a15958708a6



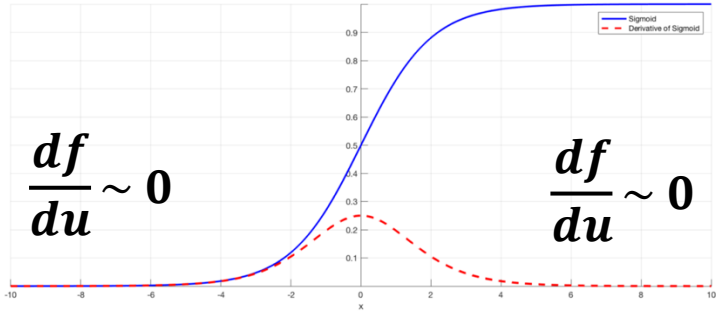
Kirschner et al. (2022) *Nat Comm*

Activation Function

DL witchcraft

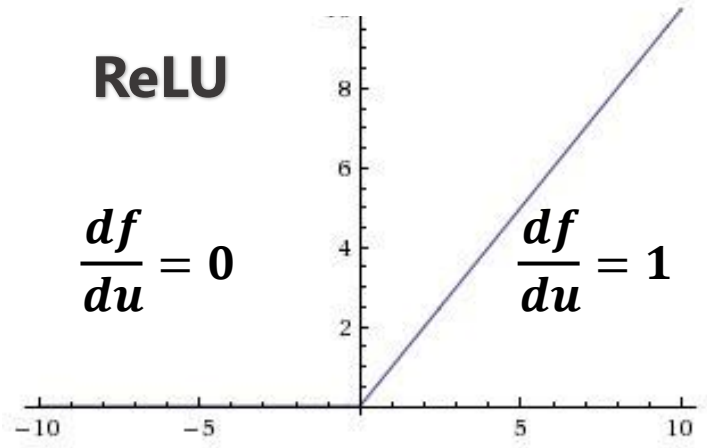


Sigmoid – Vanishing gradients



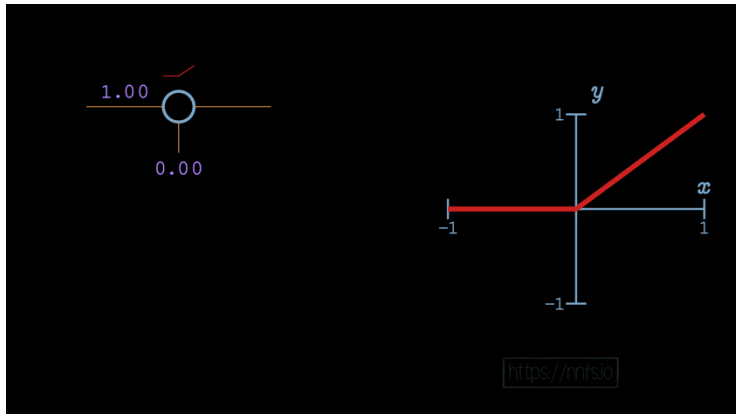
https://towardsdatascience.com/the-vanishing-gradient-problem-69bf08b15484

ReLU

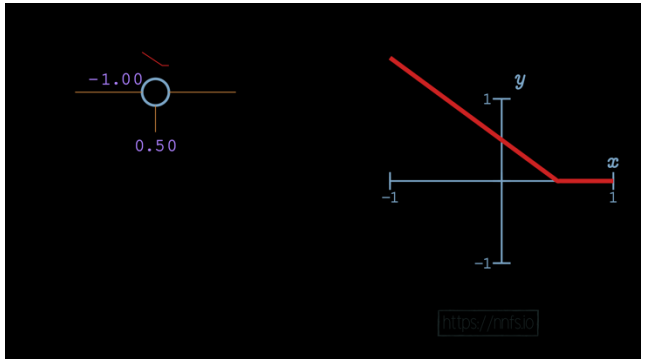


https://www.kaggle.com/code/dansbecker/rectified-linear-units-relu-in-deep-learning/notebook

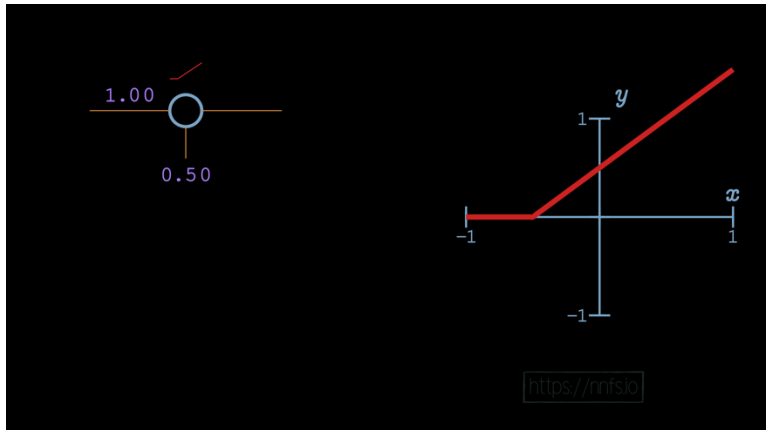
CNN Script – ReLU



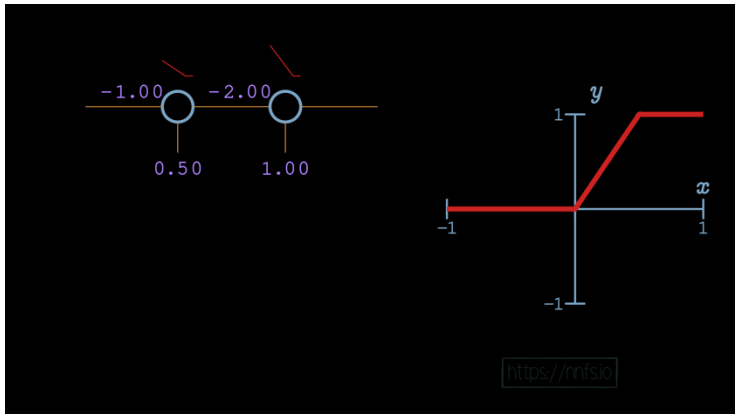
Weight = 1
Bias = 0



Weight = -1
Bias = 0.5



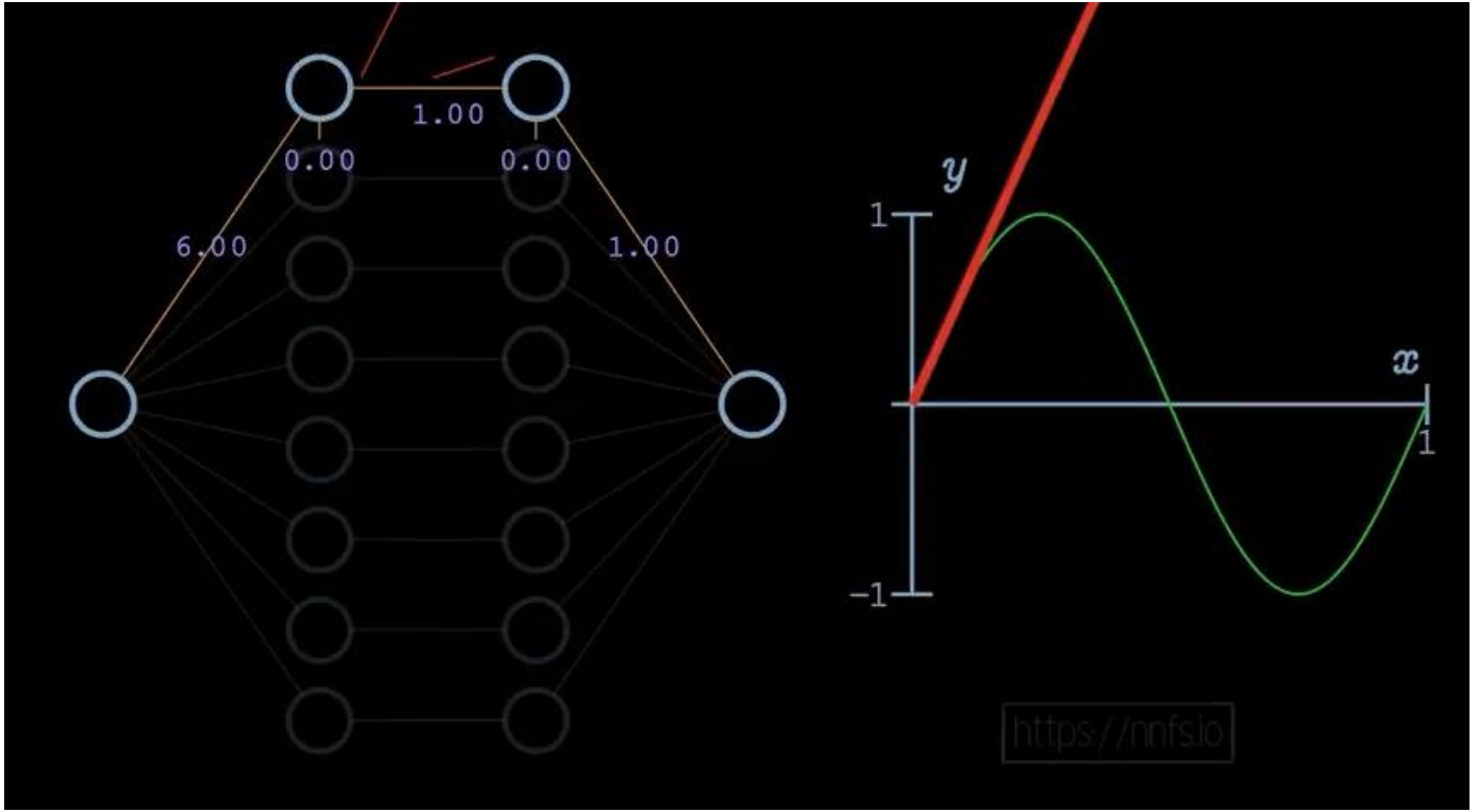
Weight = 1
Bias = 0.5



2 neurons

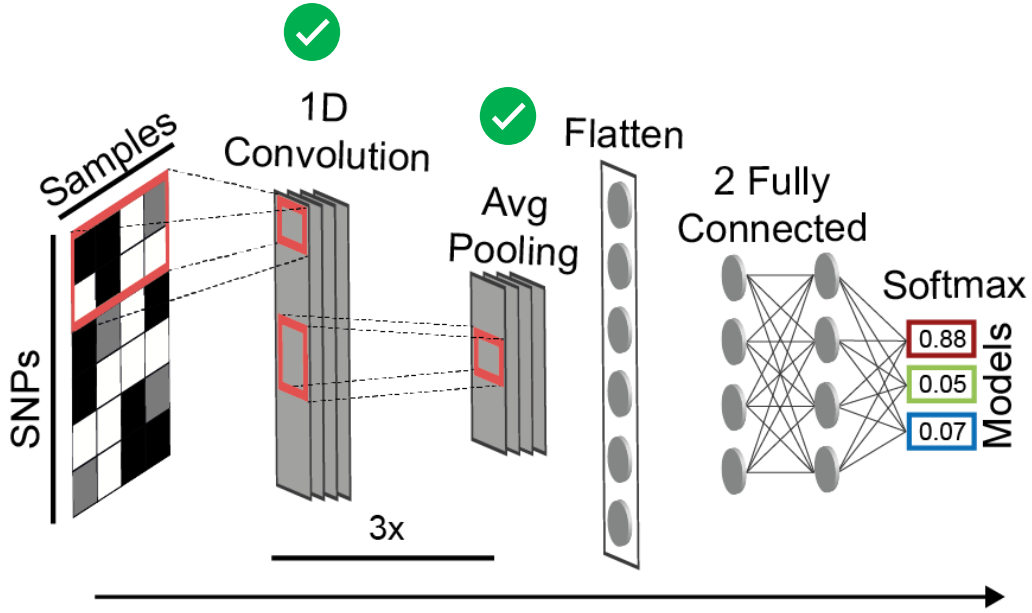
https://nnfs.io/mvp/

CNN Script – ReLU

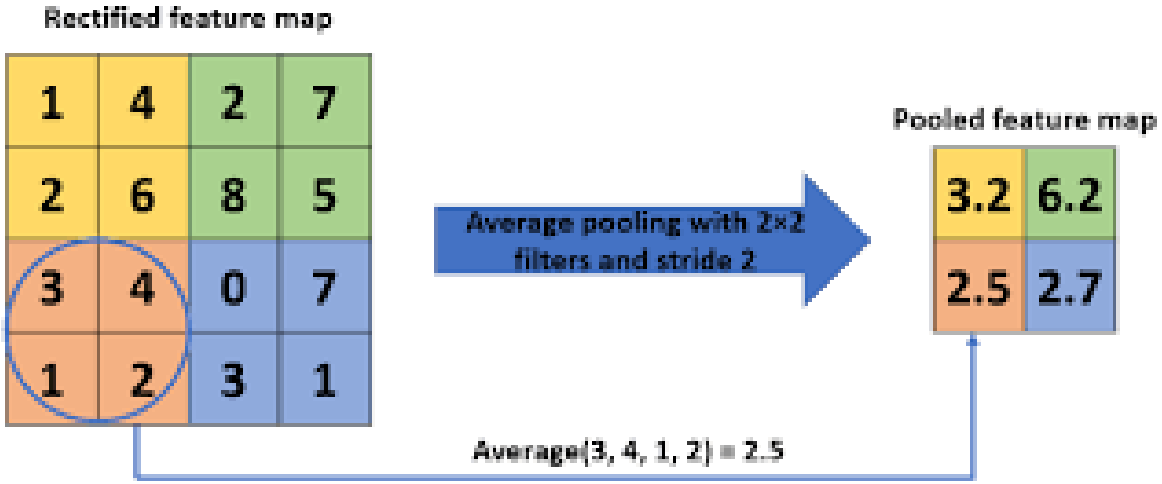


https://nnfs.io/mvp/

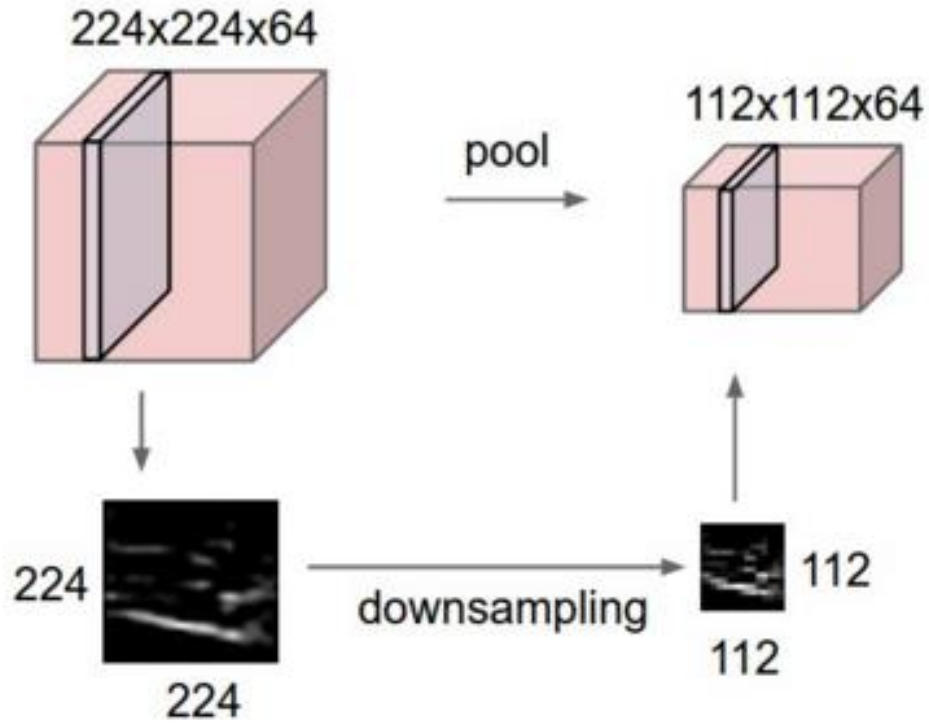
Pooling



Kirschner et al. (2022) *Nat Comm*

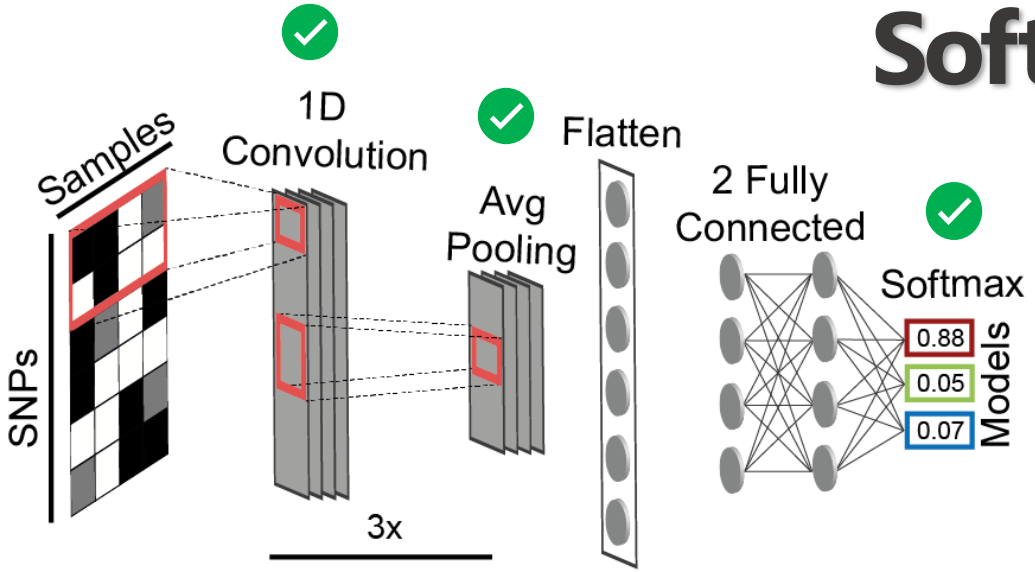


Gholamalinezhad & Khosravi (2020) *arXiv*

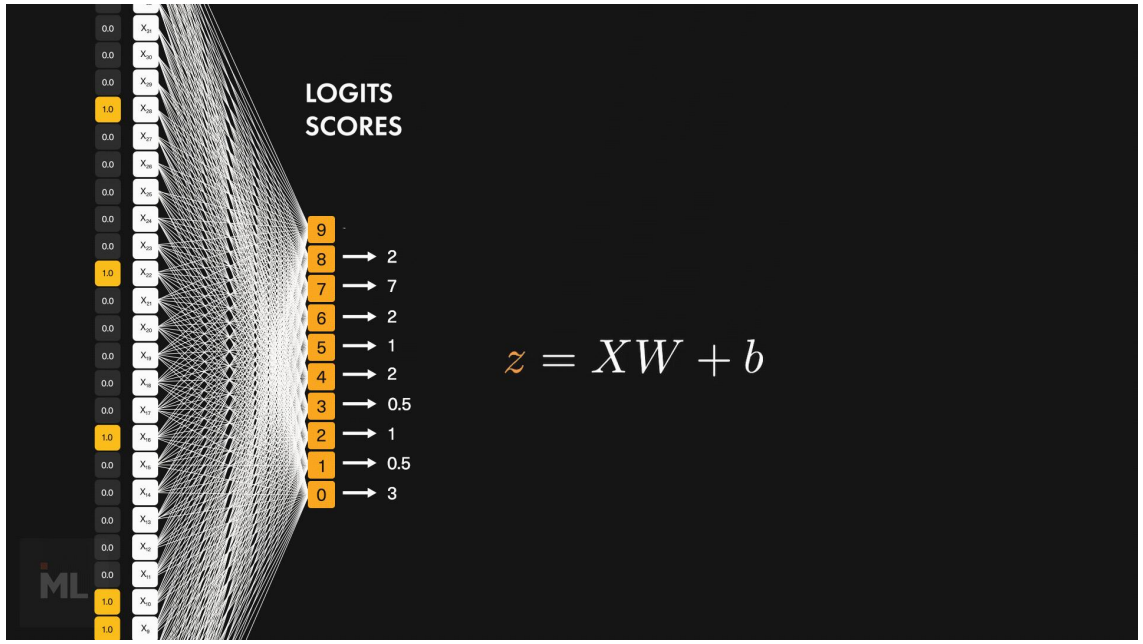


https://leonardoaraujosantos.gitbook.io/artificial-inteligence/machine_learning/deep_learning/pooling_layer

Softmax layer for Classification



Kirschner et al. (2022) *Nat Comm*



$$z = XW + b$$

Hyperparameters

Libraries for deep Learning:
Keras, Tensorflow, pyTorch

TensorFlow

PyTorch

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	

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

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

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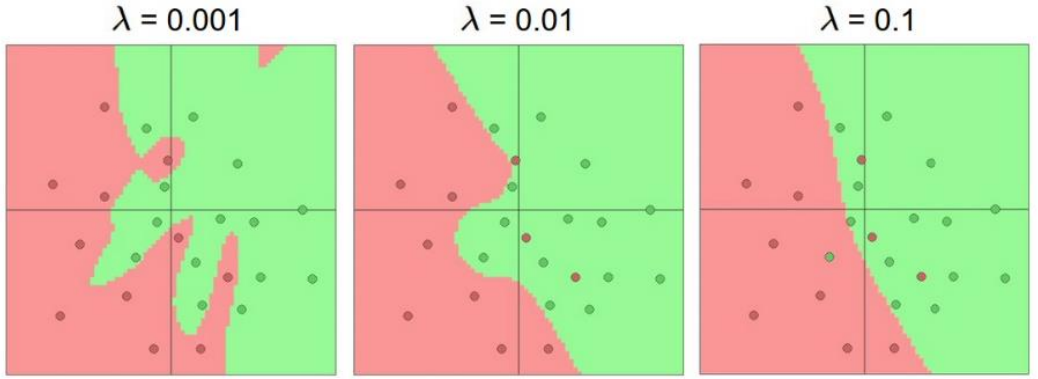
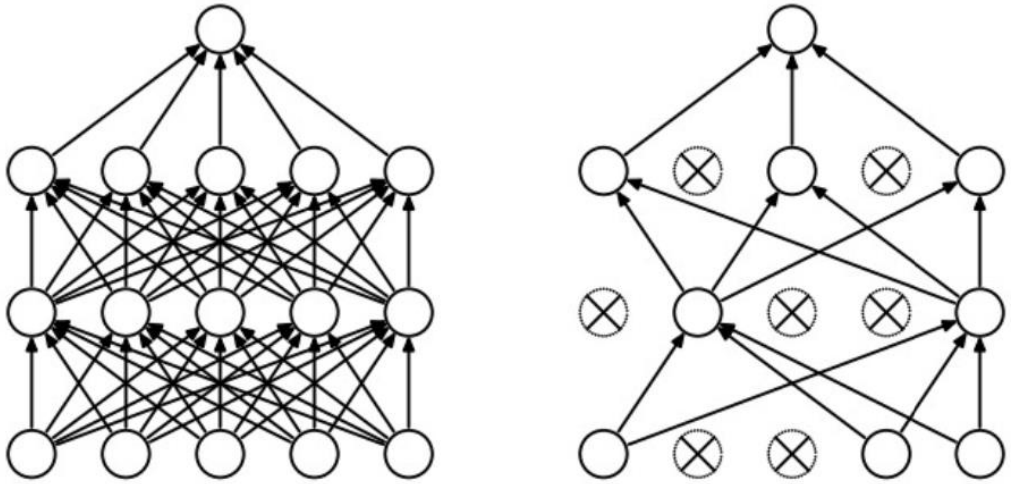
Learning rate	0.1, 0.01, 0.001, 0.0001	0.01
Batch size	64, 128, 256	128
Momentum rate	0.8, 0.9, 0.95	0.9
Weight initialization	Normal, Uniform, Glorot uniform	Glorot uniform
Per-parameter adaptive learning rate methods	RMSprop, Adagrad, Adadelta, Adam	Adam
Batch normalization	Yes, no	Yes
Learning rate 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	

Regularization





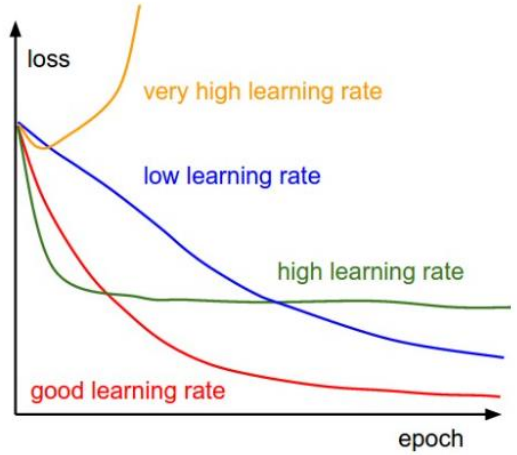
(a) Standard Neural Net

(b) After applying dropout.

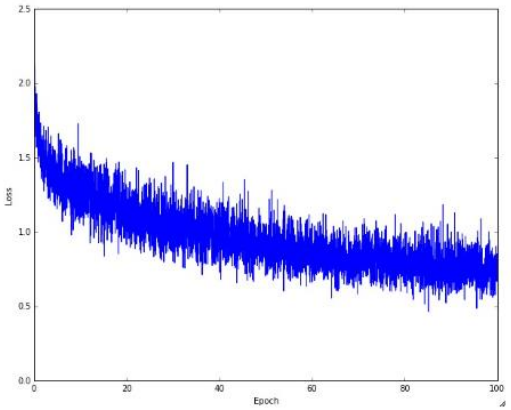
Hyperparameters

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	



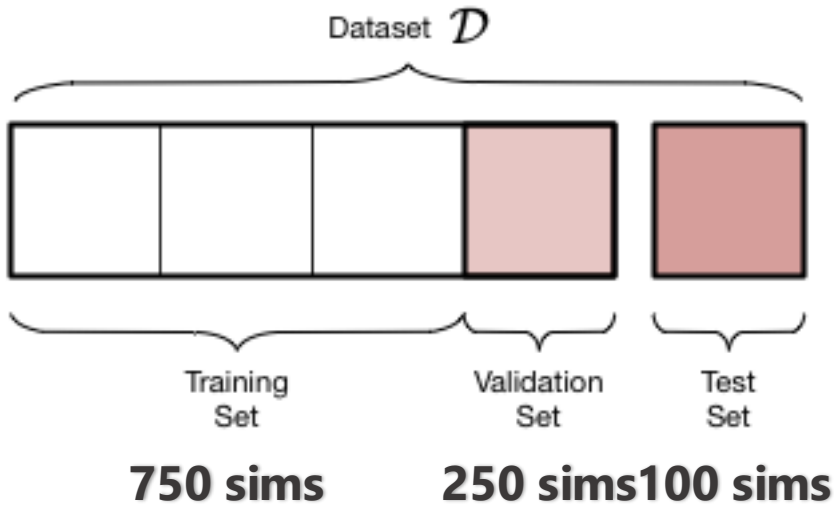
effects of different learning rates

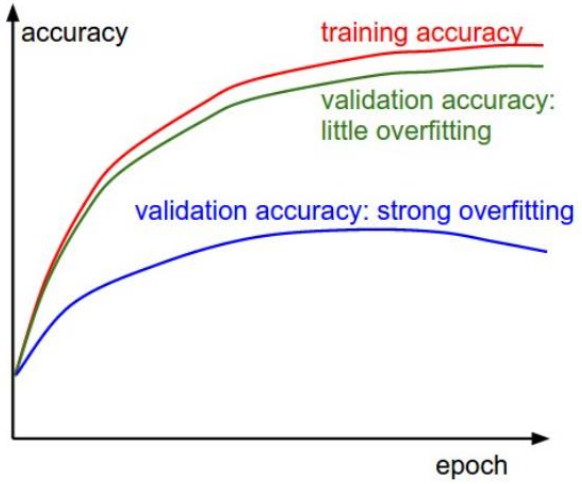


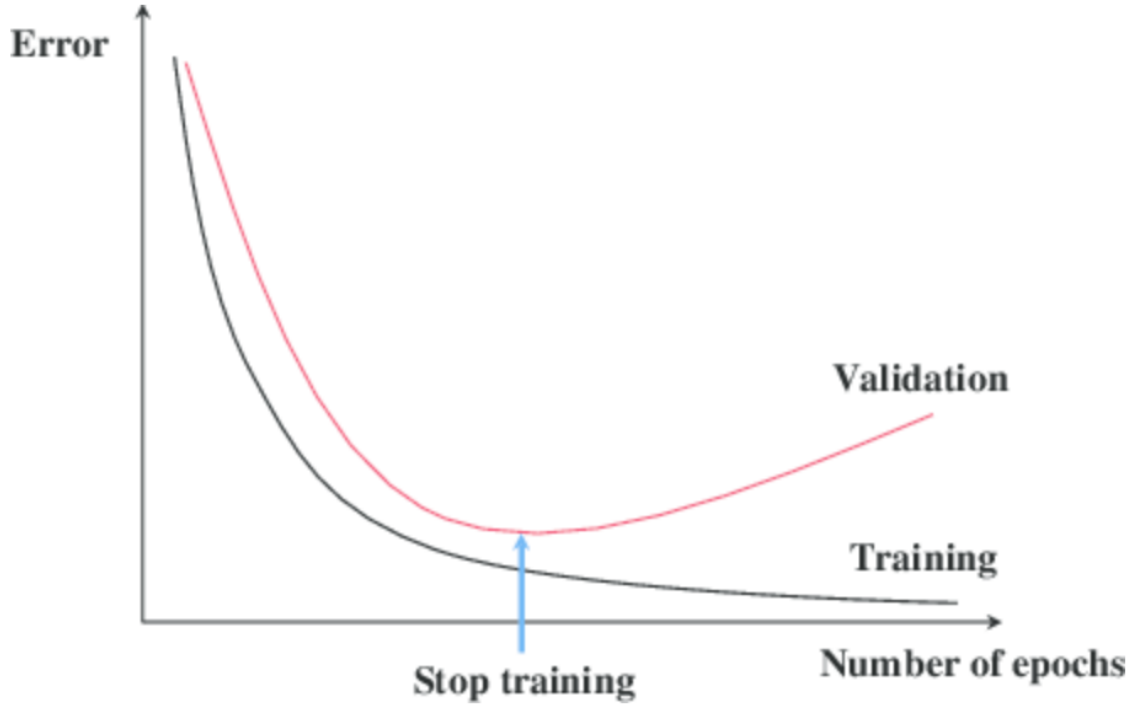
loss decay

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 4:**

- 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

DL witchcraft