PreciDIAB
National Center for
Precision Diabetic Medicine

Egid
European
Genomic
Institute
for Diabetes

Introduction to

Artificial Neural Networks

and Deep Learning

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Région
Hauts-de-France

UMR 1283 8199
Functional (Epi)genomics and Mechanisms of Type 2 Diabetes and Related Diseases


Google
self-driving car


Boston D
HD-03


ChatGPT
NI
Create an image for my presentation
Suggest a recipe based on a photo of my fridge
Create a workout plan
Write a report based on my data
Message ChatGPT
ChatGPT can make mistakes. Check important info.
?


AlphaGo
Lee Sedol

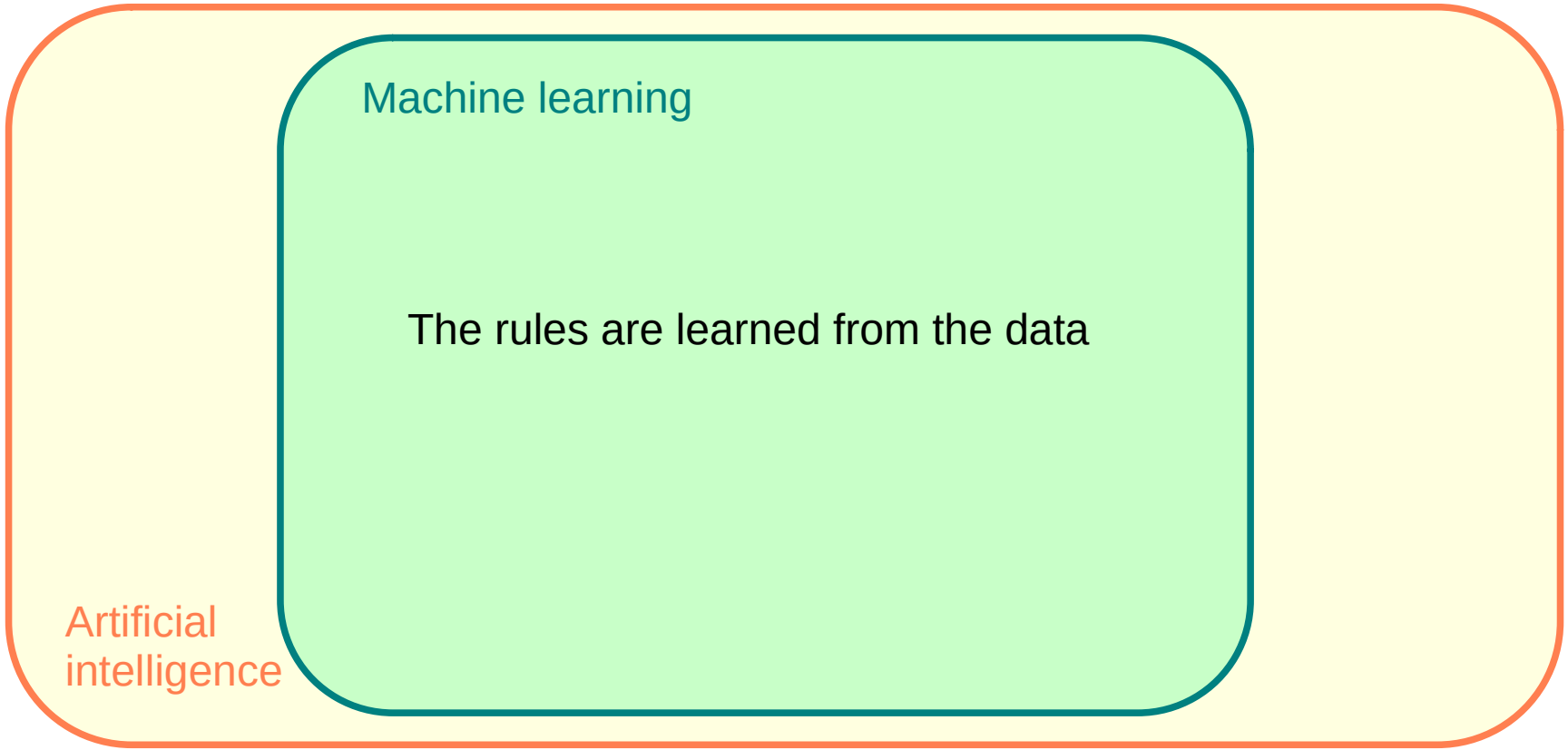

AlphaFold

Some terminology

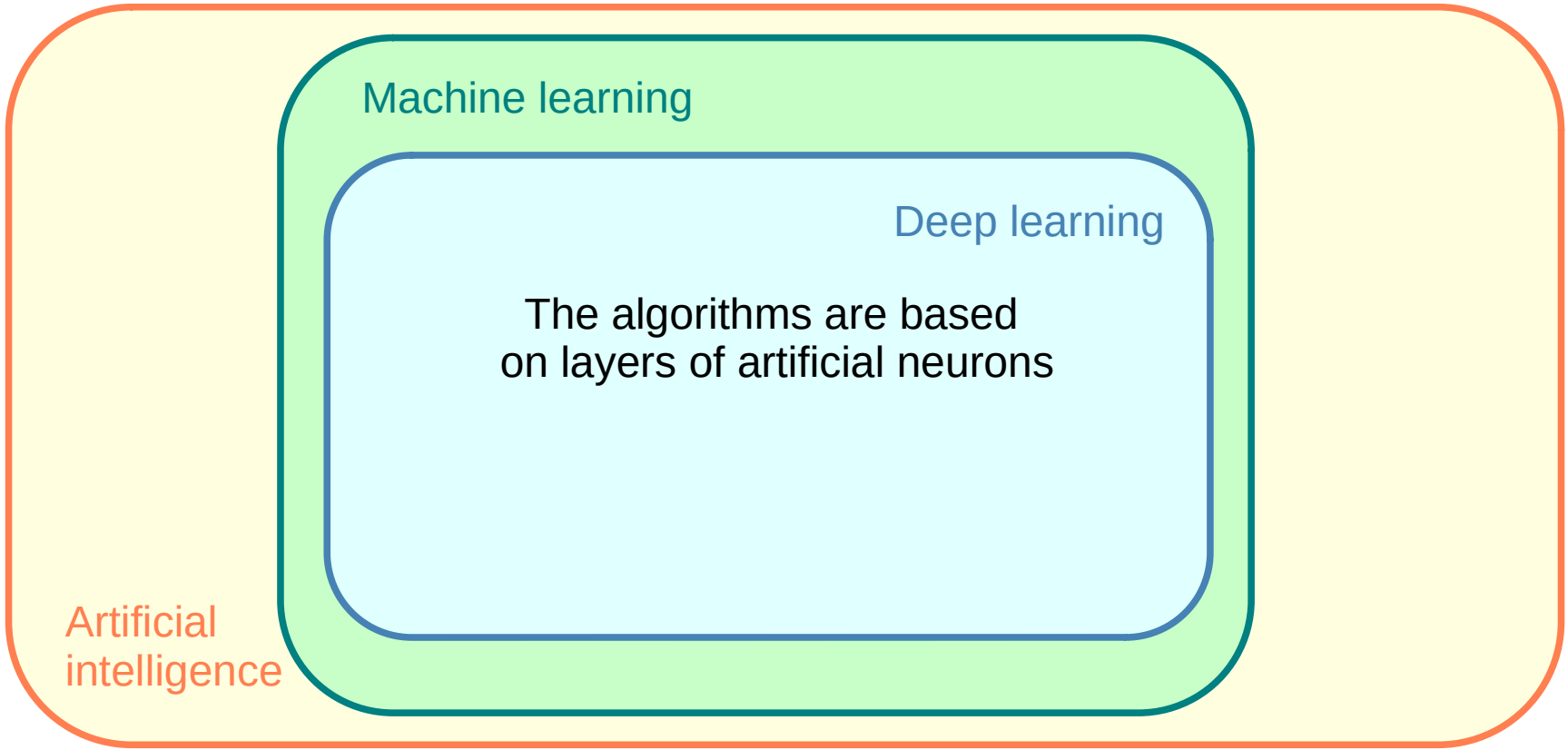
Assessments, evaluations, decisions, predictions
made by software tools

Artificial
intelligence

Some terminology



Some terminology



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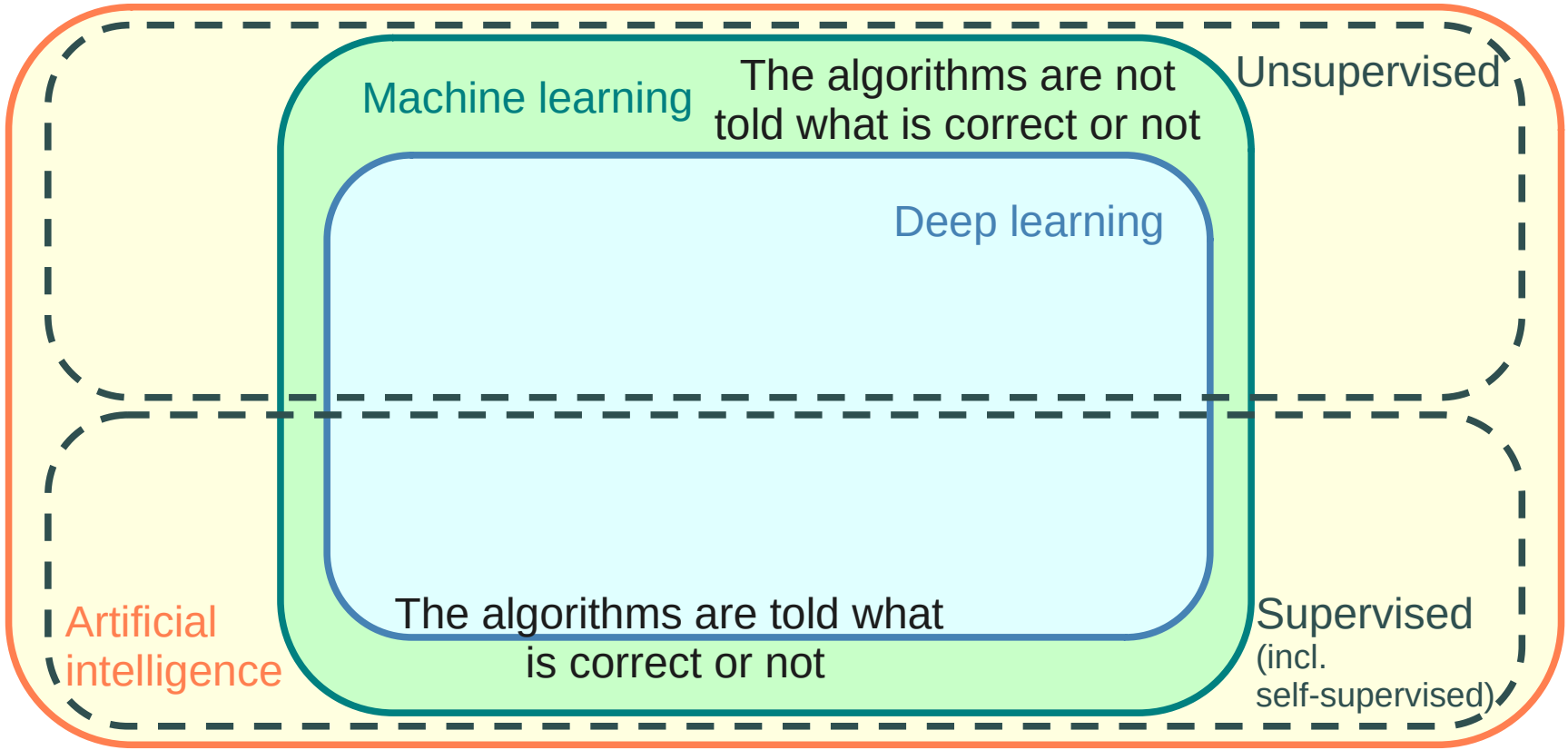
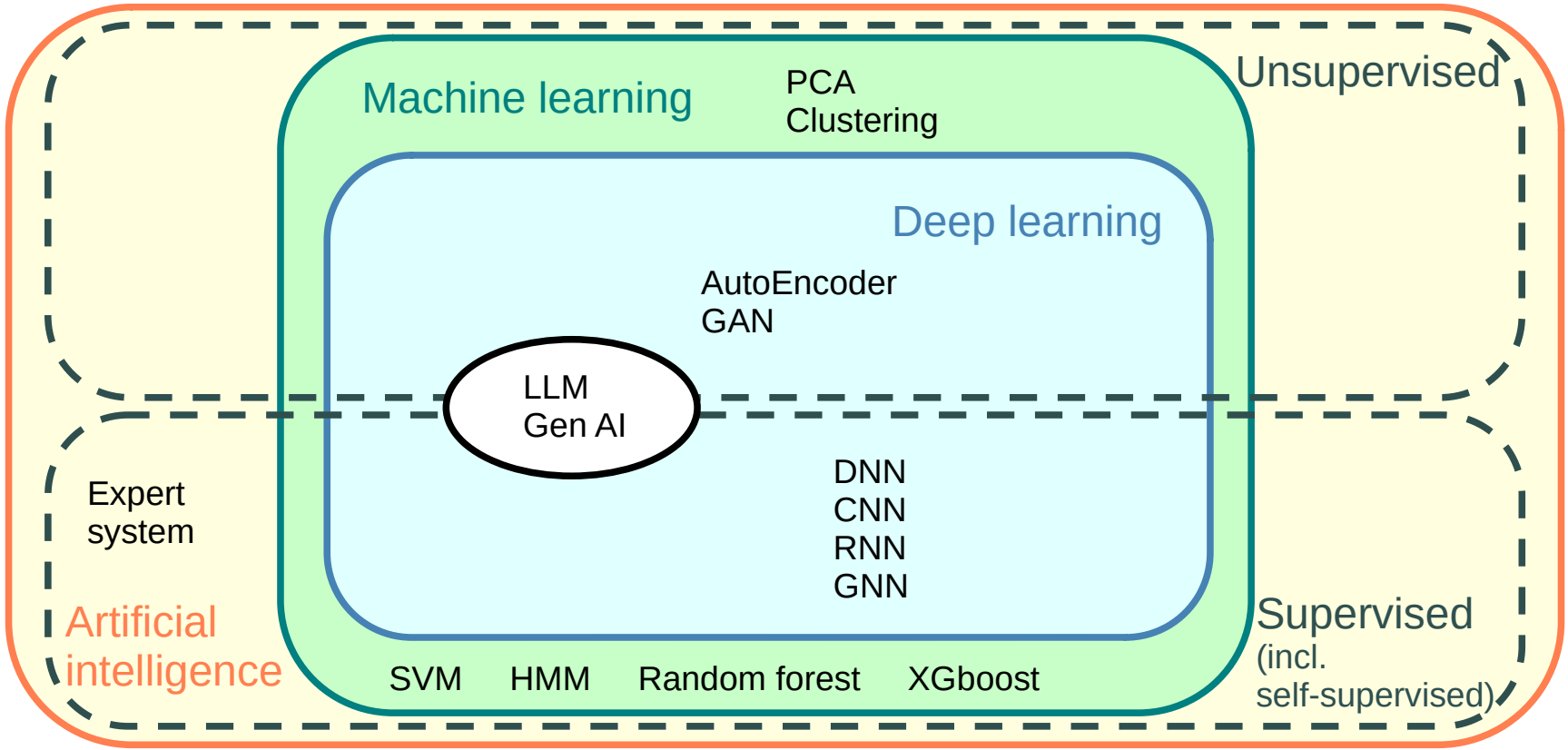


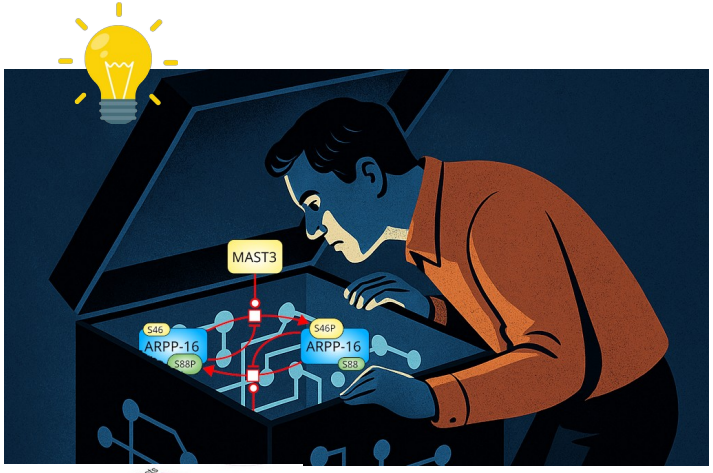
(NB: I consider reinforcement learning as part of supervised, but this is controversial)

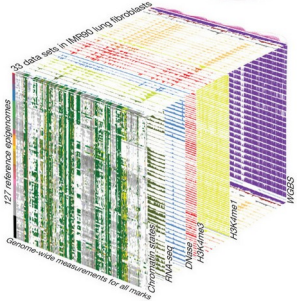
Some terminology



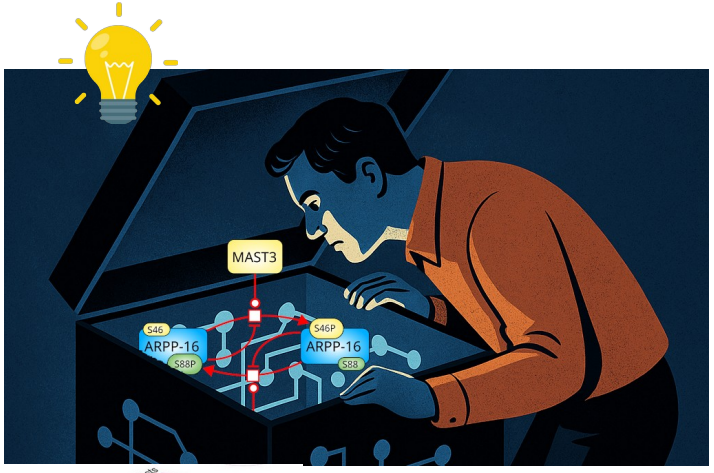
(NB: I consider reinforcement learning as part of supervised, but this is controversial)

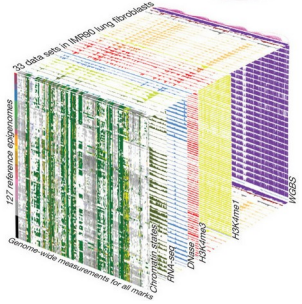
Why should we use machine learning?

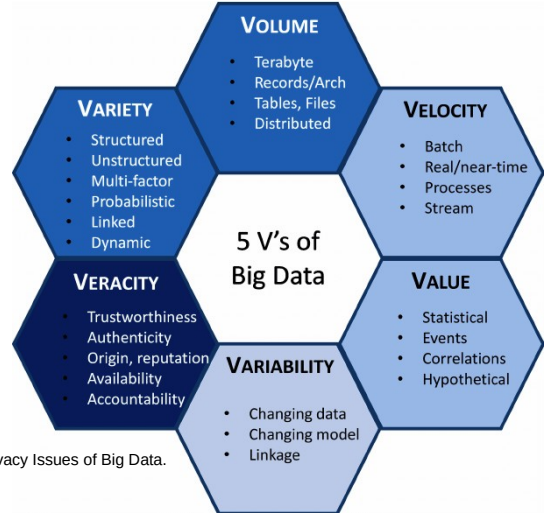




Why should we use machine learning?

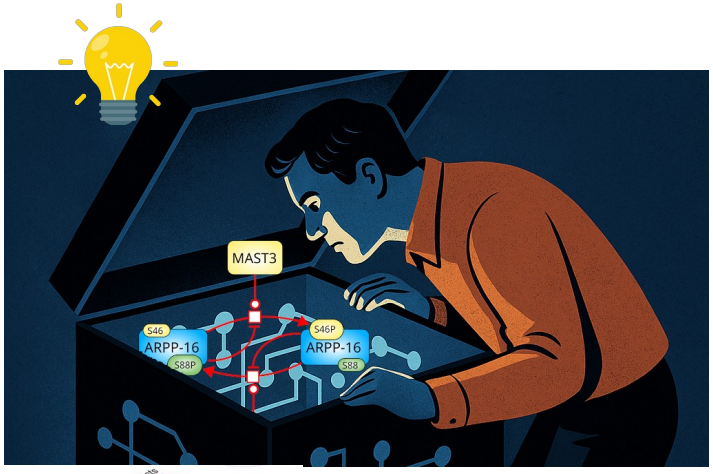


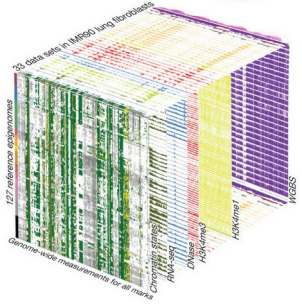


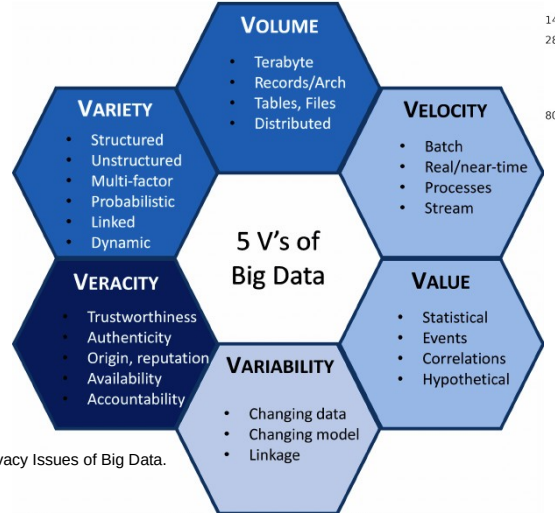


source: Moura, Serrão. Security and Privacy Issues of Big Data.
doi:10.4018/978-1-4666-8505-5.ch002

Why should we use machine learning?







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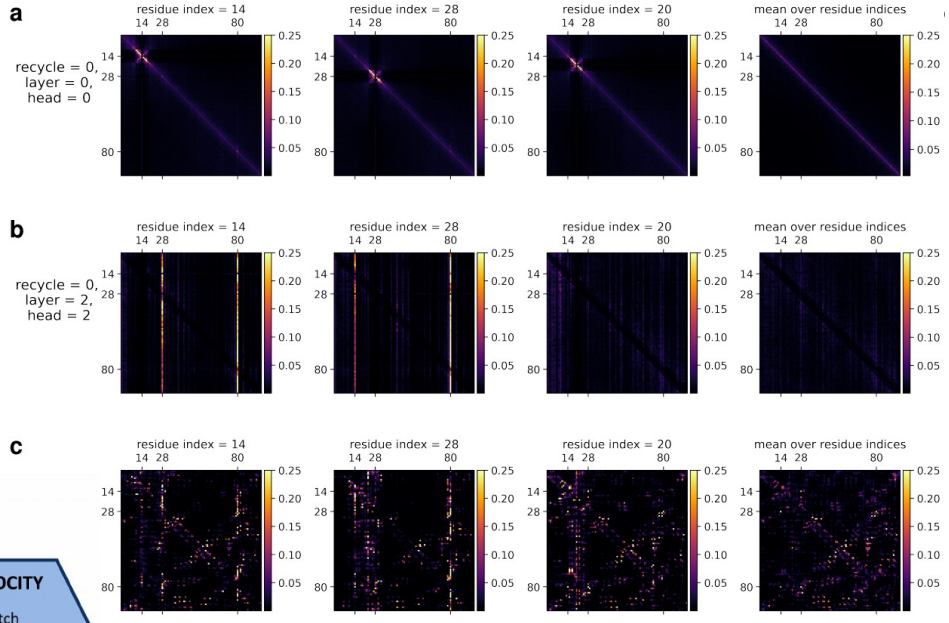
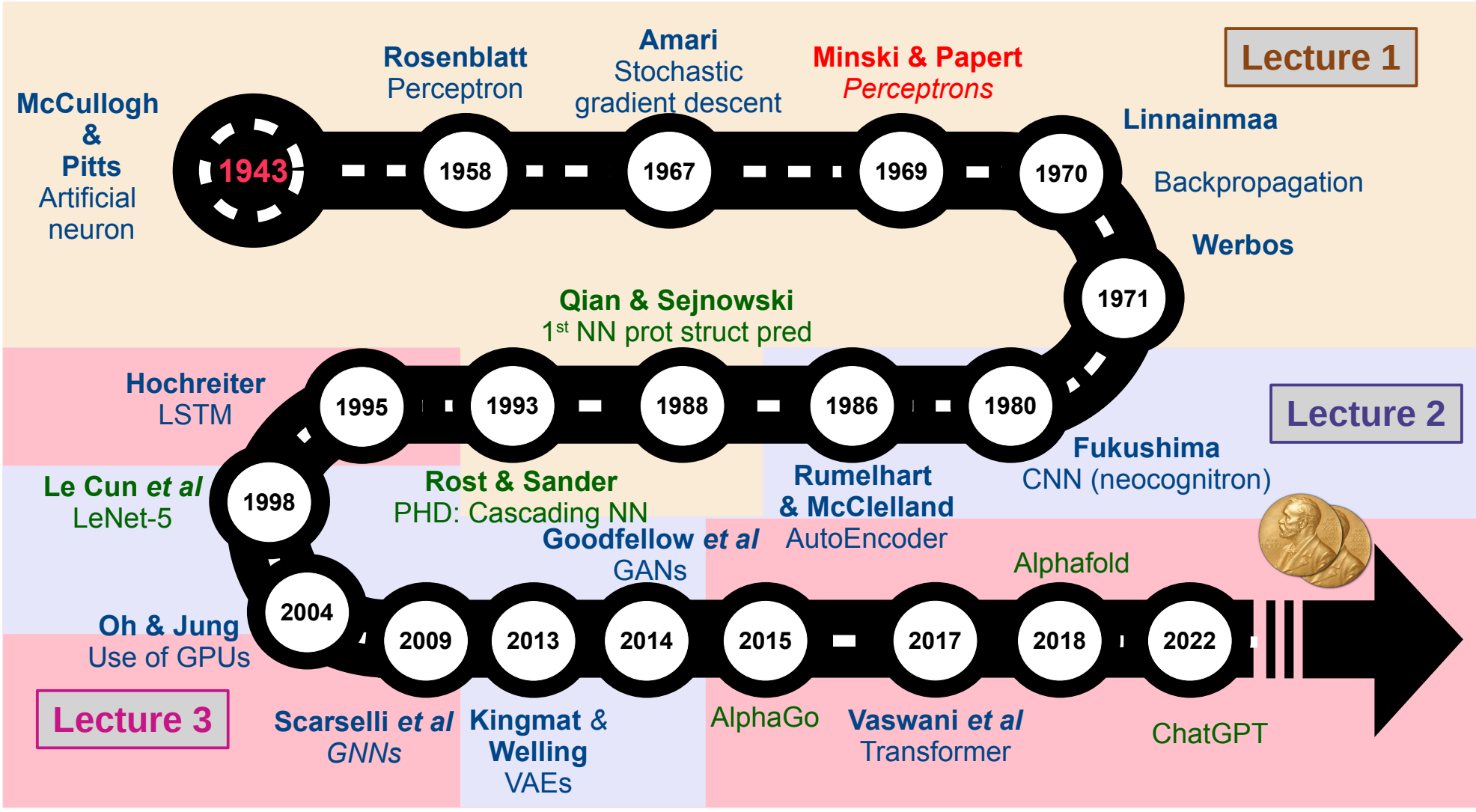


Source: Jumper *et al* (2021). Highly accurate protein structure prediction with Alphafold
doi:10.1038/s41586-021-03819-2 supplementary information


Lecture 1
McCullogh & Pitts
Artificial neuron
1943
Rosenblatt
Perceptron
1958
Amari
Stochastic gradient descent
1967
Minski & Papert
Perceptrons
1969
Linnainmaa
Backpropagation
1970
Werbos
1971
Qian & Sejnowski
1st NN prot struct pred
1980
1986
Rumelhart & McClelland
AutoEncoder
1988
Fukushima
CNN (neocognitron)
Lecture 2
1993
Rost & Sander
PHD: Cascading NN
1995
Hochreiter
LSTM
1998
Le Cun et al
LeNet-5
2004
Oh & Jung
Use of GPUs
2009
Scarselli et al
GNNs
2013
Kingmat & Welling
VAEs
2014
Goodfellow et al
GANs
2015
AlphaGo
2017
Vaswani et al
Transformer
2018
Alphafold
2022
ChatGPT
Lecture 3

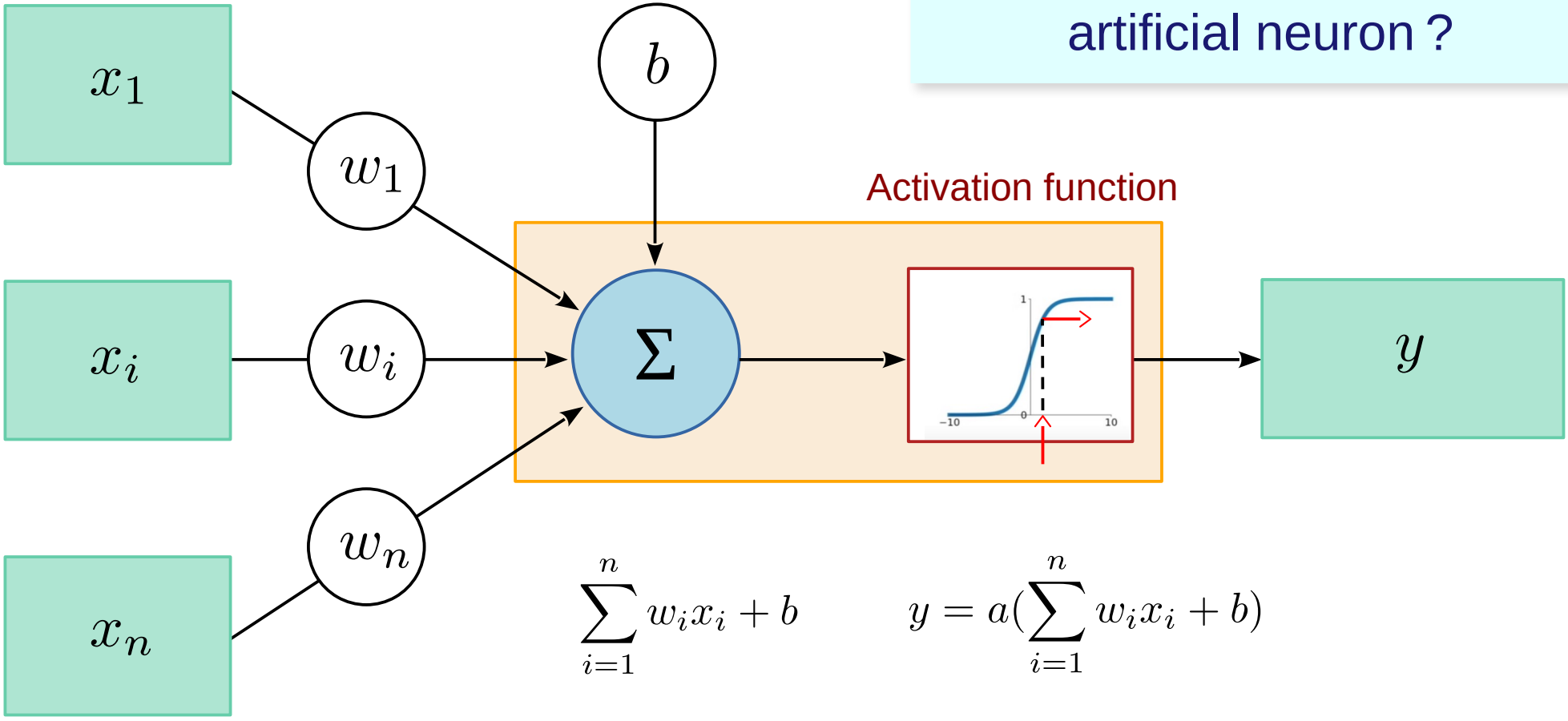
What is an ANN ?

- A method to represent any possible equation
  (Universal approximation theorem)

- A method to produce any possible curve
  in any number of dimensions

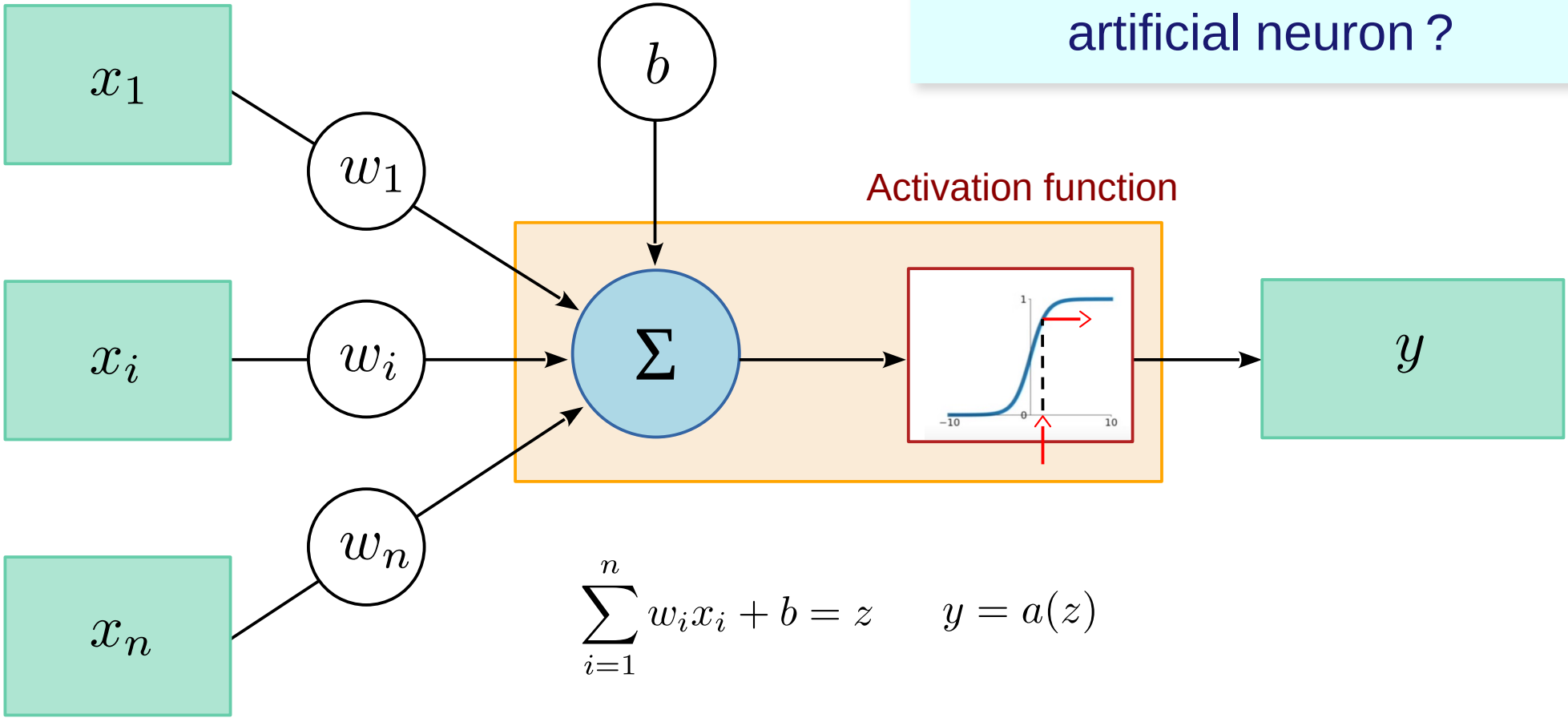
- A tool that can learn to recognize spatio-temporal patterns

What is an artificial neuron ?



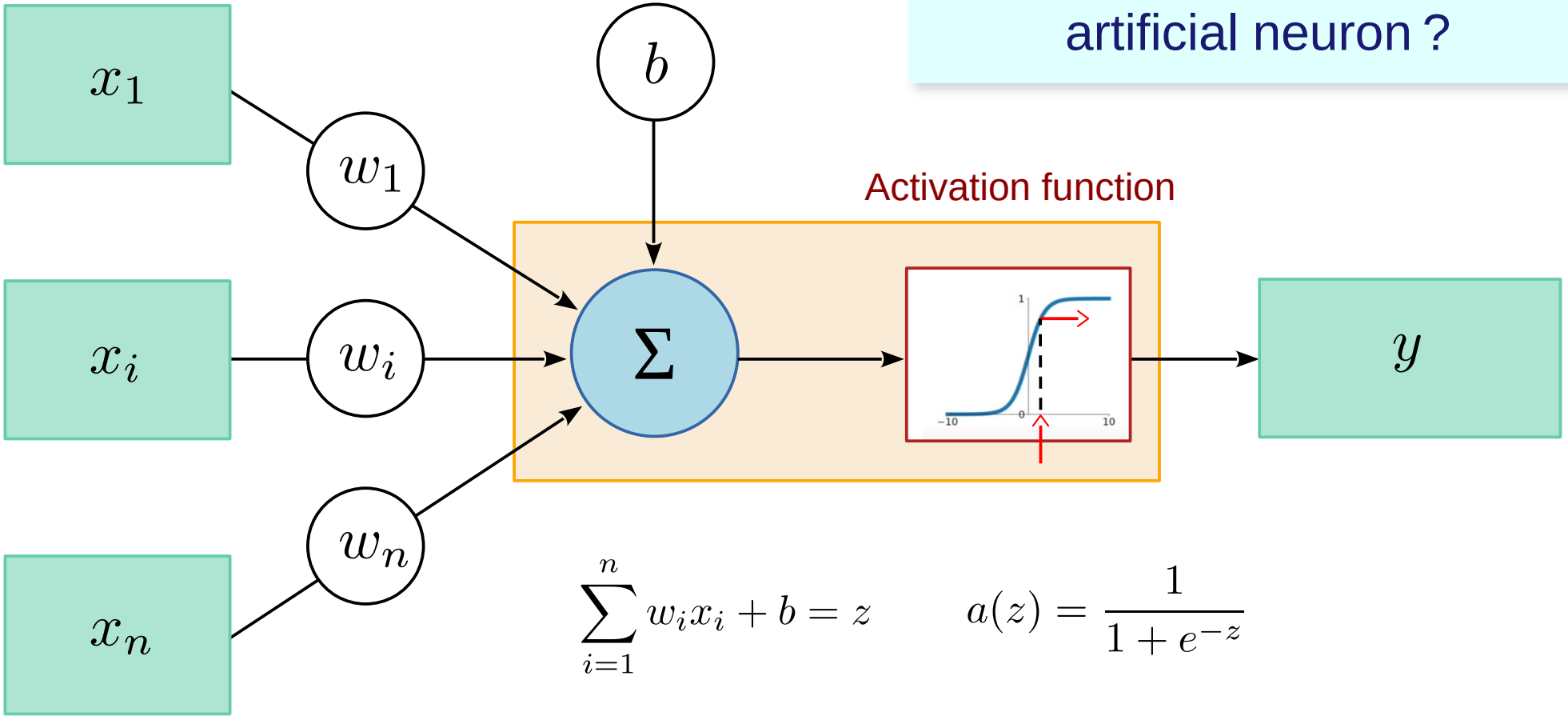
McCulloch and Pitts (1943) A logical calculus of the ideas immanent in nervous activity. *Bull Math Biophys* 5:115-133
Rosenblatt (1958) The perceptron: a probabilistic model for information storage and organization in the brain. *Psychol Rev* 65(6):386-408
Widrow and Hoff (1960) Adaptive Switching circuits. *WESCON Convention record* part IV: 96-104

What is an artificial neuron ?



$$\sum_{i=1}^{n} w_i x_i + b = z \qquad y = a(z)$$

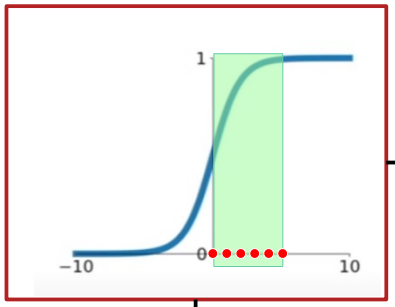
What is an artificial neuron ?



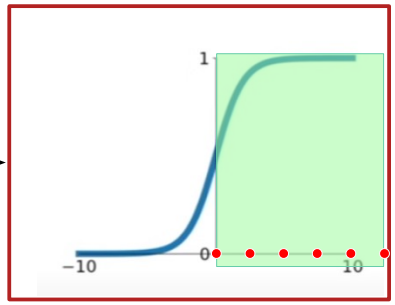
$$\sum_{i=1}^{n} w_i x_i + b = z \qquad a(z) = \frac{1}{1 + e^{-z}}$$

NB: when the activation function is logistic (sigmoid), this is actually a logistic regression...

Impact of the weights and the bias

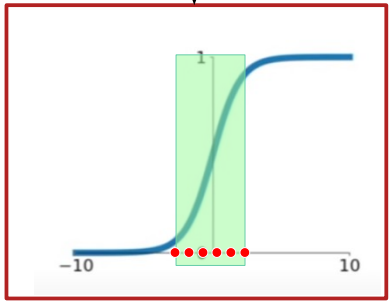


$w = 3$

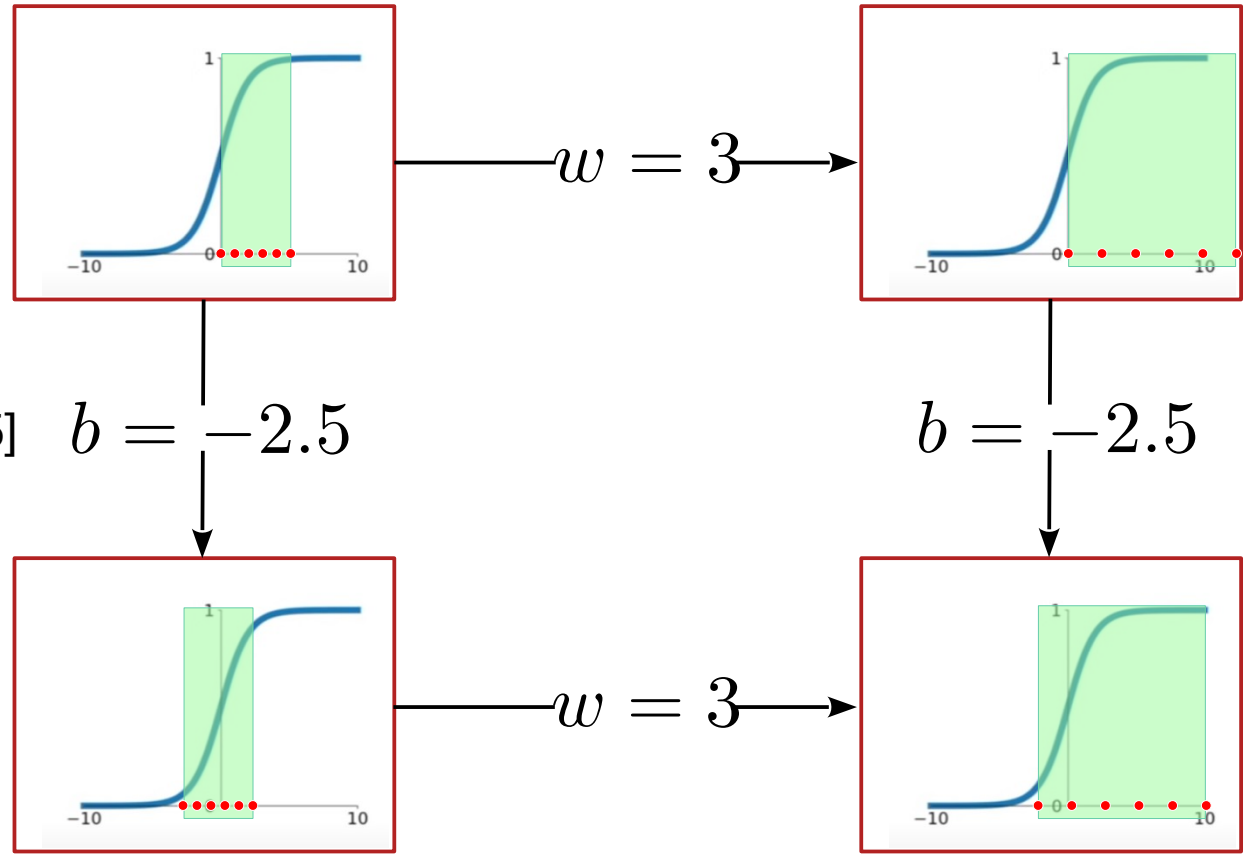


Successive inputs = [0,1,2,3,4,5]

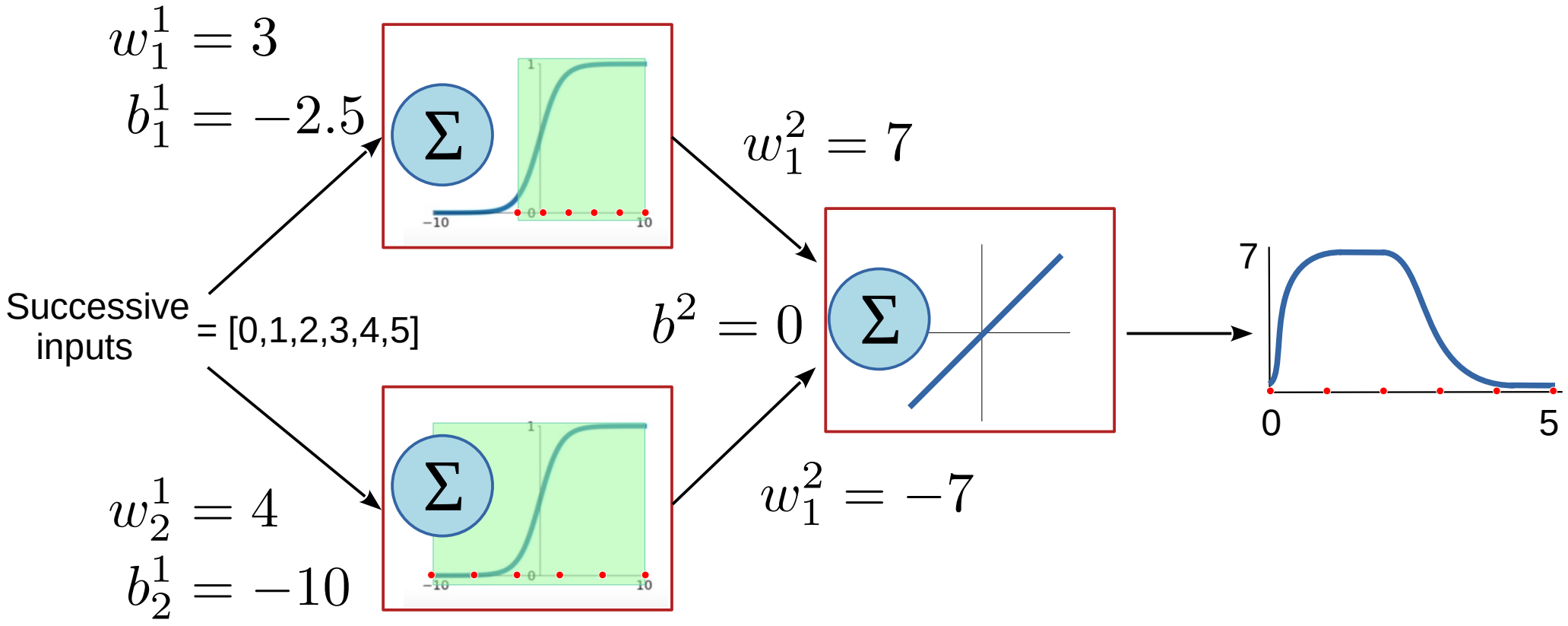
$b = -2.5$



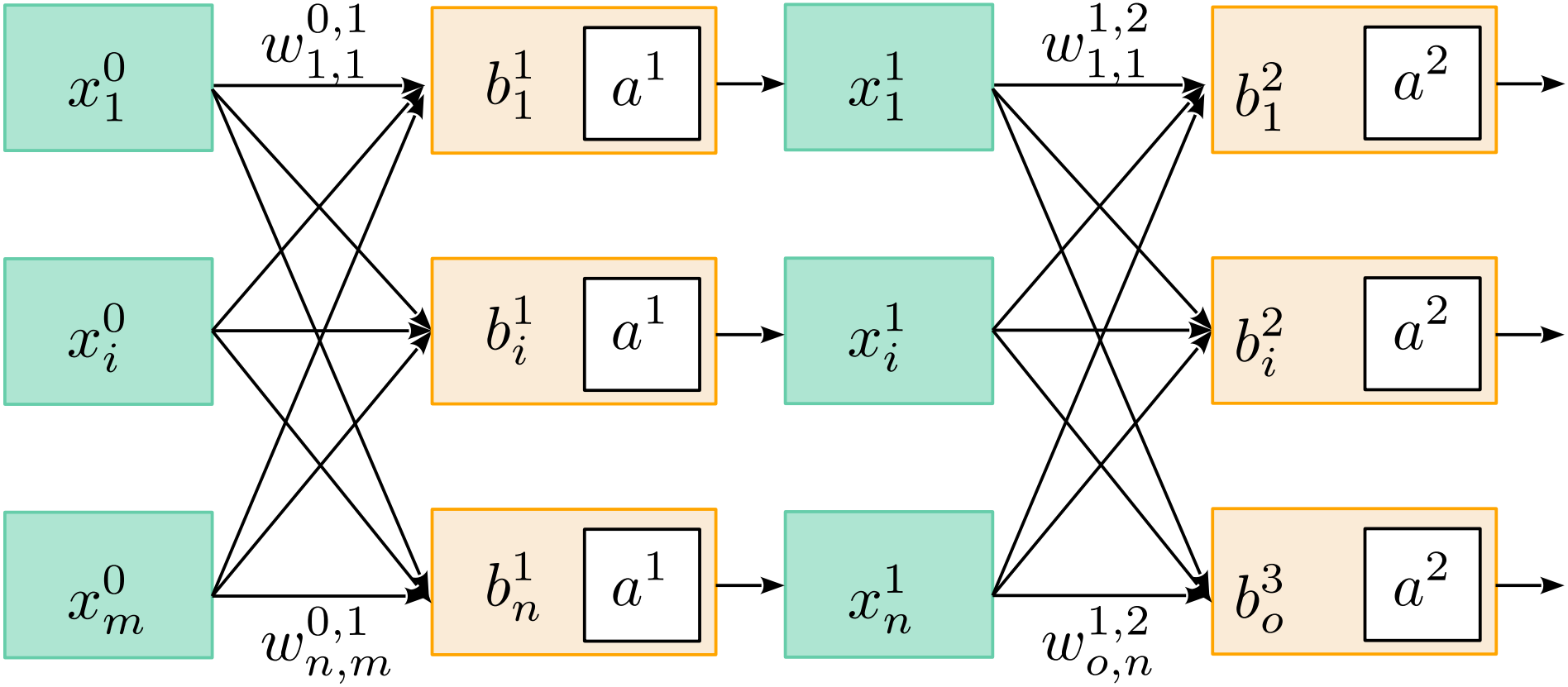
Impact of the weights and the bias



The magic happens with several neurons



And then we add layers (the “Deep”)



Rosenblatt (1958) The perceptron: a probabilistic model for information storage and organization in the brain. *Psychol Rev* 65(6):386-408

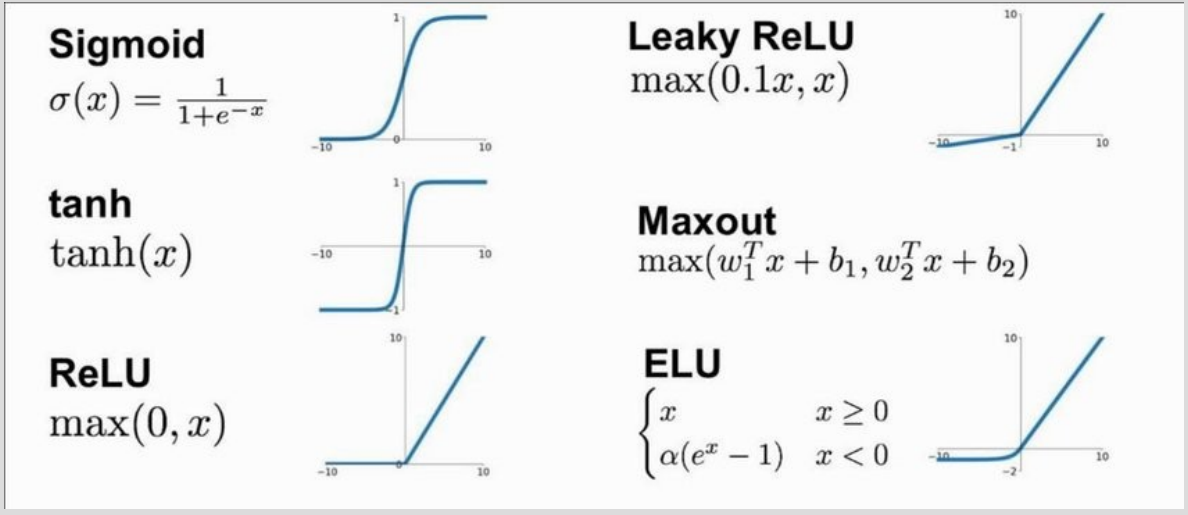
And then we add layers (the “Deep”)

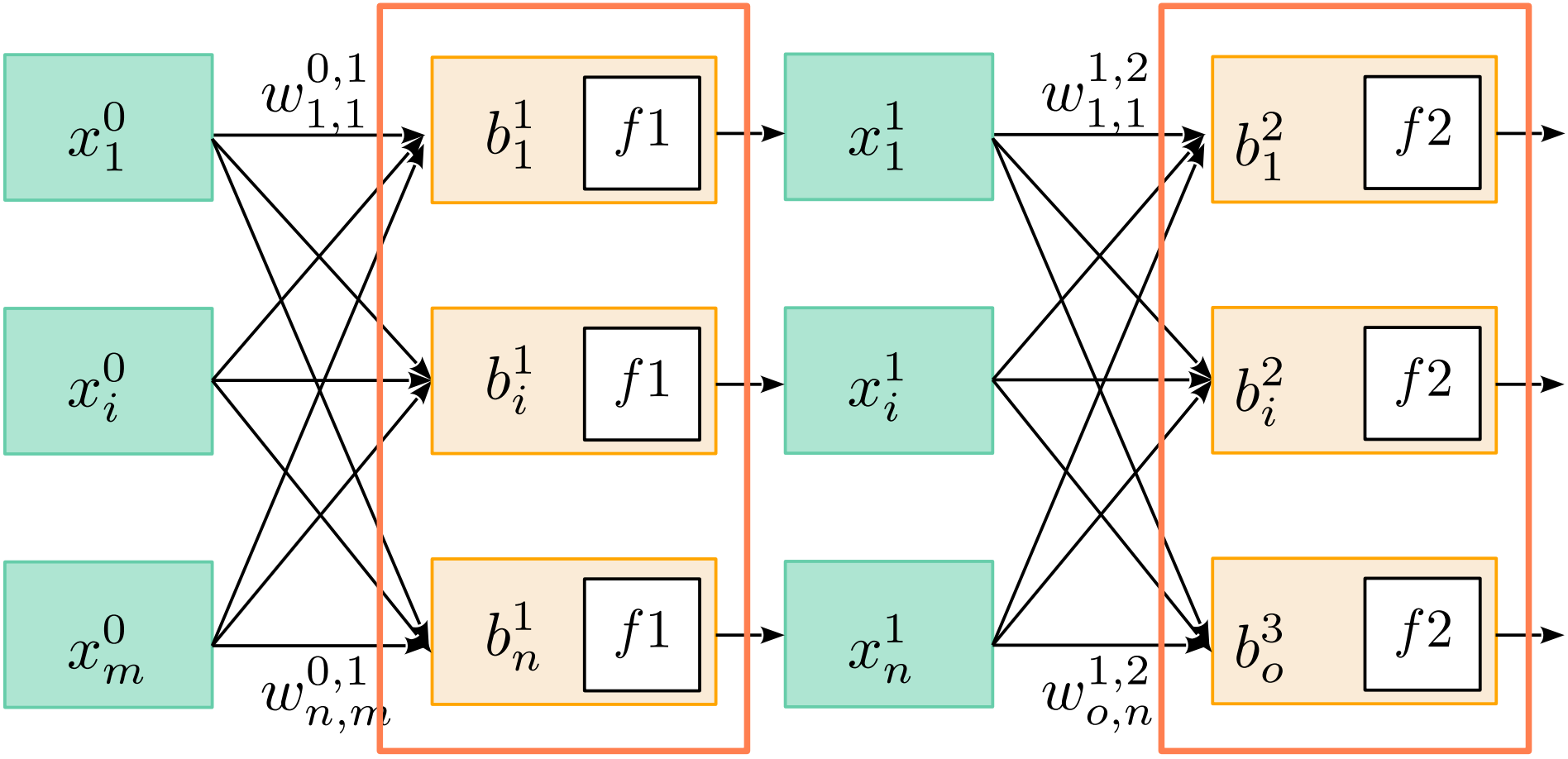
x_1^0

x_i^0

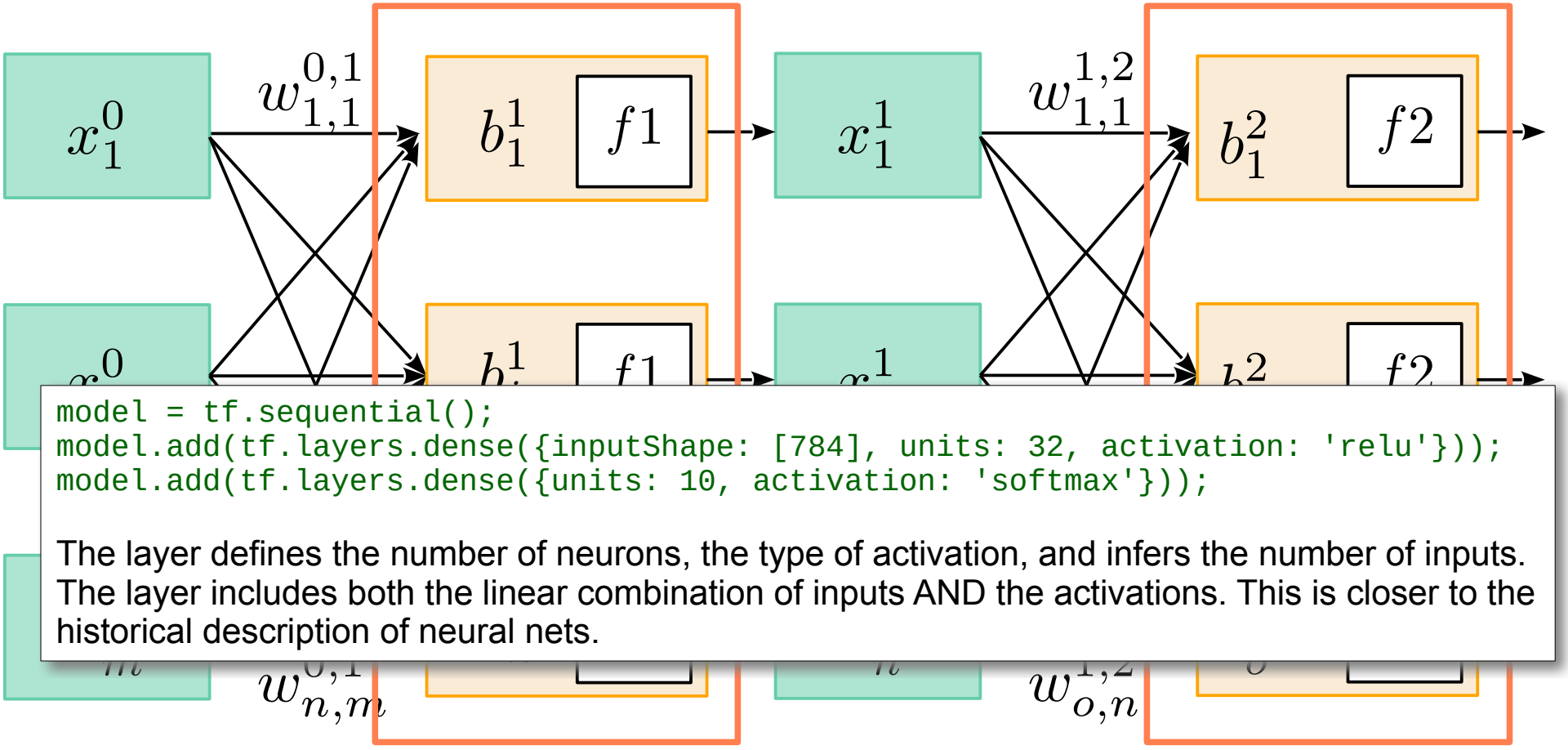
x_m^0

f1 and f2 can be different



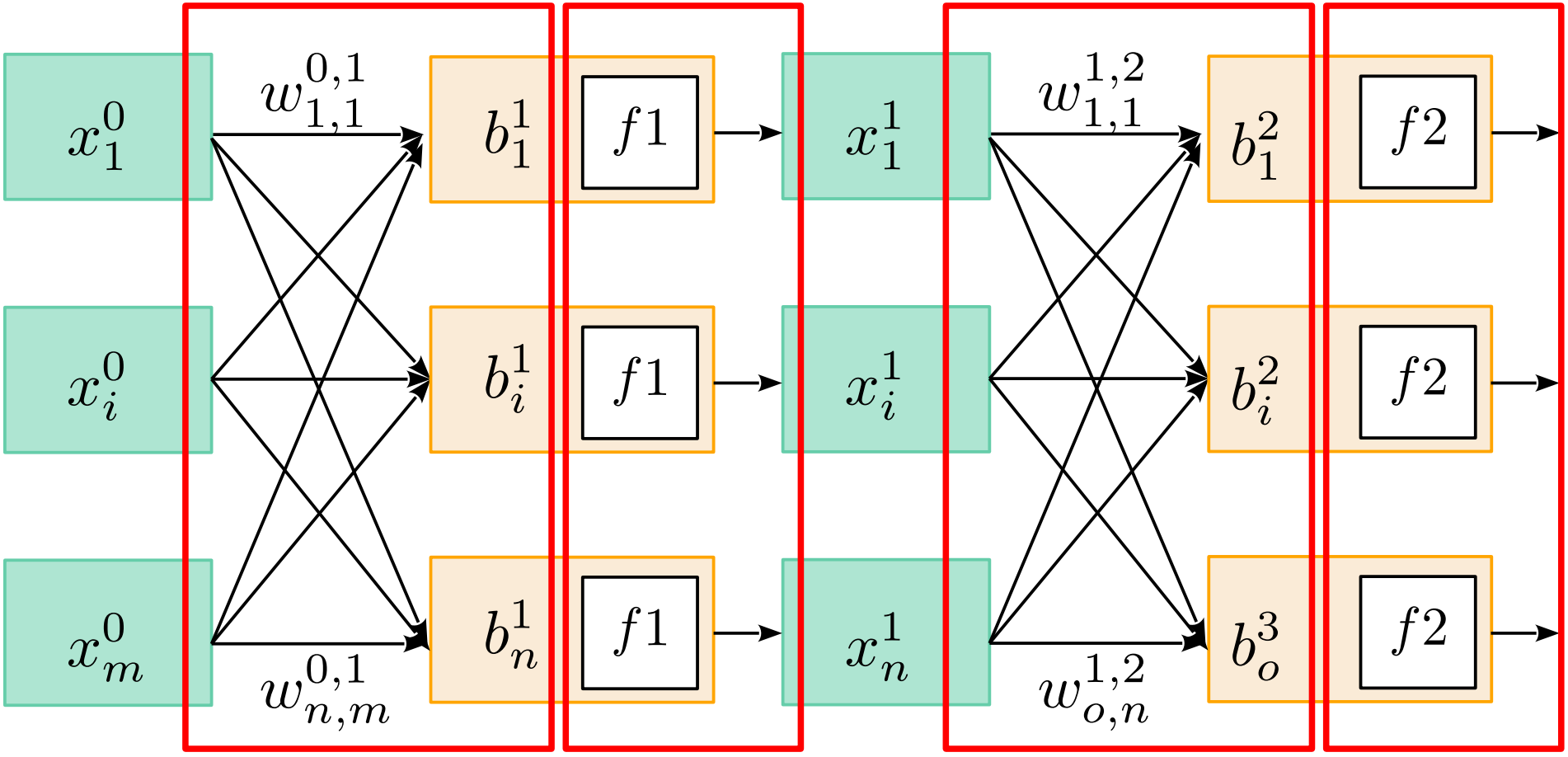

x_1^0
x_i^0
x_m^0
$w_{1,1}^{0,1}$
$w_{n,m}^{0,1}$
b_1^1
b_i^1
b_n^1
$f1$
x_1^1
x_i^1
x_n^1
$w_{1,1}^{1,2}$
$w_{o,n}^{1,2}$
b_1^2
b_i^2
b_o^3
$f2$

Layers in TensorFlow

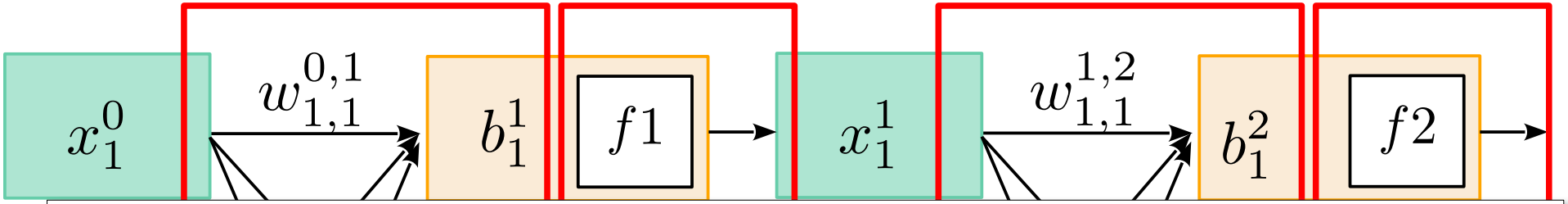



```
model = tf.sequential();
model.add(tf.layers.dense({inputShape: [784], units: 32, activation: 'relu'}));
model.add(tf.layers.dense({units: 10, activation: 'softmax'}));
```

The layer defines the number of neurons, the type of activation, and infers the number of inputs. The layer includes both the linear combination of inputs AND the activations. This is closer to the historical description of neural nets.


x_1^0
x_i^0
x_m^0
$w_{1,1}^{0,1}$
$w_{n,m}^{0,1}$
b_1^1
b_i^1
b_n^1
$f1$
$f1$
$f1$
x_1^1
x_i^1
x_n^1
$w_{1,1}^{1,2}$
$w_{o,n}^{1,2}$
b_1^2
b_i^2
b_o^3
$f2$
$f2$
$f2$

Layers in PyTorch



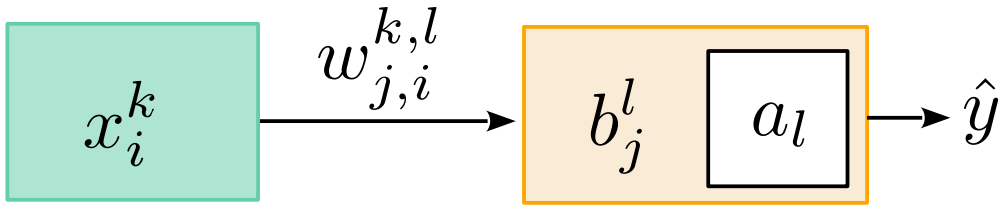

```
SimpleNN(nn.Module):
    def __init__(self, input_size, hidden_size, output_size):
        super(SimpleNN, self).__init__()
        self.fc1 = nn.Linear(input_size, hidden_size)
        self.fc2 = nn.Linear(hidden_size, output_size)

    def forward(self, x):
        x = F.relu(self.fc1(x))
        x = self.fc2(x)
        return x
```

The linear combination and activation layers are defined separately. Input and output size are specified. This is closer to the actual internal structures of neural nets, and in particular of tensors.

A word on standard notation

$k =$ source layer

$l =$ target layer



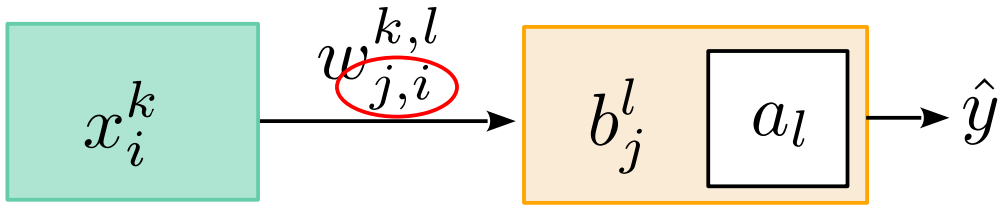
$i =$ source neuron

$j =$ target neuron

A word on standard notation

$k =$ source layer

$l =$ target layer



$i =$ source neuron

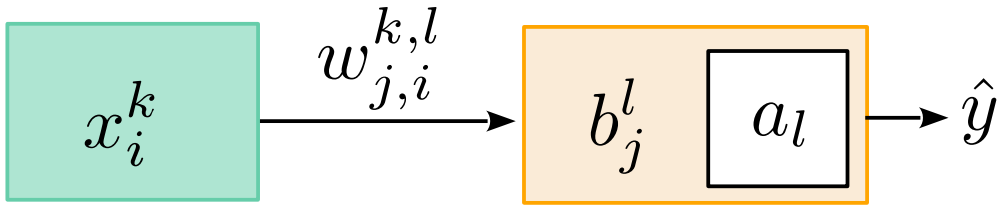
$j =$ target neuron

why???

A word on standard notation

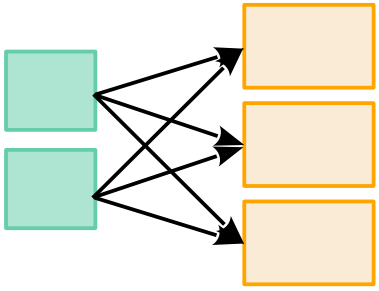
k = source layer

l = target layer



i = source neuron

j = target neuron



$$\begin{pmatrix} z_1 \\ z_2 \\ z_3 \end{pmatrix} = \begin{pmatrix} w_{1,1} & w_{1,2} \\ w_{2,1} & w_{2,2} \\ w_{3,1} & w_{3,2} \end{pmatrix} \cdot \begin{pmatrix} x_1 \\ x_2 \end{pmatrix} = \begin{pmatrix} x_1 w_{1,1} + x_2 w_{1,2} \\ x_1 w_{2,1} + x_2 w_{2,2} \\ x_1 w_{3,1} + x_2 w_{4,2} \end{pmatrix}$$

Each portion of an ANN is stored as a multidimensional array: a tensor
There are tensors of numbers and also tensors of functions connecting other tensors

Why piling linear layers is useless

1) Output of a two linear activation layer

$$y_1 = b_1 + w_{1,1} \cdot x_1 + w_{1,2} \cdot x_2$$
$$y_2 = b_2 + w_{2,1} \cdot x_1 + w_{2,2} \cdot x_2$$

2) Input to a neuron of the next layer

$$z = b_z + w_{z,1} \cdot y_1 + w_{z,2} \cdot y_2$$

3) Substitution

$$z = b_z + w_{z,1}(b_1 + w_{1,1} \cdot x_1 + w_{1,2} \cdot x_2) + w_{z,2}(b_2 + w_{2,1} \cdot x_1 + w_{2,2} \cdot x_2)$$
$$z = b_z + w_{z,1} \cdot b_1 + w_{z,1} \cdot w_{1,1} \cdot x_1 + w_{z,1} \cdot w_{1,2} \cdot x_2 + w_{z,2} \cdot b_2 + w_{z,2} \cdot w_{2,1} \cdot x_1 + w_{z,} \cdot w_{2,2} \cdot x_2$$

4) Reorganising

$$z = b_z + w_{z,1} \cdot b_1 + w_{z,2} \cdot b_2 + (w_{z,1} \cdot w_{1,1} + w_{z,2} \cdot w_{2,1})x_1 + (w_{z,1} \cdot w_{1,2} + w_{z,2} \cdot w_{2,2})x_2$$

5) Let's define

B = bz + w1z*b1 + w2z*b2

W1 = w1z*w11 + w2z*w12

W2 = w1z*w21 + w2z*w22

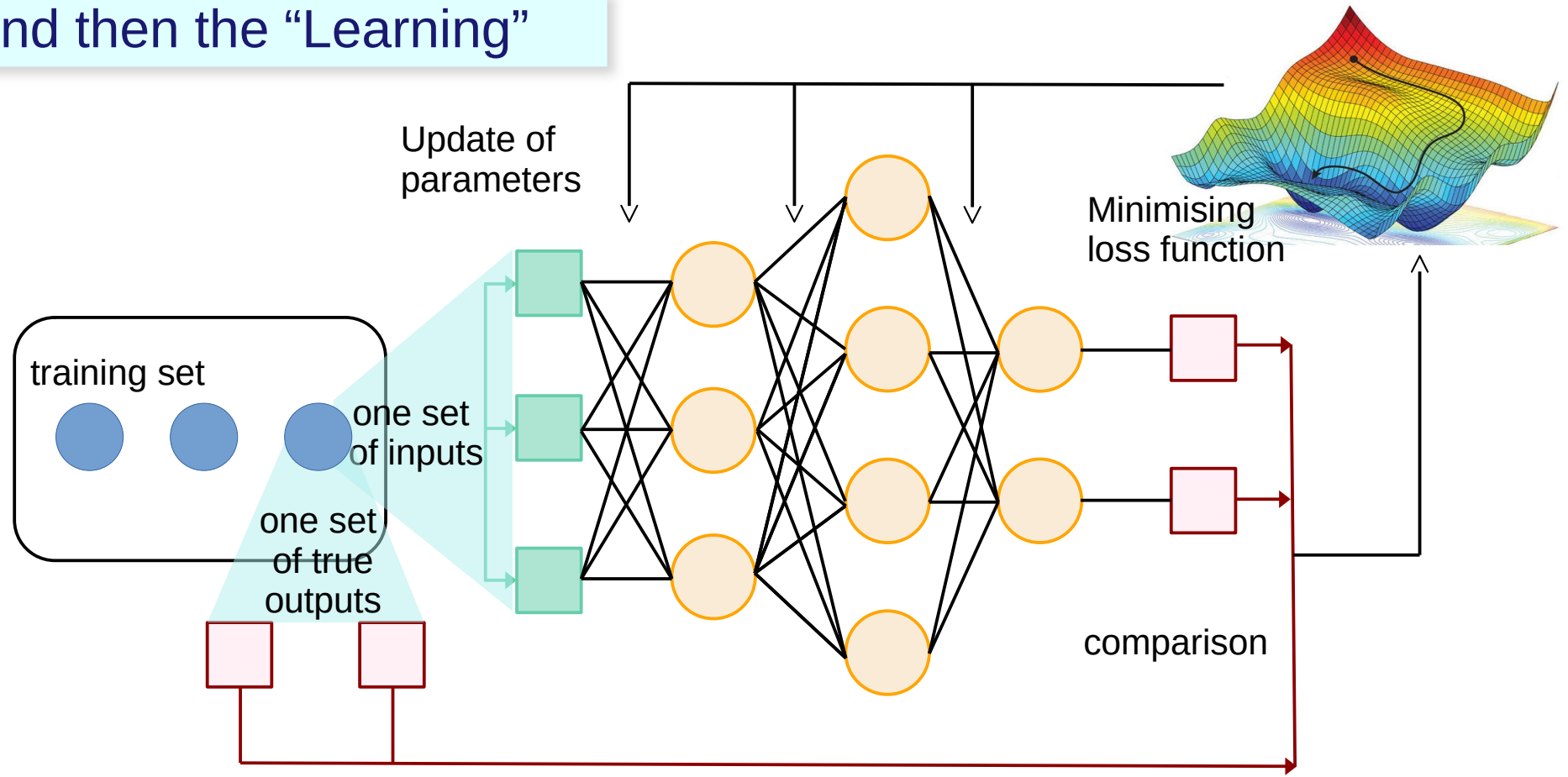
6) Which gives

Z = B + W1*x1 + W2*x2

Therefore, the two linear neurons acted like one neuron linear neurons. This would still be the case with 100 layers of 100 linear activations.

NB: This goes for ReLU activations as well
if no other processing between layers (e.g. convolutions)

And then the “Learning”



Widrow and Hoff (1960) Adaptive Switching circuits. *WESCON Convention record* part IV: 96-104; S Amari (1967). A theory of adaptive pattern classifier. *IEEE Transactions*. EC (16): 279–307; S Linnainmaa (1970-1976). The representation of the cumulative rounding error of an algorithm as a Taylor expansion of the local rounding errors (Masters). University of Helsinki. p. 6–7; P Werbos (1971-1982) Applications of advances in non-linear sensitivity analysis. *LNCIS* 38: 762-770
LeCun Y (1985) Une procédure d'apprentissage pour réseau à seuil asymétrique. *Proc Cognitiva* 85, 599-604.
Rumelhart, Hinton, and Williams (1986) Learning representations by back-propagating errors." *Nature* 323(6088): 533-536.

Parameters vs hyperparameters in DL

Parameters are learned: weights and biases
Models can have a dozen to several hundreds billions parameters

Hyperparameters are set

Architecture: # layers, # neurons, type of activation functions and regularisations

Evaluation: Loss function, optimiser, learning rate, decay

Training duration: Epochs, batch size, early stop

Optimisation, e.g., gradient descent

Objective: to minimise a *loss function*
(~*cost function* in optimisation)

Regression:

Number of samples

$$\mathrm{MSE} = \frac{1}{S}\sum_{i=1}^{S}(y_{(i)} - \hat{y_{(i)}})^2$$

True value

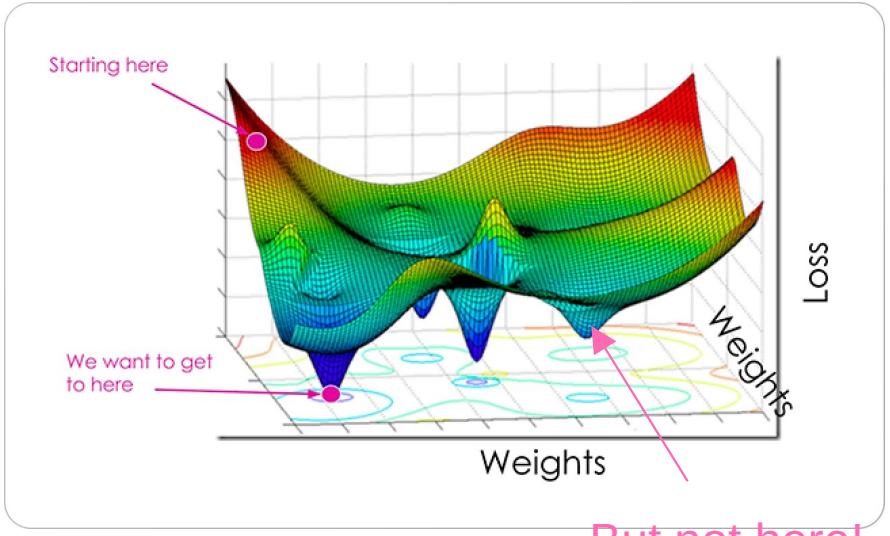
Predicted value

$$\mathrm{MAE} = \frac{1}{S}\sum_{i=1}^{S}|y_{(i)} - \hat{y_{(i)}}|$$

Classification:

$$\mathrm{BCE} = -\frac{1}{S}\sum_{i=1}^{S} y_{(i)}\log(\hat{y_{(i)}}) + (1 - y_{(i)})\log(1 - \hat{y_{(i)}})$$

$$\mathrm{CCE} = -\frac{1}{S}\sum_{i=1}^{S}\sum_{j=1}^{C} y_{(i)j}\log(\hat{y_{(i)j}})$$

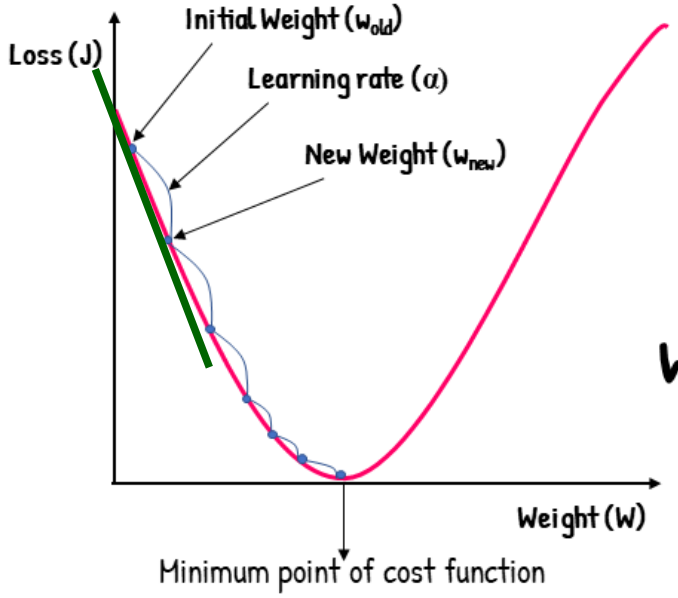


But not here!

MSE: mean squared error
MAE: mean averaged error
BCE: binary cross-entropy
CCE: categorical cross-entropy

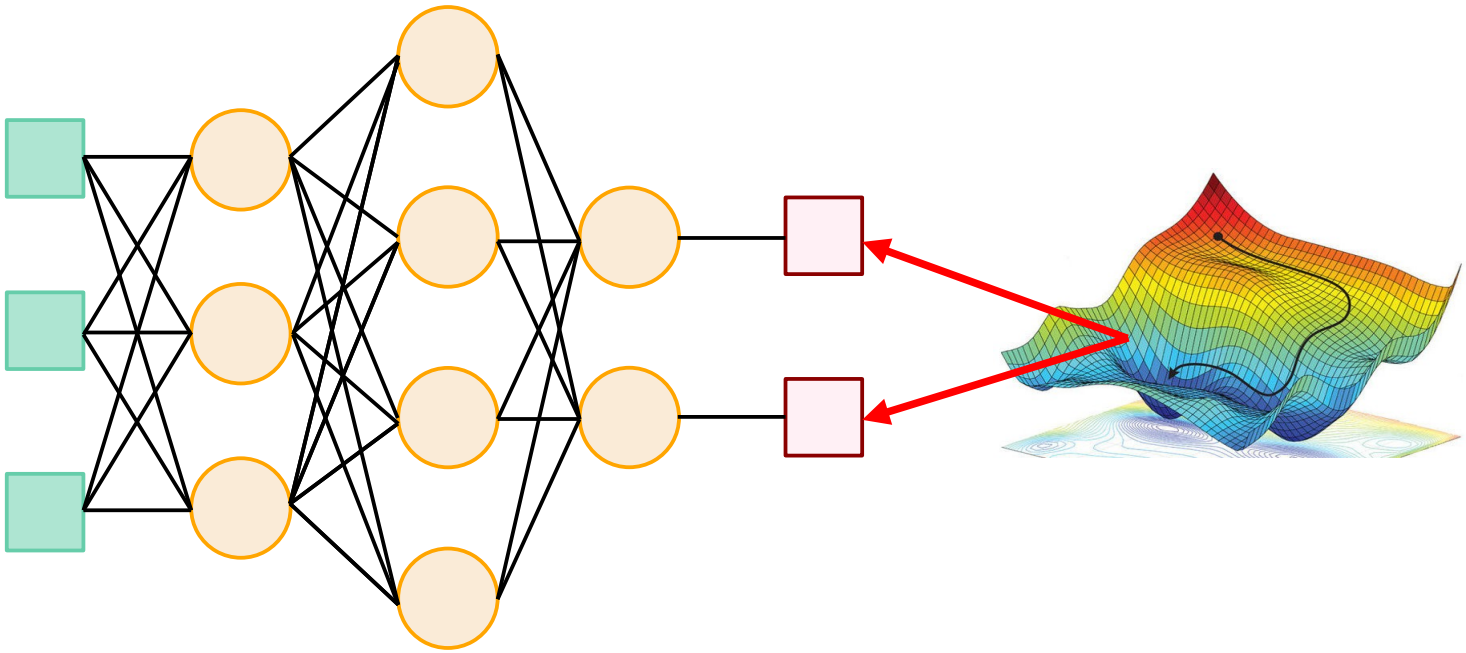
Optimization, e.g., gradient descent

To minimise the loss function (called L, C, or most often J), we will calculate the “gradient” – the derivative – of the loss function with a set of parameters and calculate a new set using this gradient and the *learning rate*.

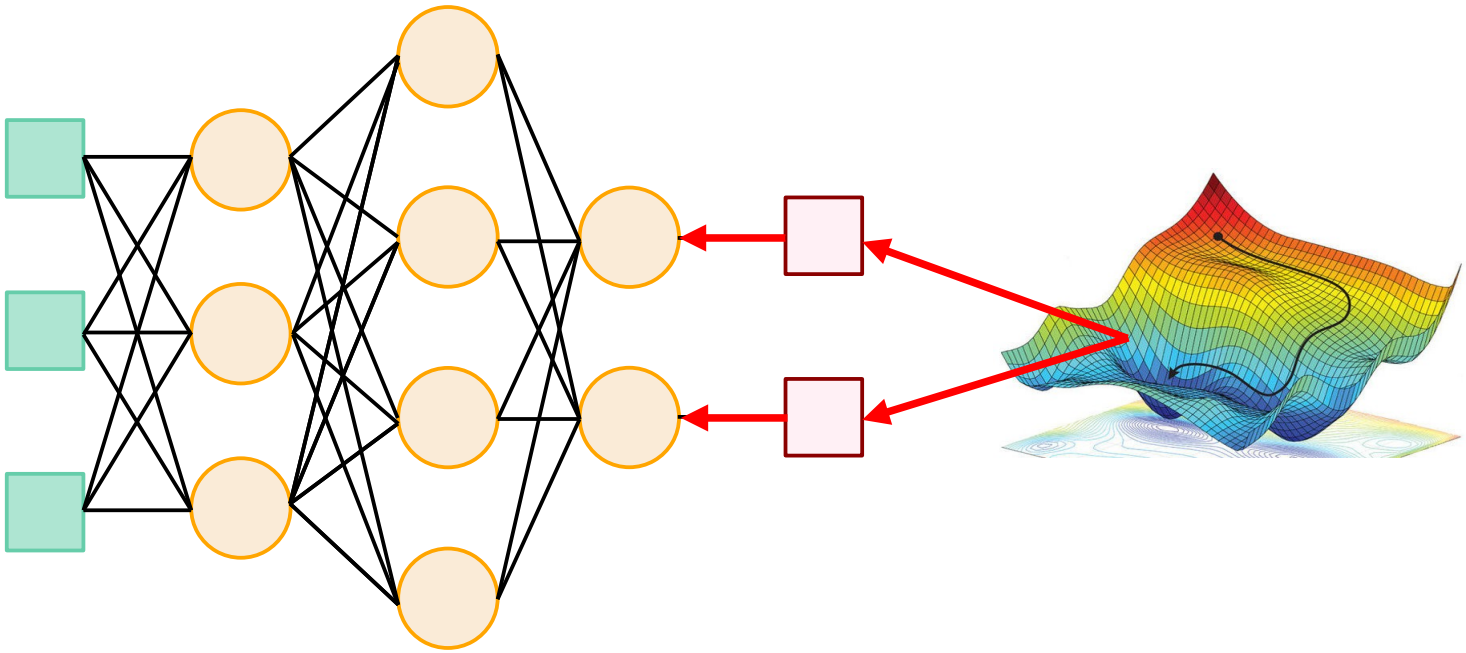


$$w_{new} = w_{old} - \alpha \frac{\delta J}{\delta w}$$

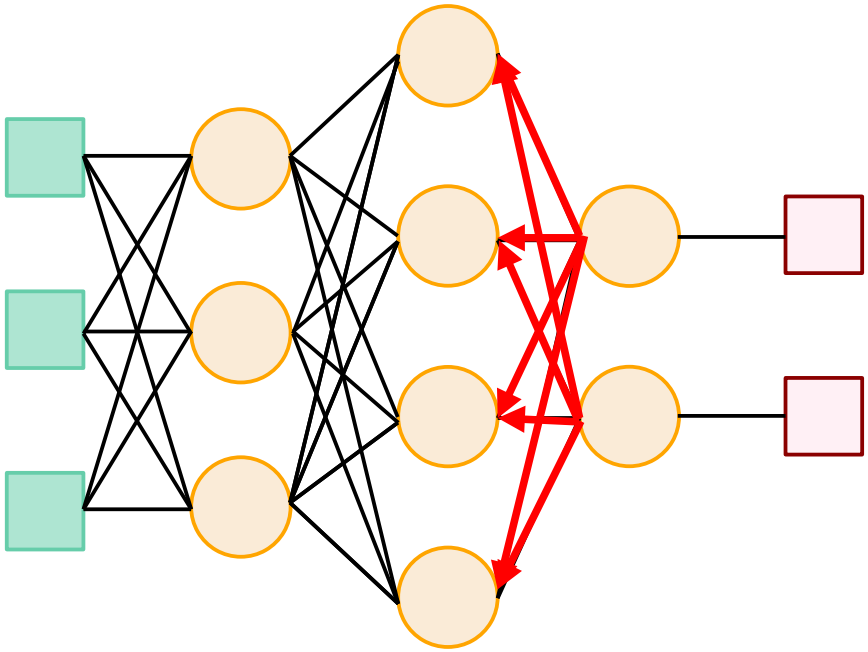
Error backpropagation one layer at a time

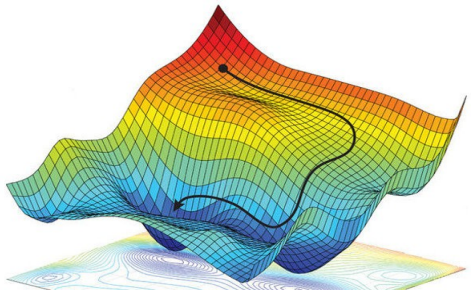


Error backpropagation one layer at a time

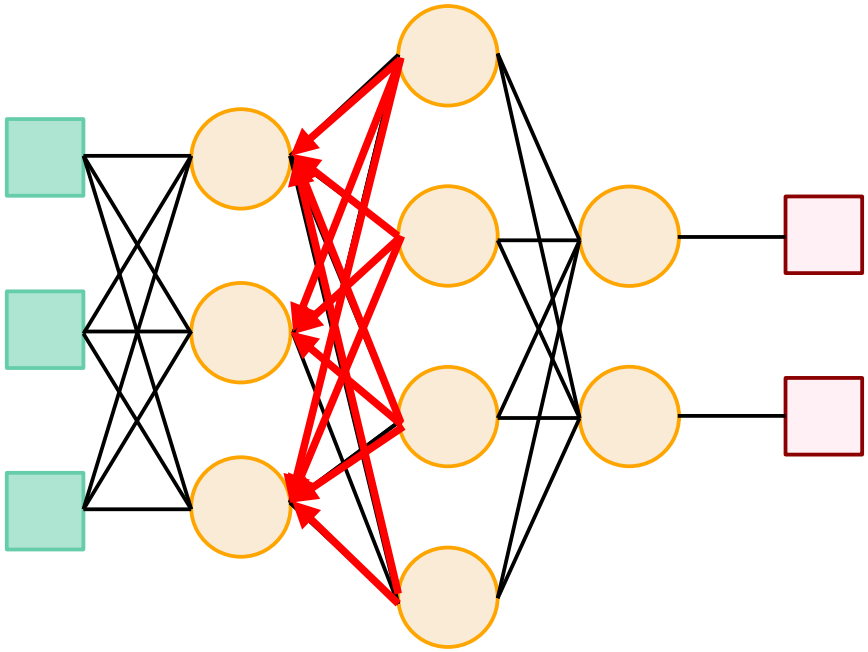


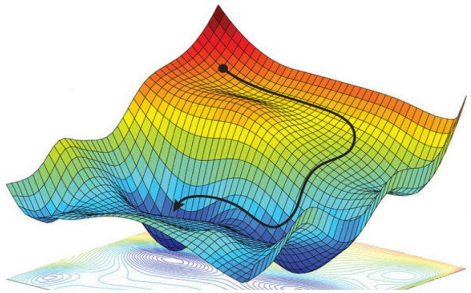
Error backpropagation one layer at a time



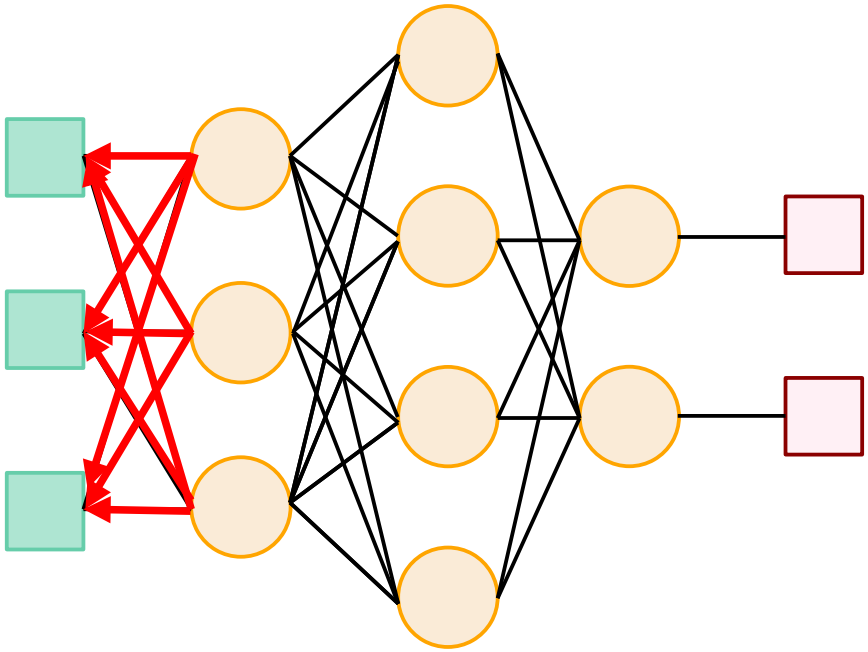


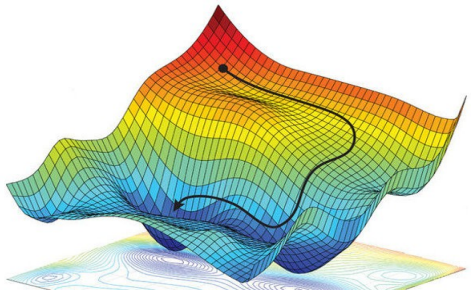
Error backpropagation one layer at a time



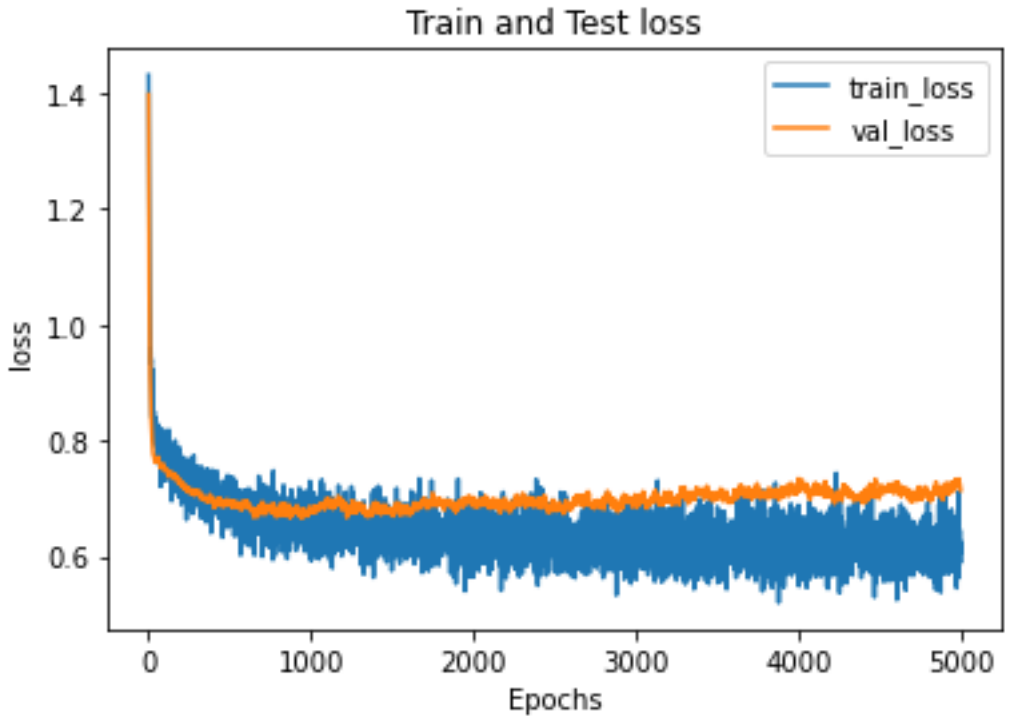


Error backpropagation one layer at a time



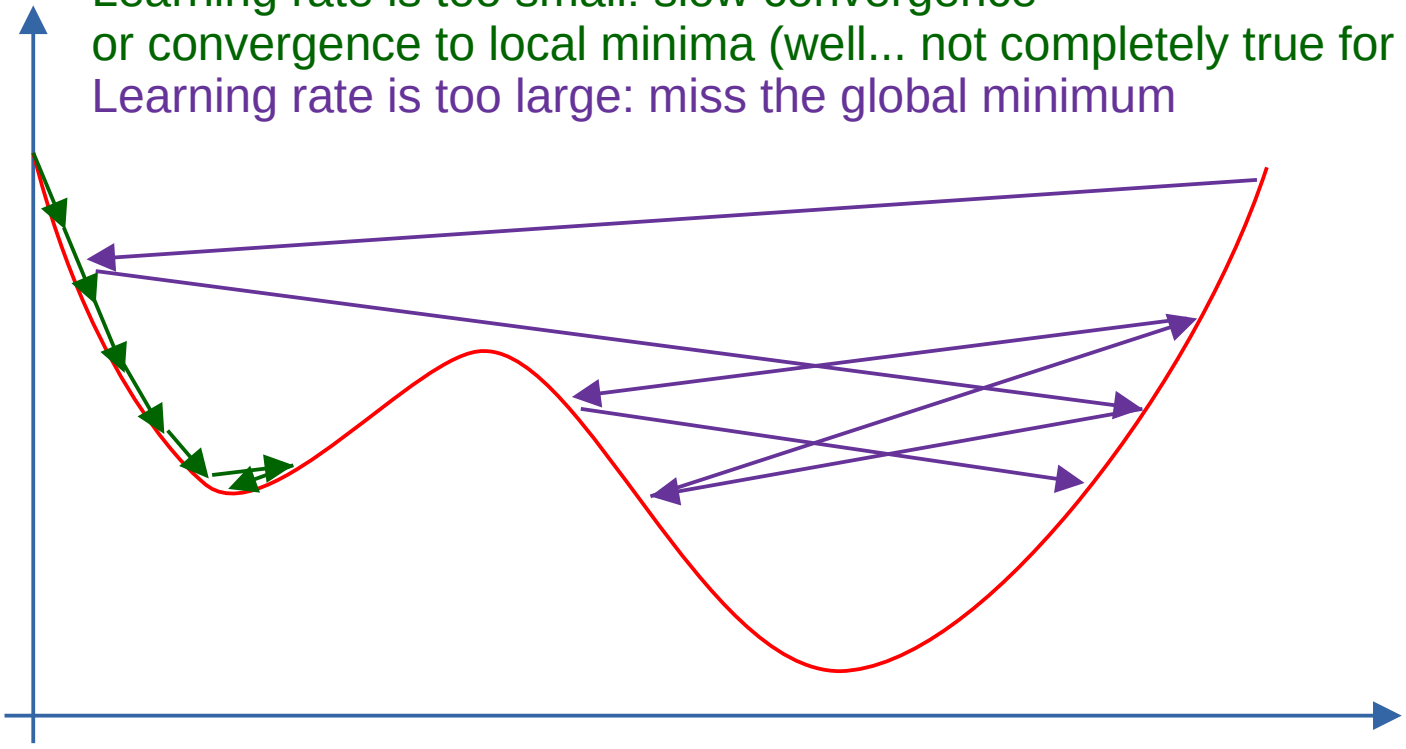


Learning progress

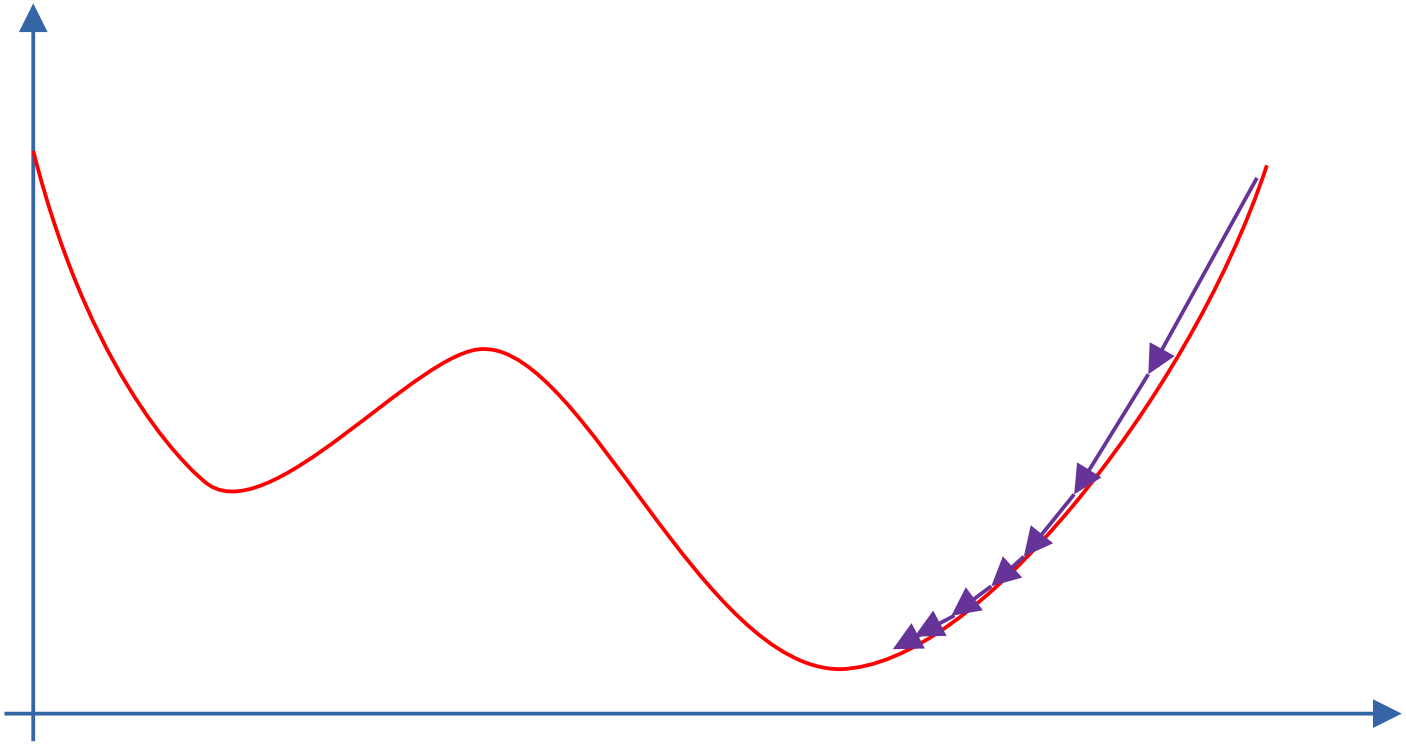


Impact of the learning rate

Learning rate is too small: slow convergence
or convergence to local minima (well... not completely true for DL)
Learning rate is too large: miss the global minimum



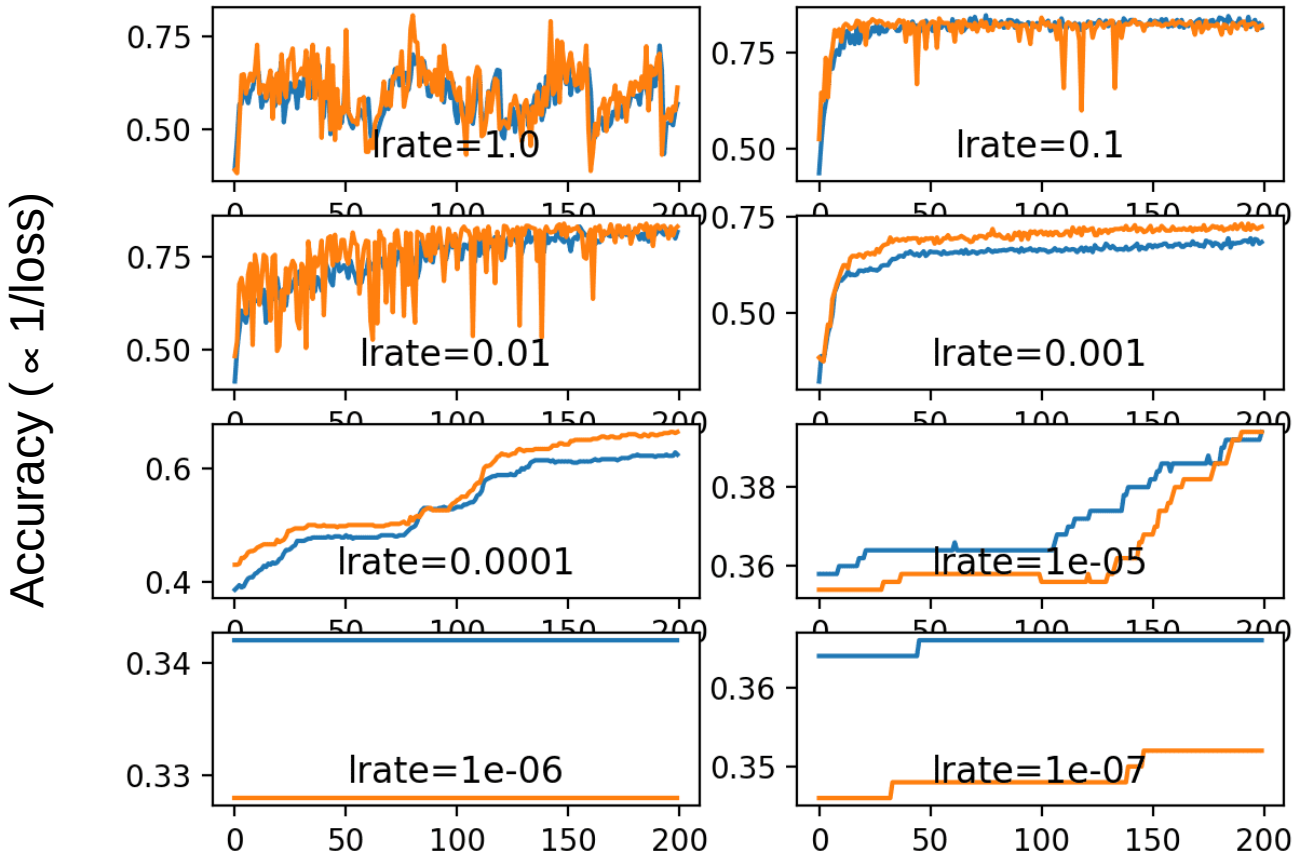
Impact of the learning rate



Adaptive algorithms adapt the learning steps according to the gradient of the cost function

Kingma and Lei Ba (2015) Adam: a method for stochastic optimisation. *ICLR 2015*

Impact of the learning rate



Training, testing, and validation sets

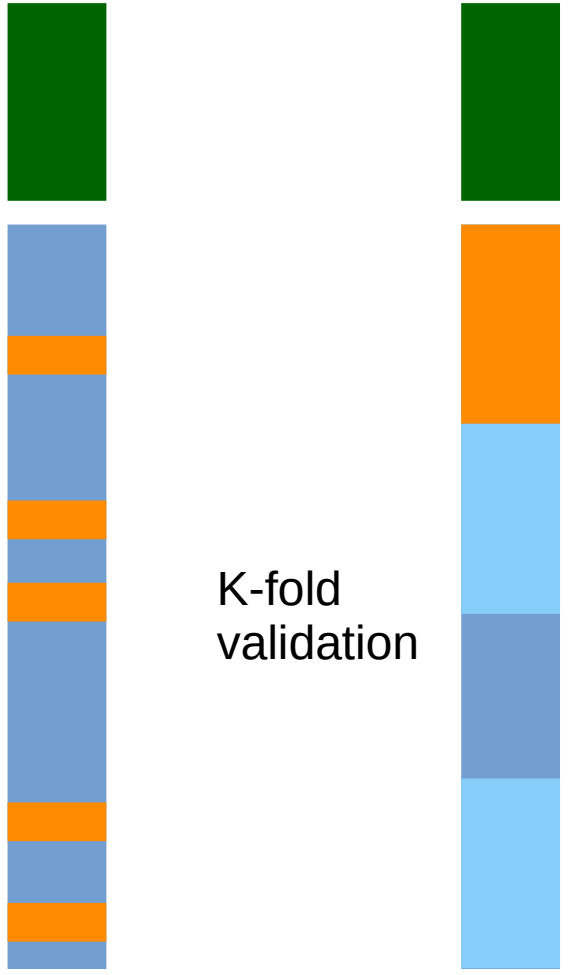
"validation" (never seen)
Same for all model instances
Used to assess the model at the end

Training set: used to learn

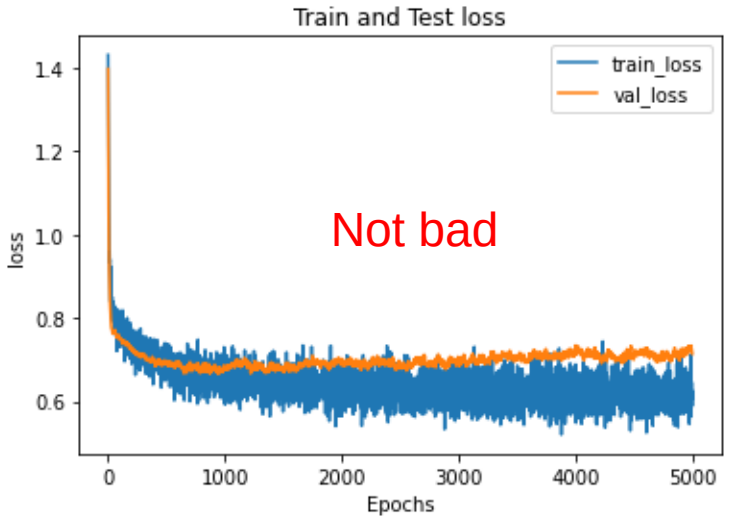
(perso: training + test set = learning set)

"test" set: used to assess the model during the learning phase
Different for each model instance

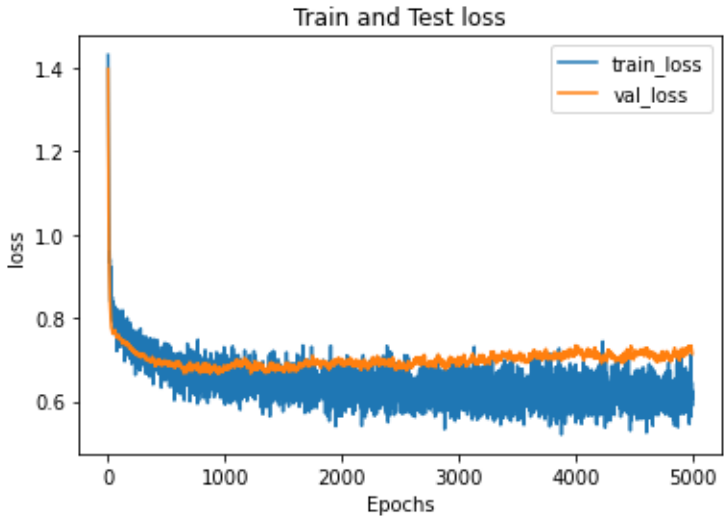
Beware: "validation" and "test" are used the other way around a lot in deep learning, at the opposite of all other fields of machine learning, or even life science in general

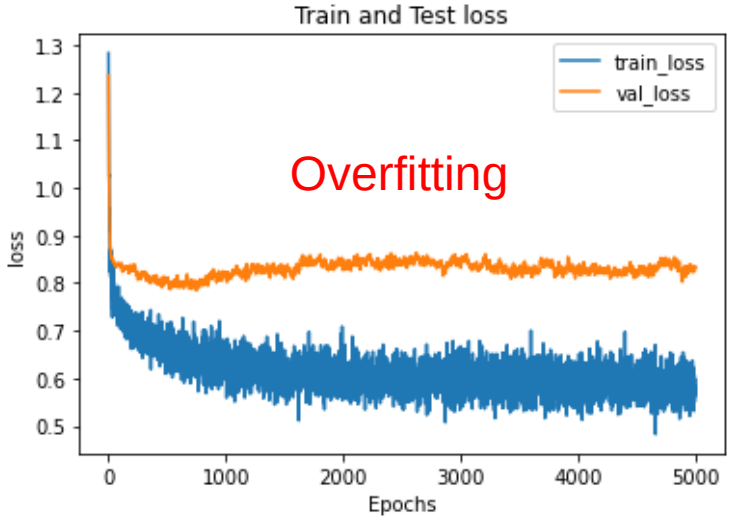


Learning and overfitting

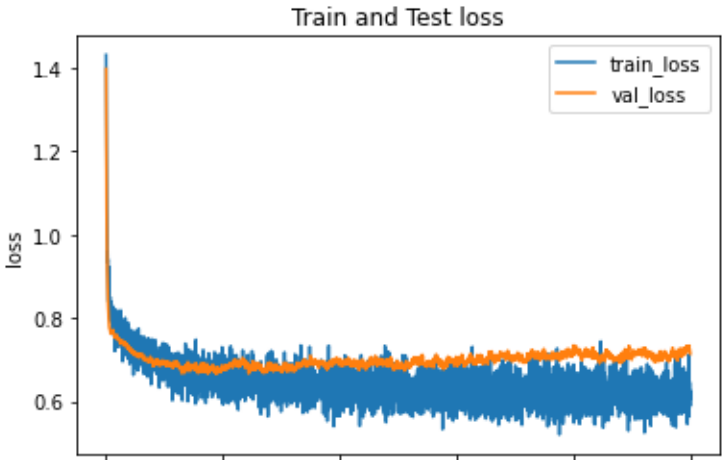


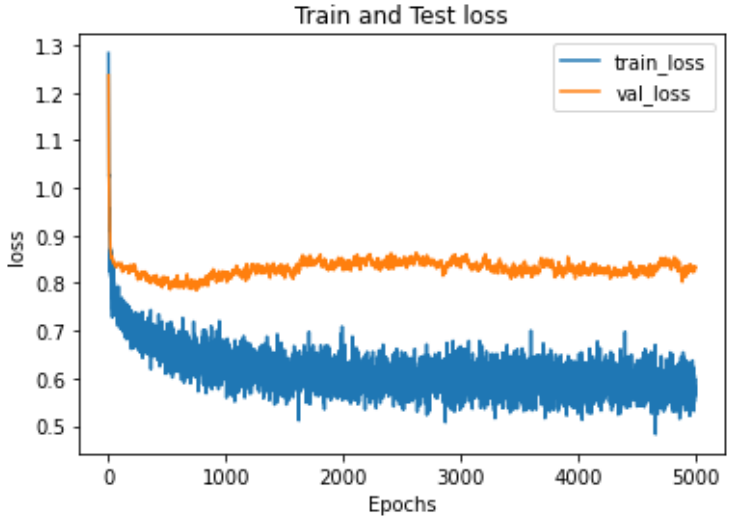
Learning and overfitting



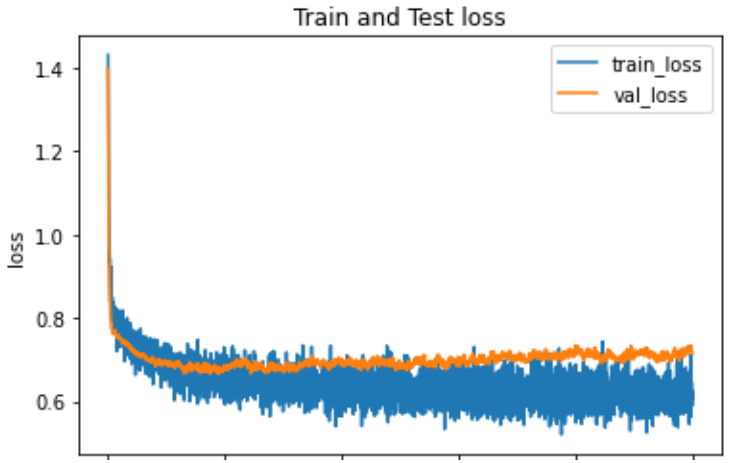


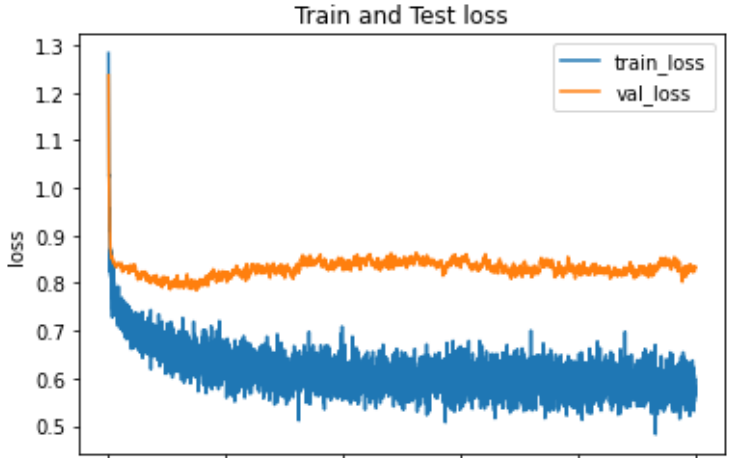
Learning and overfitting

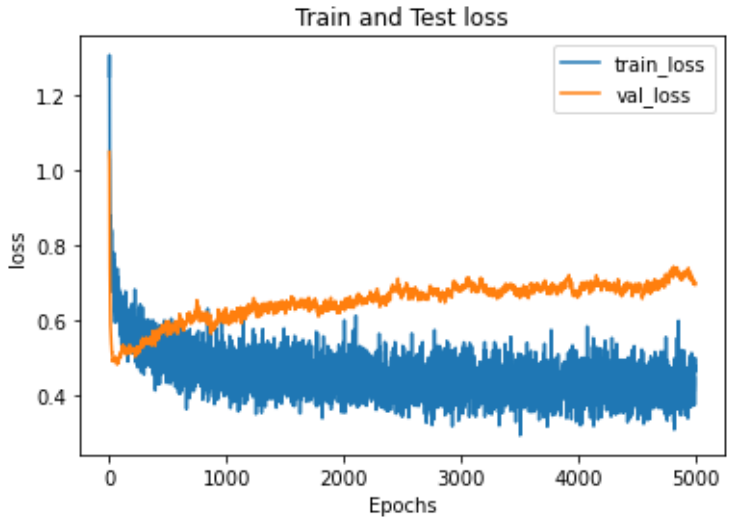


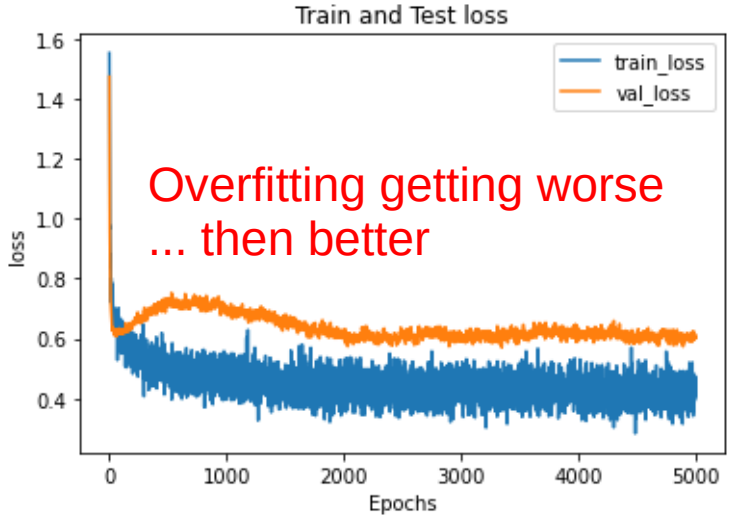


Learning and overfitting









Why a test AND a validation set?

Underperforming on the test set means the model overfitted the training set, the parameters are too specific of the samples in the training set

Underperforming on the validation set means the hyperparameters are too specific of the test set as well! When you modify the structure of the model to avoid overfitting, you actually make the model overfit the entire learning set

Let’s predict the diabetes status

Dataset: Pima Indians Diabetes Database. Smith *et al* (1988) Using the ADAP learning algorithm to forecast the onset of diabetes mellitus. *Proceedings of the Symposium on Computer Applications and Medical Care* (pp. 261--265). IEEE Computer Society Press

Variables:

1) Number of times pregnant
2) Plasma [glucose] at 2 h in an OGTT
3) Diastolic blood pressure (mm Hg)
4) Triceps skin fold thickness (mm)
5) 2-Hour serum insulin (mu U/ml)
6) Body mass index (weight in kg/(height in m)^2)
7) Diabetes pedigree function
8) Age (years)

   +

9) Diabetes status: 500 healthy (0), 268 diabetic (1)

	A	B	C	D	E	F	G	H	I
1	6	148	72	35	0	33.6	0.627	50	1
2	1	85	66	29	0	26.6	0.351	31	0
3	8	183	64	0	0	23.3	0.672	32	1
4	1	89	66	23	94	28.1	0.167	21	0
5	0	137	40	35	168	43.1	2.288	33	1
6	5	116	74	0	0	25.6	0.201	30	0
7	3	78	50	32	88	31	0.248	26	1
8	10	115	0	0	0	35.3	0.134	29	0
9	2	197	70	45	543	30.5	0.158	53	1
10	8	125	96	0	0	0	0.232	54	1
11	4	110	92	0	0	37.6	0.191	30	0
12	10	168	74	0	0	38	0.537	34	1
13	10	139	80	0	0	27.1	1.441	57	0
14	1	189	60	23	846	30.1	0.398	59	1

Software stack

High-level library

Low-level library

Language

IDE

Software stack

High-level library

Low-level library

Language

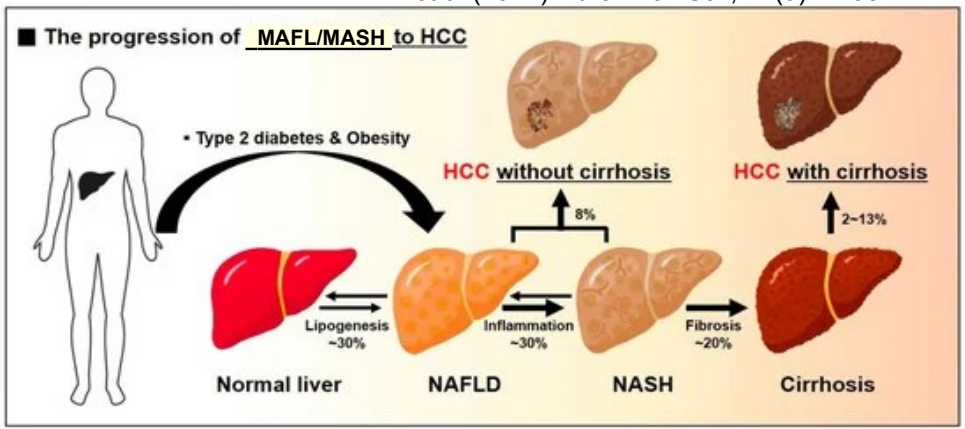
IDE

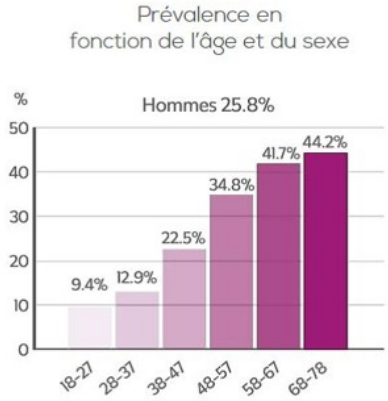
But instead
you c/should use

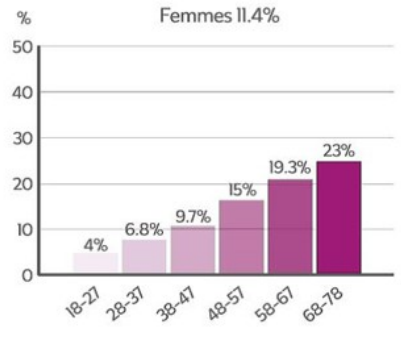
Demo in Google Colab

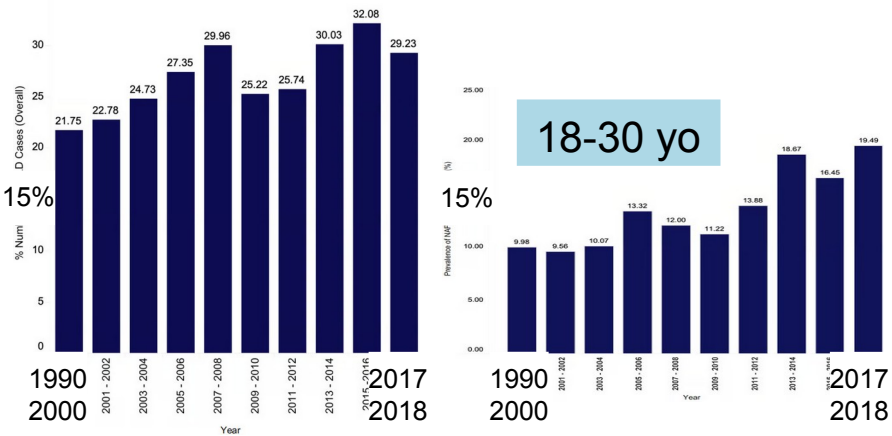
Let's try to recognise a disease severity

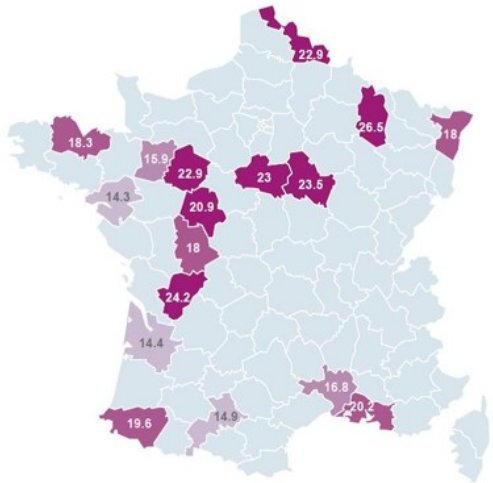
Kim *et al* (2021) *Int. J. Mol. Sci.*, 22(9): 4495











Répartition par régions

NASH (now MASH)

Paris MASH Meeting

(11-12 juillet 2019)

Kim *et al* (2022) *Met. Target Organ Damage*, 2: 19

NALFD (now MASLD)

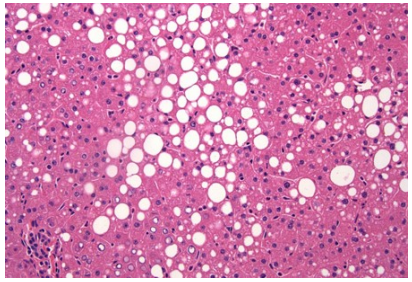
Subject grouping

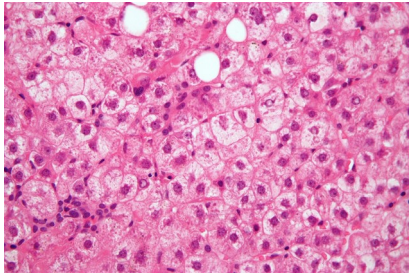
Scoring on liver biopsy with the method from Kleiner and Brunt 2005

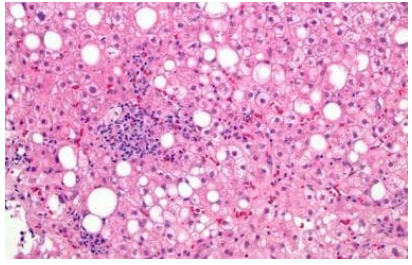
Steatosis
Categorical [0-3] from quantitative measurement

Ballooning
Categorical [0-2]
= {none, some, much}

Inflammation
Categorical [0-3] from number of foci





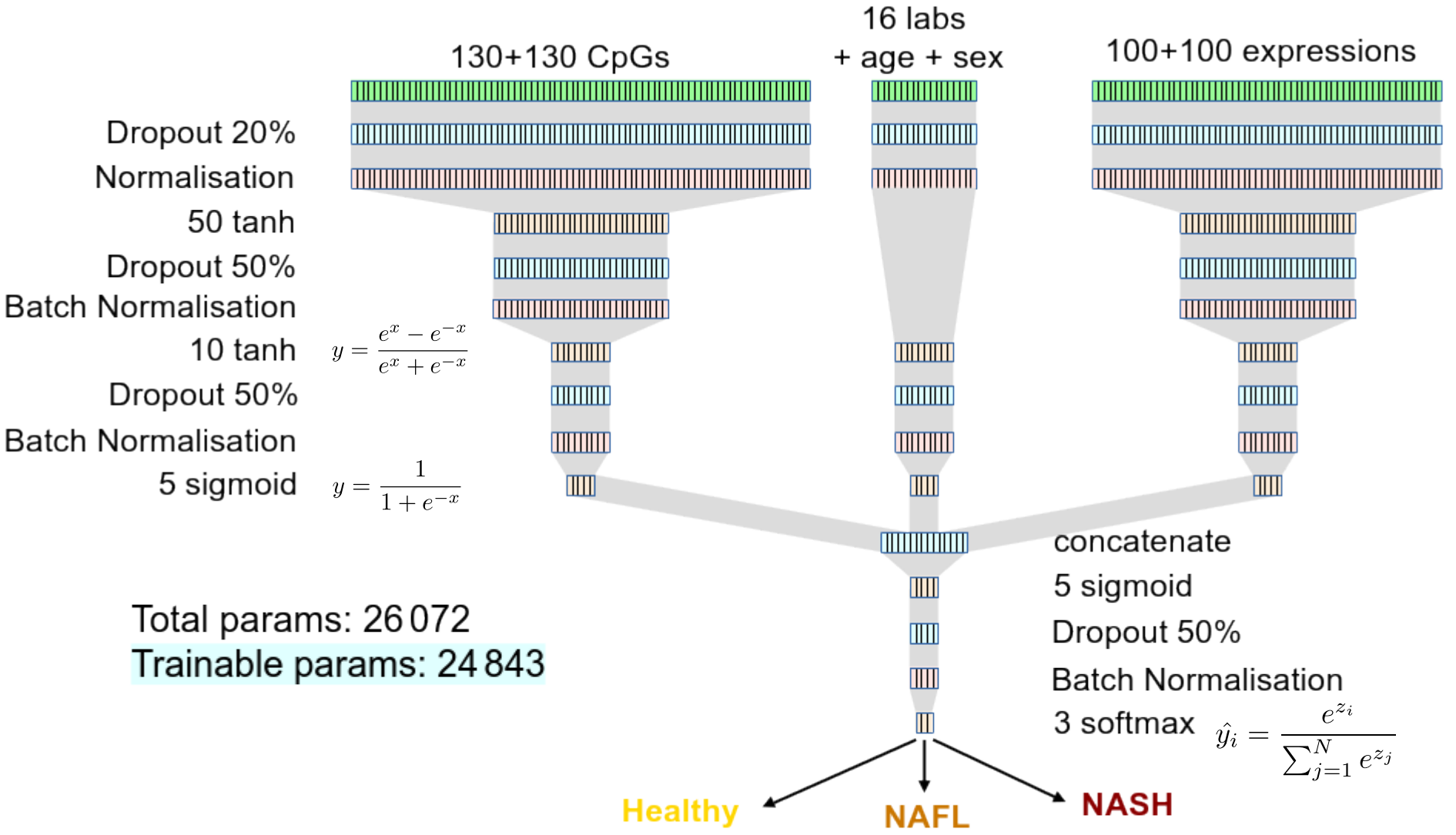


Final score:

Healthy: S = 0, B = 0, I = 0 n = 80

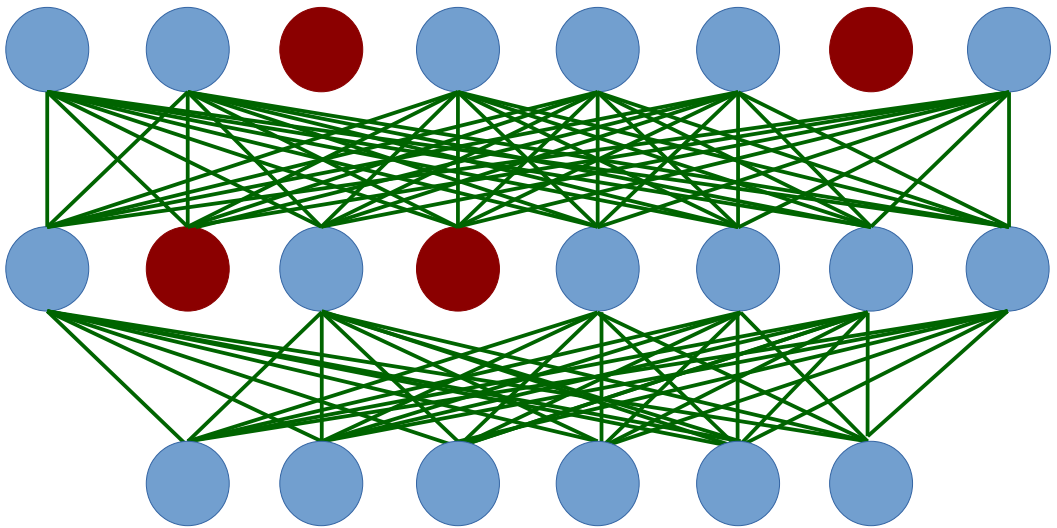
NAFL: S > 1, B = 0, I ≥ 1 n = 137
S > 1, B > 1, I = 0

NASH: S > 0, B > 0, I > 0 n = 83


130+130 CpGs
16 labs
+ age + sex
100+100 expressions
Dropout 20%
Normalisation
50 tanh
Dropout 50%
Batch Normalisation
10 tanh
$y = \frac{e^x - e^{-x}}{e^x + e^{-x}}$
Dropout 50%
Batch Normalisation
5 sigmoid
$y = \frac{1}{1 + e^{-x}}$
concatenate
5 sigmoid
Dropout 50%
Batch Normalisation
3 softmax
$\hat{y}_i = \frac{e^{z_i}}{\sum_{j=1}^{N} e^{z_j}}$
Healthy
NAFL
NASH
Total params: 26 072
Trainable params: 24 843

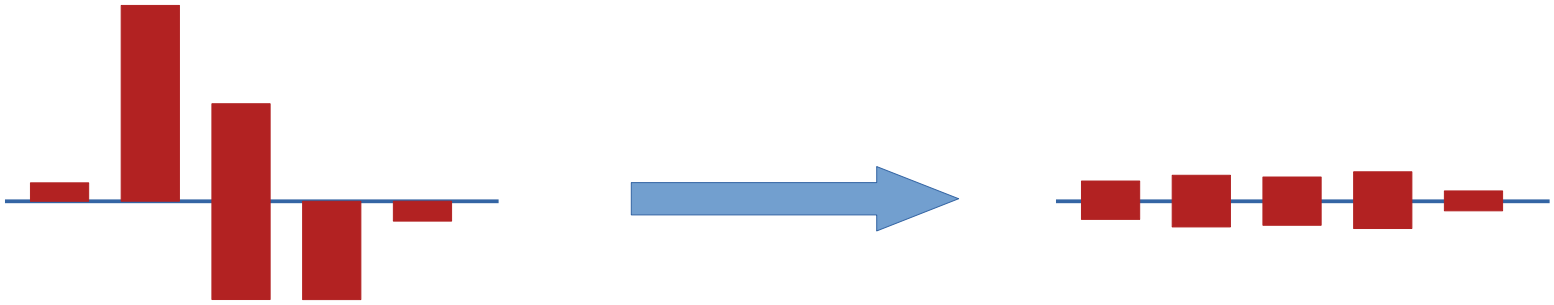
Dropout

- Purpose: avoiding overfitting
- Disable some connections at random (set the weights at 0)



Srivastava et al (2014) Dropout: A Simple Way to Prevent Neural Networks from Overfitting. JMLR 15(56):1929−1958

Normalisation



- Normalisation during data processing
- Normalisation before training: on the whole dataset
- Normalisation during training: after dropout
- Batch normalisation: normalisation on the current batch (not on the entire dataset)
- Layer normalisation: normalisation of the input of a layer

Ba, Kiros, Hinton (2016) Layer Normalization. arXiv:1607.06450v1
Ioffe and Czegedy (2015) Batch Normalization: Accelerating Deep Network Training by Reducing Internal Covariate Shift. Proc 32nd Intl Conf Machine Learning, Lille, France volume 37

Balance the datasets!

If your learning dataset is made up of 90% of class A and 10% of class B, you reach 90% accuracy by predicting all cases as A...

Selective sampling:

e.g., randomly select the same number of class A as in class B

Data augmentation:

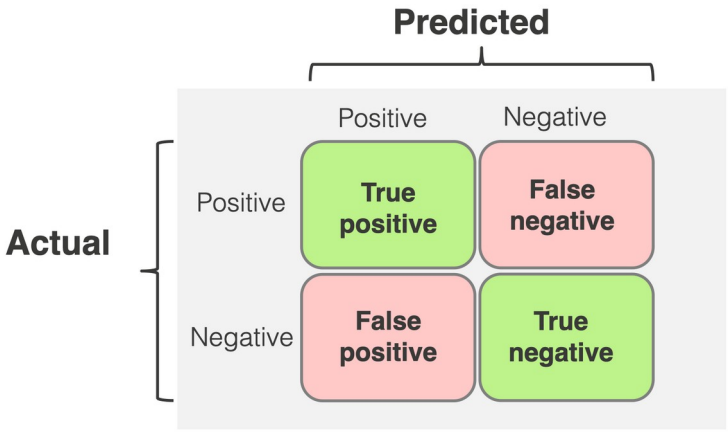
e.g., sample repeatedly in class B; Synthesise class B samples

Balance learning:

e.g., weight loss function to correct for class unbalance

Demo in Spyder

Evaluating a model's performance



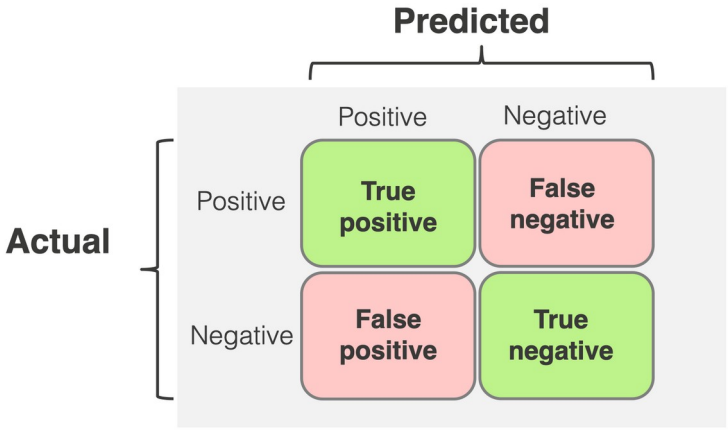
Accuracy = (TP+TN)/(TP+FN+TN+FP)

Precision = TP/(TP+FP)

Sensitivity (true positive rate) = TP/(TP+FN)

Specificity (true negative rate) = TN/(TN+FP)

Evaluating a model's performance



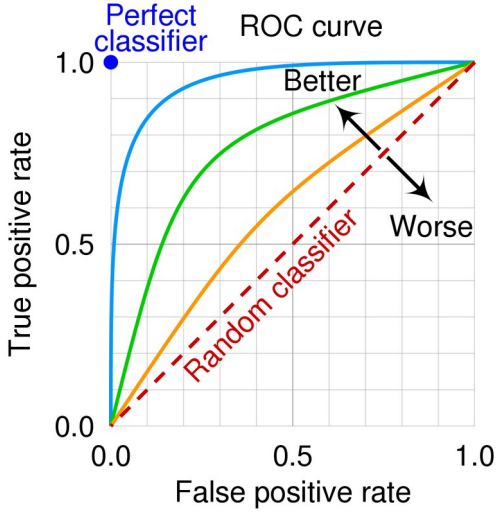
Accuracy = (TP+TN)/(TP+FN+TN+FP)

Precision = TP/(TP+FP)

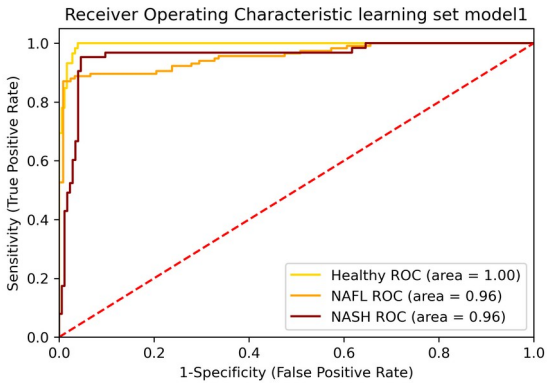
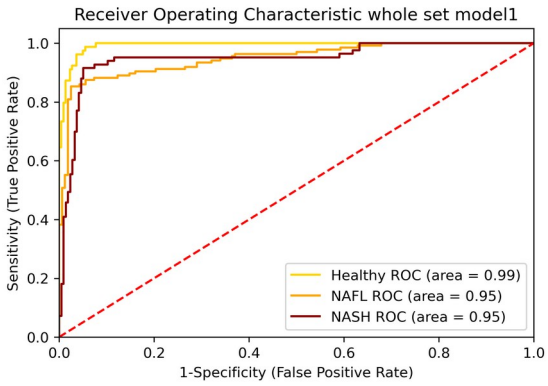
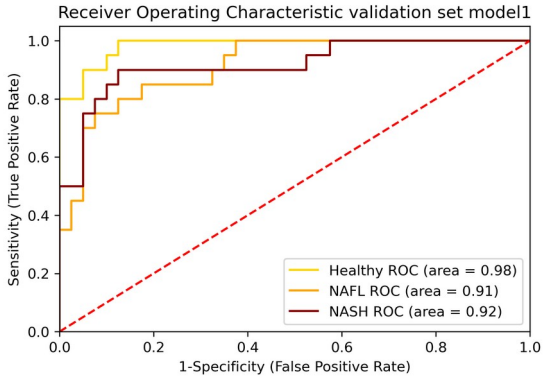
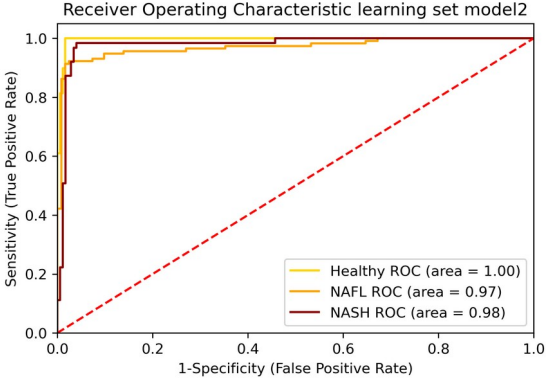
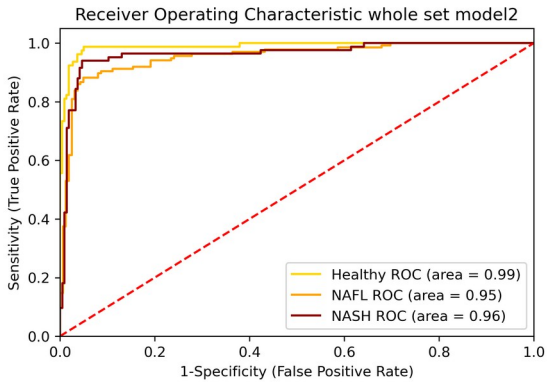
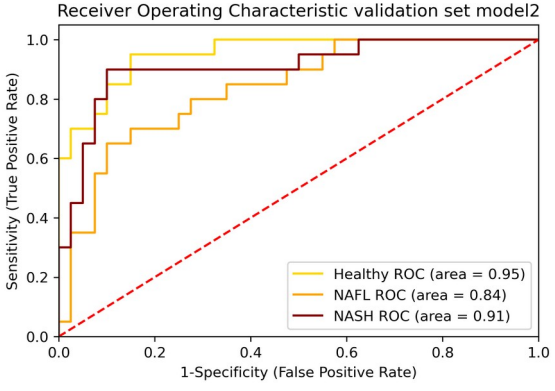
Sensitivity (true positive rate) = TP/(TP+FN)

Specificity (true negative rate) = TN/(TN+FP)

Receiver operating characteristic (ROC) curve

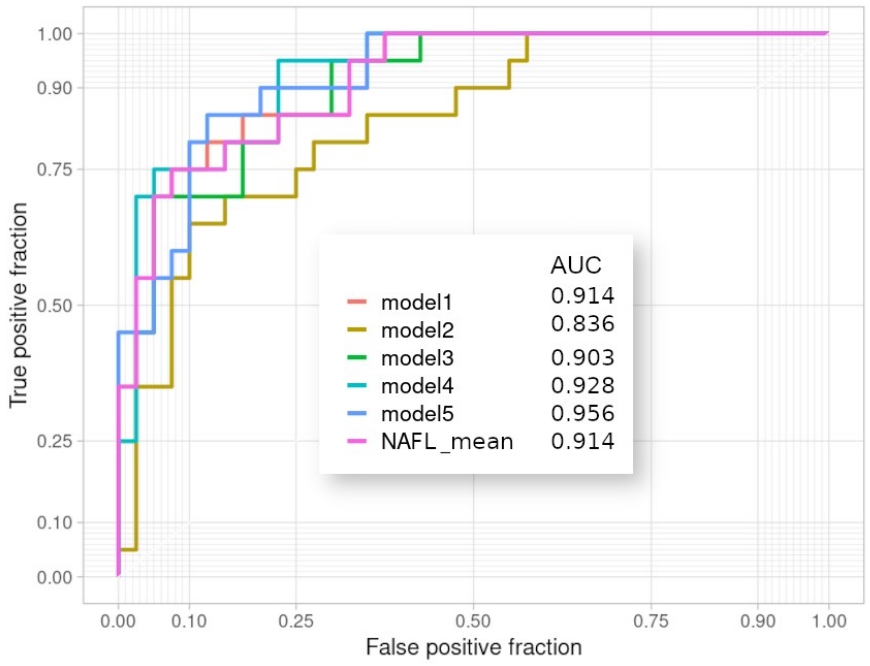


Different accuracies on different datasets

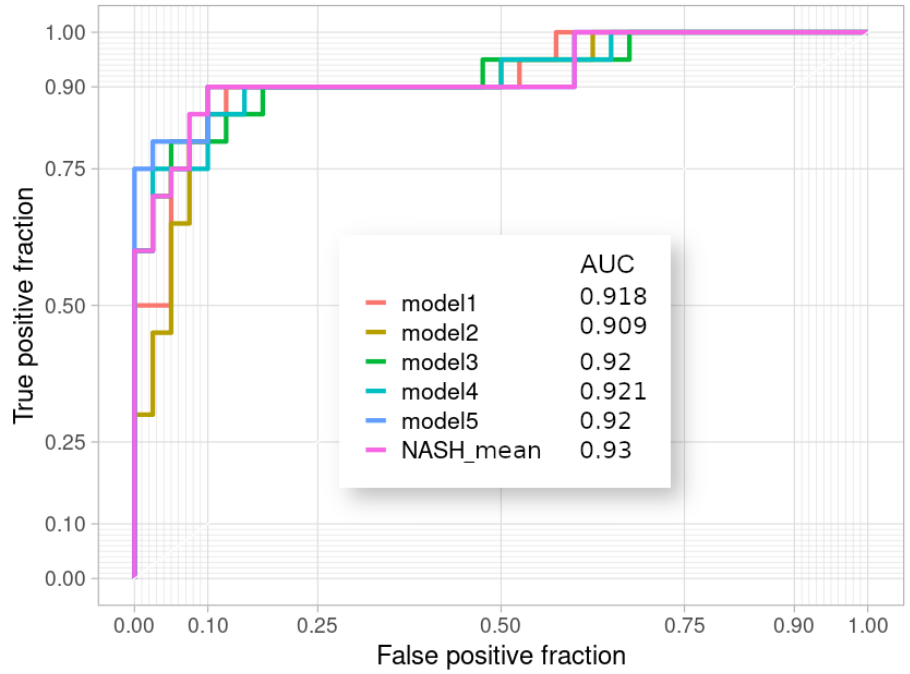
	Learning set	Whole set	Validation set
Model 1			
Model 2			

How good is the model to distinguish NAFL and NASH?

sensitivity

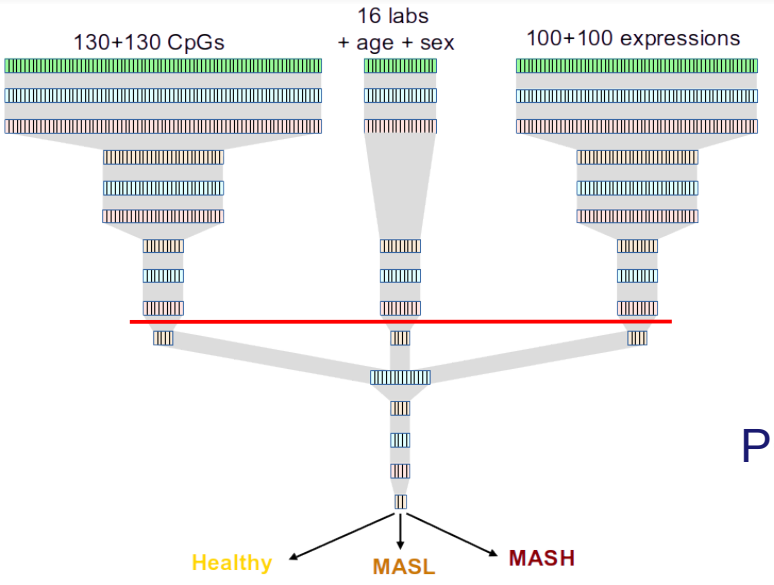


1 - specificity



1 - specificity

Exploring latent spaces

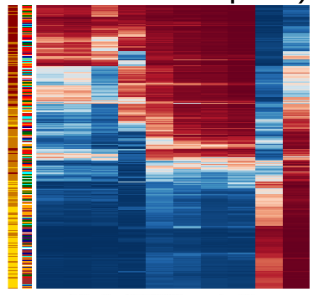


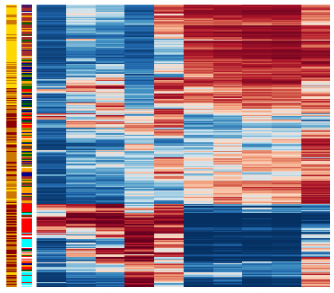
Clinical data: several populations
(see Raverdy *et al* (2025))

RNA-seq: recognises the 3 conditions

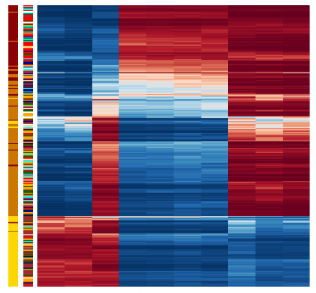
Methylation: continuum of severity

activations (coordinates in the latent space)

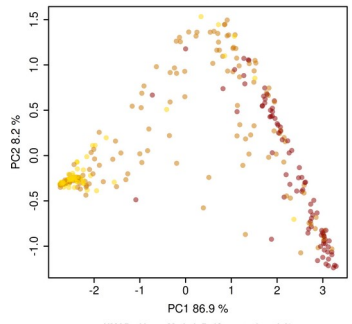


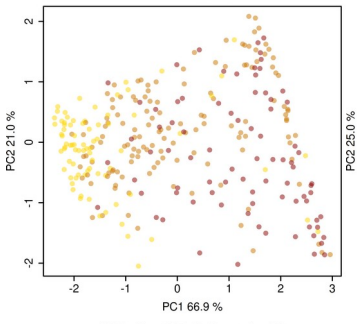


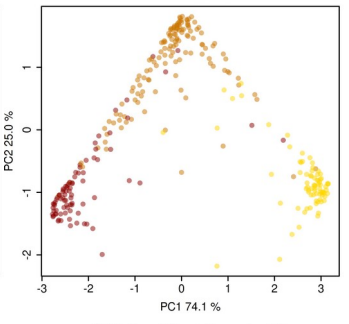
Score -1 1



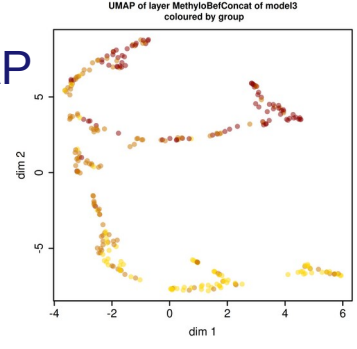
PCA

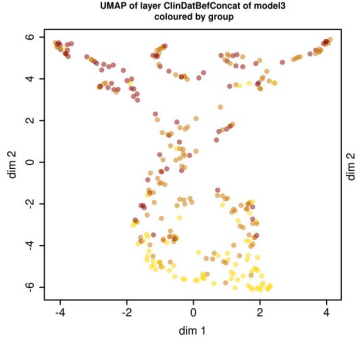


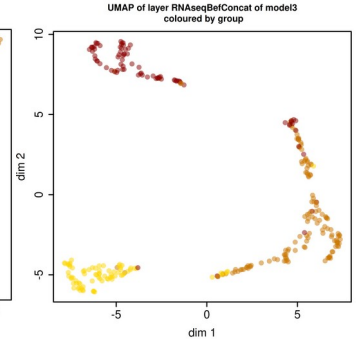




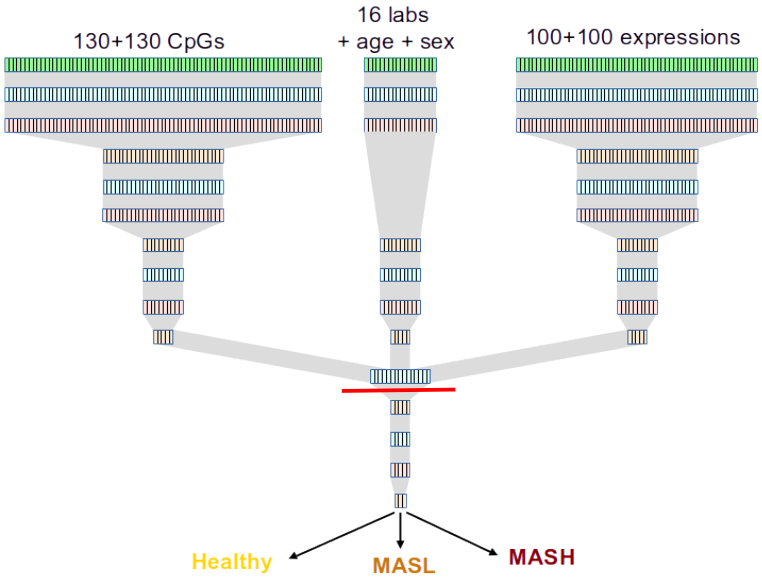
UMAP



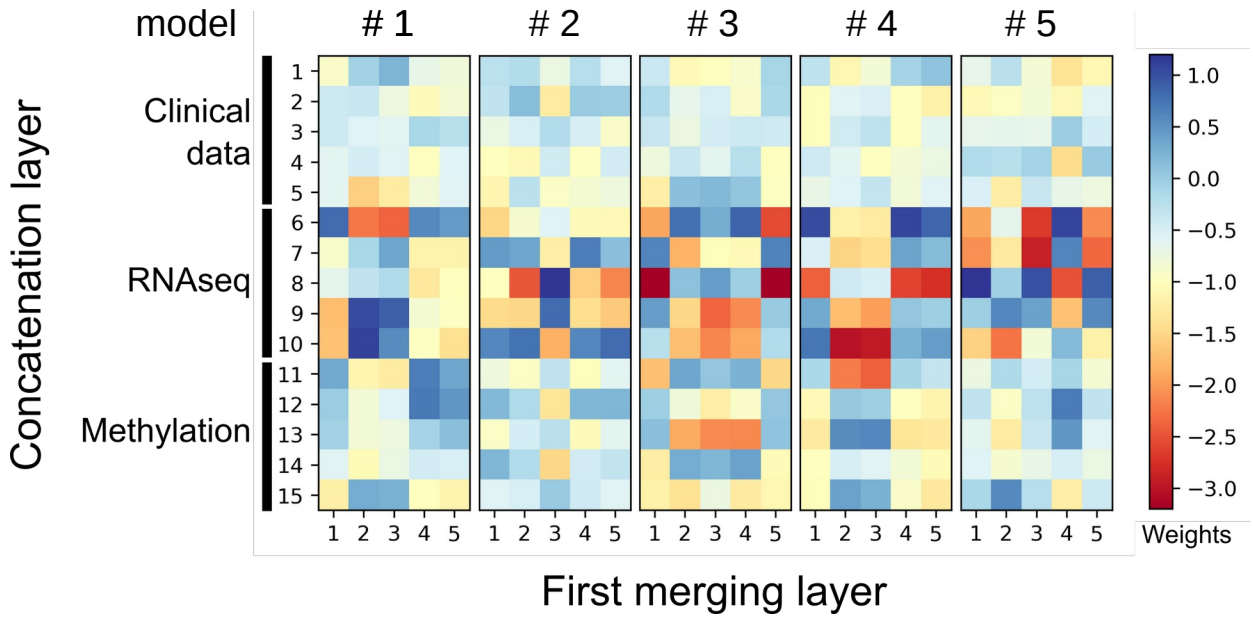




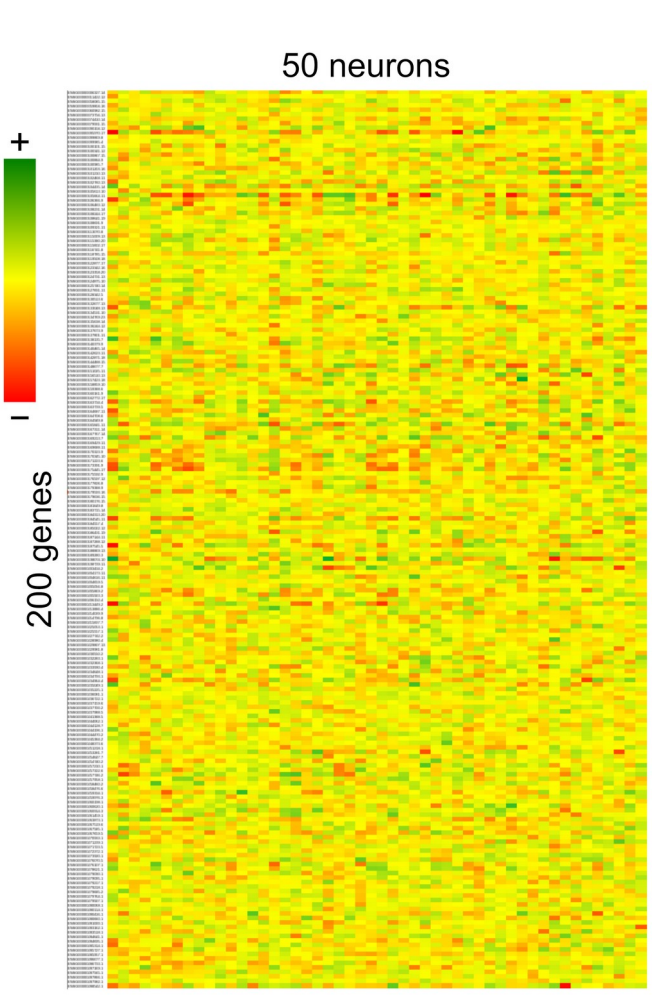
Peeping into the black box: the weights

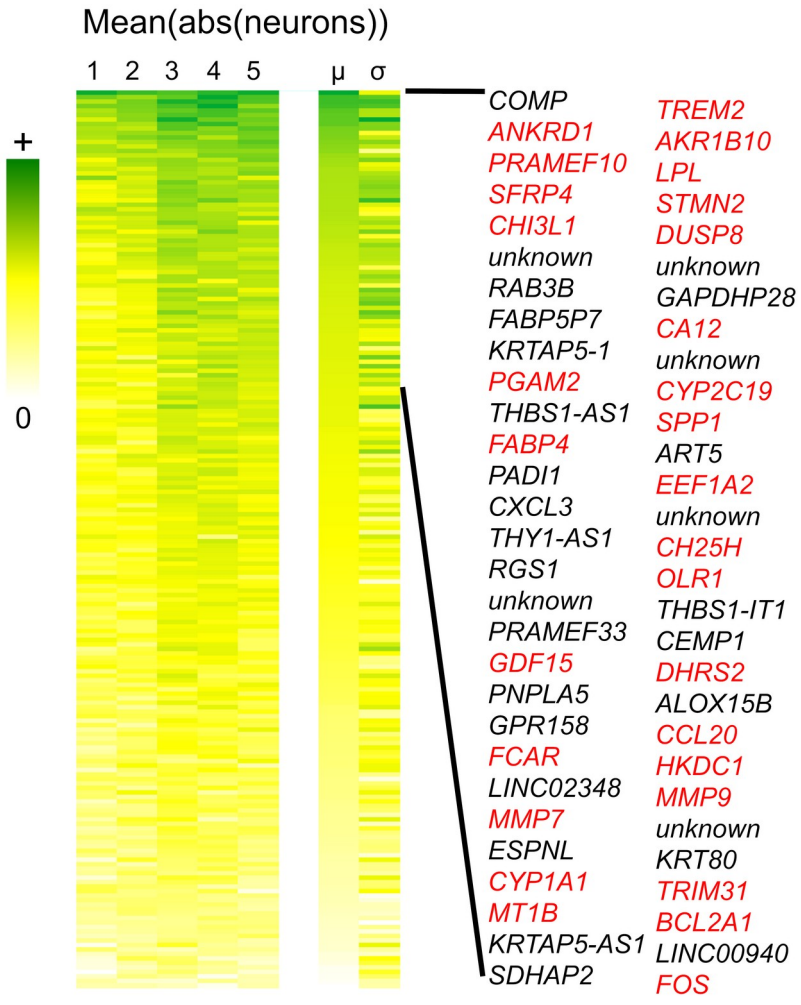


The weights reading the RNAseq module are larger → most impact on output



Independently trained models learn from the same genes





Known
to be involved

New suggestions

Want to go further?

Fidle:
https://fidle.cnrs.fr/w3/
https://www.youtube.com/@CNRS-FIDLE

StatQuest: Start by
https://www.youtube.com/watch?v=GKZoOHXGcLo
And move backward to get to the start you need.

3 blue 1 brown:
https://www.youtube.com/@3blue1brow
Search for deep learning, chapter 1 to 4

Also, a large number of tutorial with code at:
https://machinelearningmastery.com/category/deep-learning/

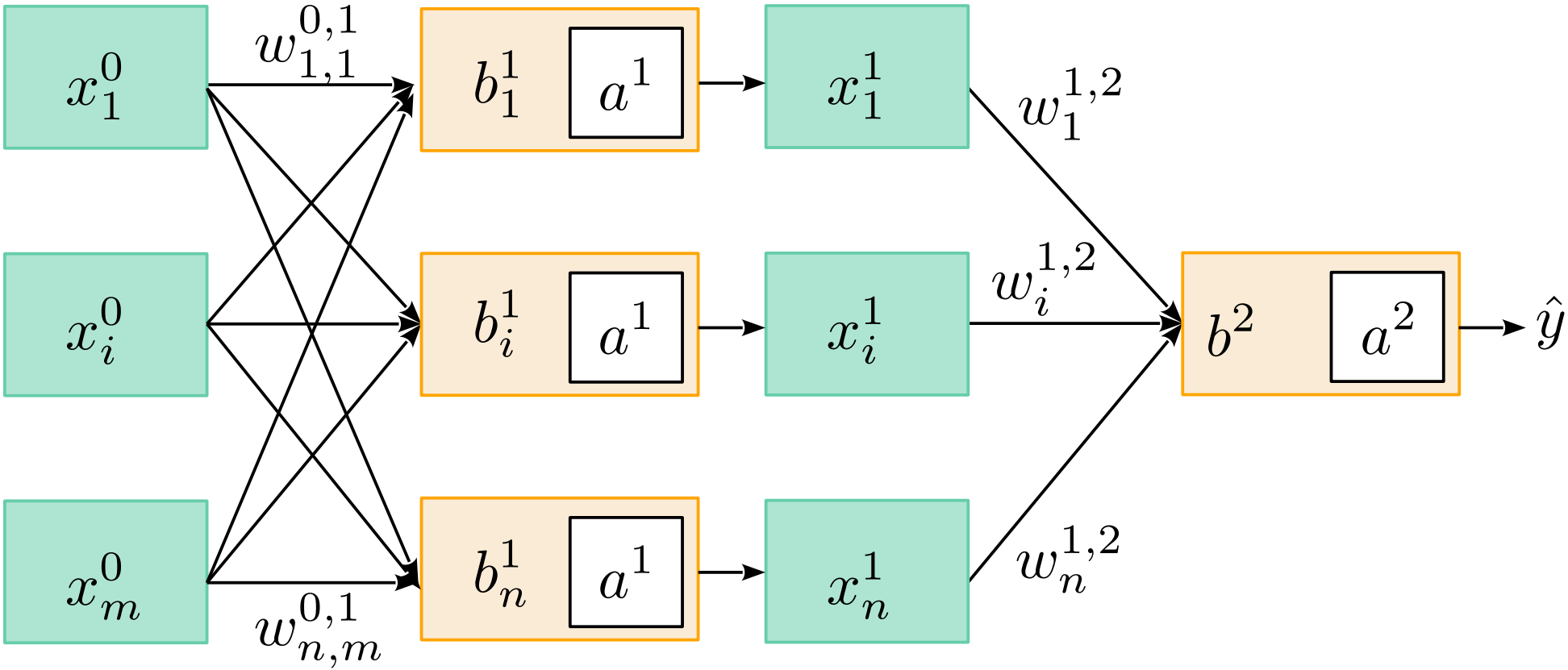
PreciDIAB
National Center for
Precision Diabetic Medicine

E.g.i.d.
European
Genomic
Institute
for Diabetes

Région
Hauts-de-France

UMR 1283
8199
Functional (Epi)genomics and Mechanisms of Type 2 Diabetes
and Related Diseases

Backpropagation: example



Backpropagation: the chain rule

$$h(x) = f(g(x)) \quad \Longrightarrow \quad h'(x) = f'(g(x))g'(x) \qquad \frac{df}{dx} = \frac{df}{dg} \cdot \frac{dg}{dx}$$

Backpropagation: the chain rule

$$h(x) = f(g(x)) \quad \Longrightarrow \quad h'(x) = f'(g(x))g'(x) \qquad \frac{df}{dx} = \frac{df}{dg} \cdot \frac{dg}{dx}$$

Correction of the bias b^2

$$\frac{\partial \text{MSE}}{\partial b^2} = \frac{\partial \text{MSE}}{\partial \hat{y}} \cdot \frac{\partial \hat{y}}{\partial z^2} \cdot \frac{\partial z^2}{\partial b^2}$$

Backpropagation: the chain rule

$$h(x) = f(g(x)) \quad \Longrightarrow \quad h'(x) = f'(g(x))g'(x) \qquad \frac{df}{dx} = \frac{df}{dg} \cdot \frac{dg}{dx}$$

Correction of the bias b_i^1

$$\frac{\partial \text{MSE}}{\partial b_i^1} = \frac{\partial \text{MSE}}{\partial \hat{y}} \cdot \frac{\partial \hat{y}}{\partial z^2} \cdot \frac{\partial z^2}{\partial a_i^1} \cdot \frac{\partial a_i^1}{\partial b_i^1}$$

Backpropagation: intermediate calculations are reused

$$h(x) = f(g(x)) \quad \Longrightarrow \quad h'(x) = f'(g(x))g'(x) \qquad \frac{df}{dx} = \frac{df}{dg} \cdot \frac{dg}{dx}$$

Correction of the bias b_i^1

$$\frac{\partial \text{MSE}}{\partial b_i^1} = \boxed{\frac{\partial \text{MSE}}{\partial \hat{y}} \cdot \frac{\partial \hat{y}}{\partial z^2}} \cdot \frac{\partial z^2}{\partial a_i^1} \cdot \frac{\partial a_i^1}{\partial b_i^1}$$

Already computed for the correction of b^2

Backpropagation: everything at once

$$h(x) = f(g(x)) \quad \Longrightarrow \quad h'(x) = f'(g(x))g'(x) \qquad \frac{df}{dx} = \frac{df}{dg} \cdot \frac{dg}{dx}$$

Correction of the bias b_i^1

$$\frac{\partial \text{MSE}}{\partial b_i^1} = \boxed{\frac{\partial \text{MSE}}{\partial \hat{y}} \cdot \frac{\partial \hat{y}}{\partial z^2}} \cdot \frac{\partial z^2}{\partial a_i^1} \cdot \frac{\partial a_i^1}{\partial b_i^1}$$

Already computed for the correction of b^2

All that is done simultaneously for all weights and biases of a layer using tensors and Hadamard products (i.e. element-wise multiplication $\odot$)

To know much more than you would like:
http://neuralnetworksanddeeplearning.com/chap2.html and
LeCun, Bengio, and Hinton (2015) Deep learning. *Nature*, 521 (7553), pp.436-444.