Machine Learning in Bioinformatics

Artificial Neural Networks

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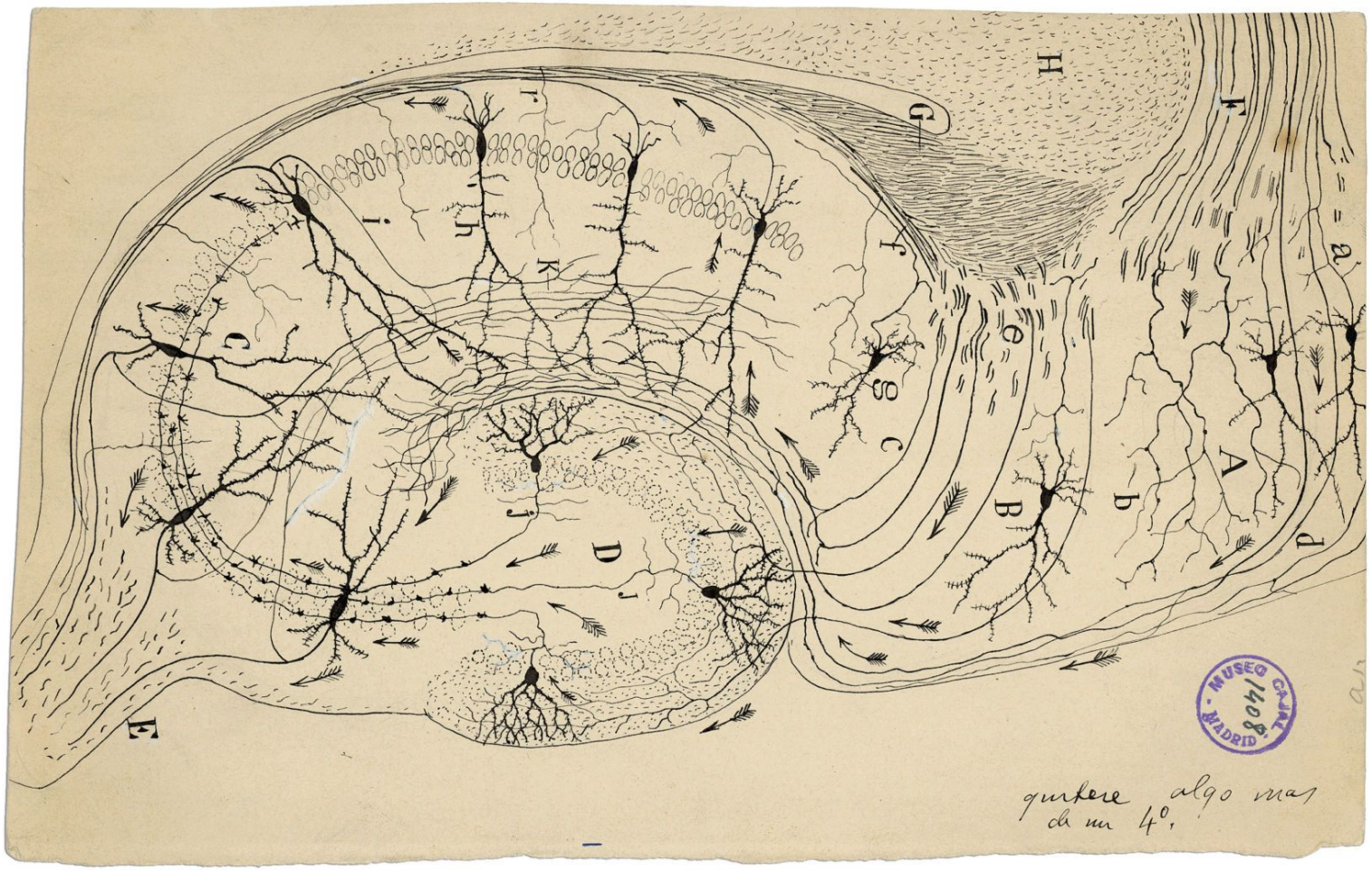
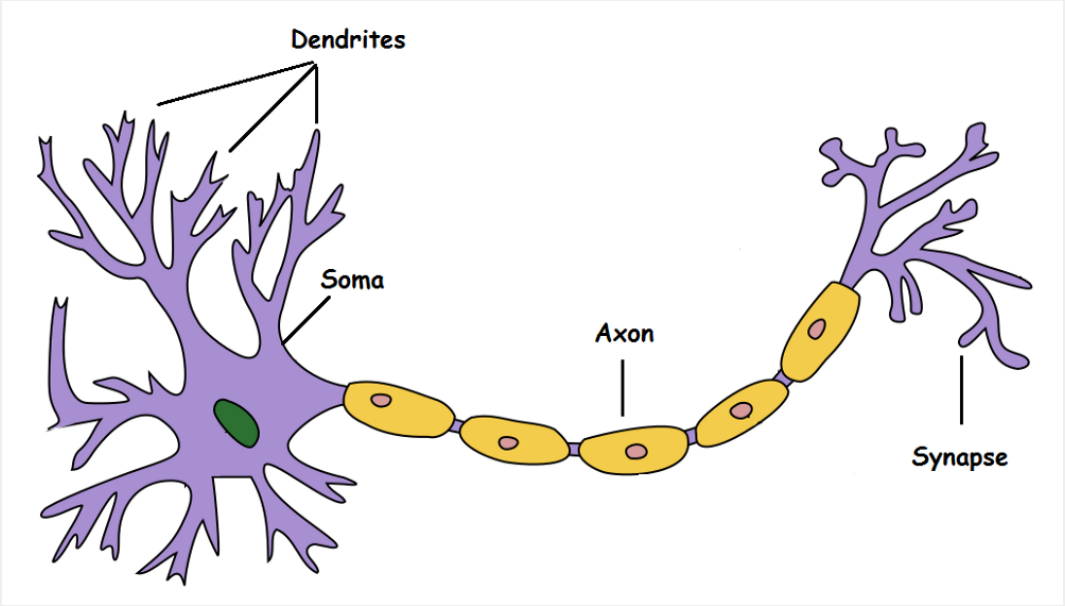
Outline

- We will discuss a particular class of *Artificial Neural Networks (ANNs)* called *Multilayer Perceptrons (MLPs)*
- MLPs are feed-forward networks, i.e. without any loops (directed acyclic graphs)
- We motivate MLPs from logistic regression

Drawings by Ramon y Cajal (∼ 1900)



A BIOLOGICAL NEURON

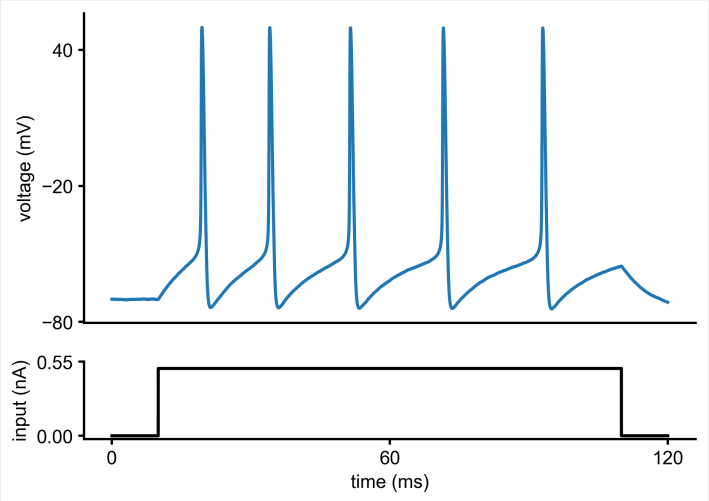


Hodgkin-Huxley model [Hodgkin and Huxley, 1952]

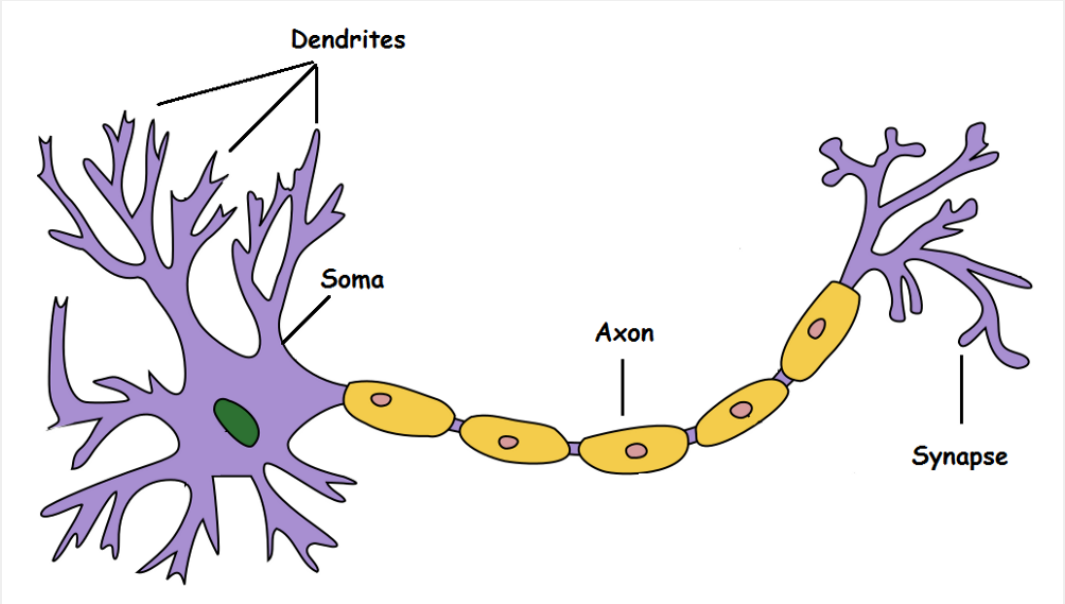
$$I = C_m \frac{\mathrm{d}V_m}{\mathrm{d}t} + \bar{g}_K n^4 (V_m - V_K) + \bar{g}_{Na} m^3 h (V_m - V_{Na}) + \bar{g}_l (V_m - V_l)$$

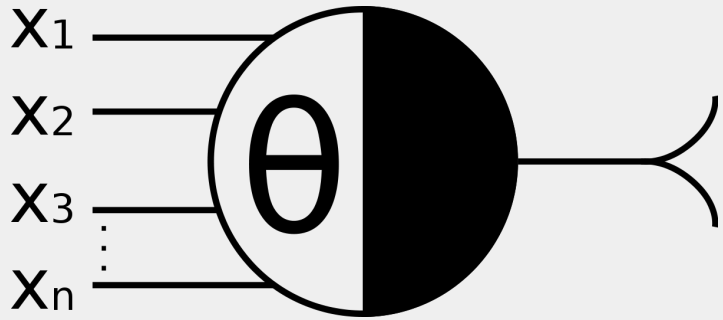
$$\frac{\mathrm{d}n}{\mathrm{d}t} = \alpha_n(V_m)(1-n) - \beta_n(V_m)n\,, \qquad \frac{\mathrm{d}m}{\mathrm{d}t} = \alpha_m(V_m)(1-m) - \beta_m(V_m)m$$

$$\frac{\mathrm{d}h}{\mathrm{d}t} = \alpha_h(V_m)(1-h) - \beta_h(V_m)h$$



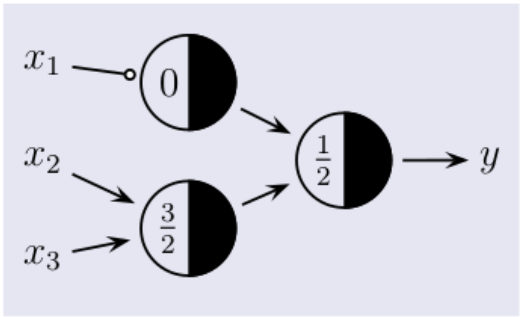
First mathematical models [McCulloch and Pitts, 1943]



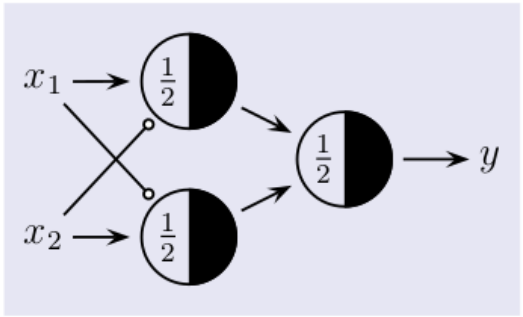


First mathematical models [McCulloch and Pitts, 1943]

- combining several McCullogh/Pitts neurons, we can build more complex boolean functions, e.g.:
  - $y = \neg x_1 \vee (x_2 \wedge x_3)$:



  - $y = XOR(x_1, x_2) = (x_1 \wedge \neg x_2) \vee (\neg x_1 \wedge x_2)$:



- Theorem: Networks of McCullogh/Pitts neurons can realize all boolean functions

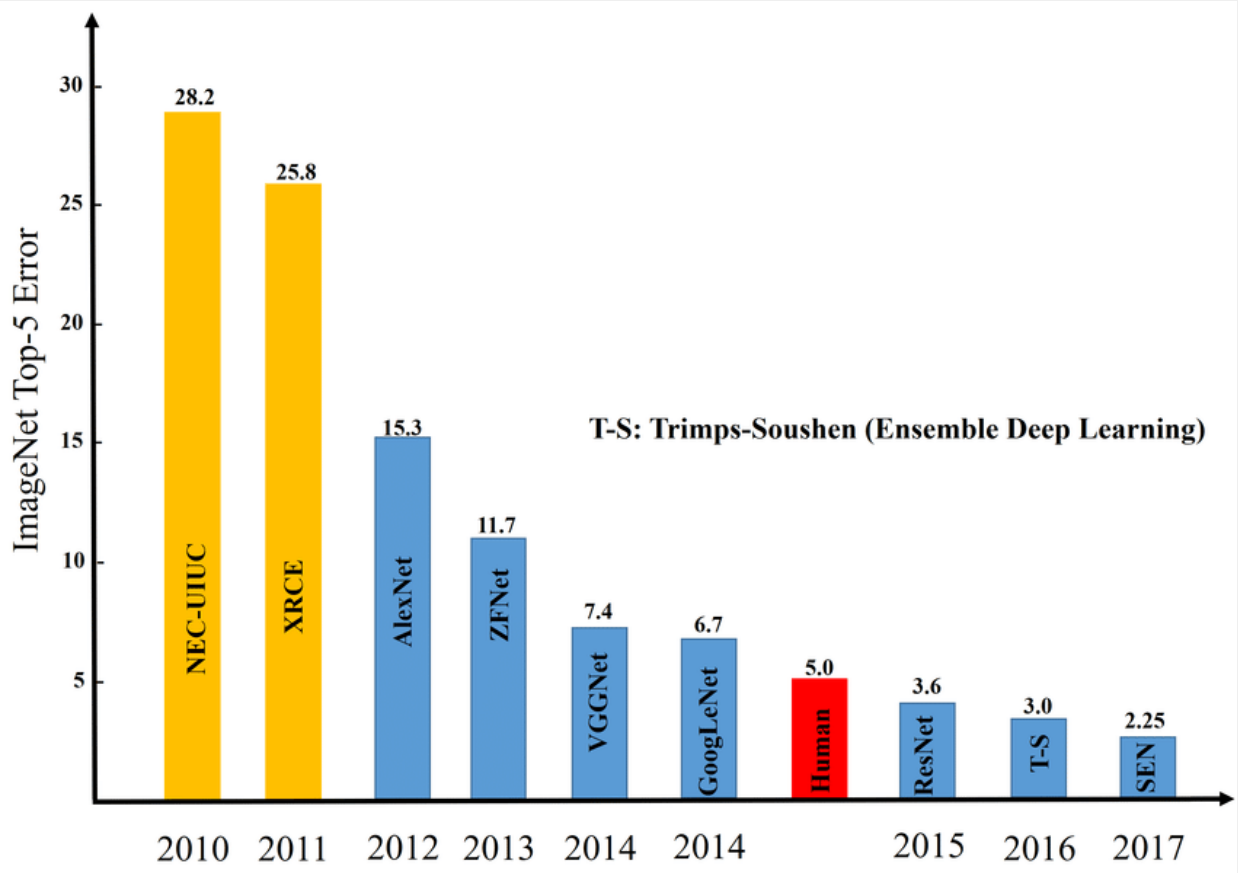
- McCulloch-Pitts networks must be designed, i.e. there exists no training algorithm

Mathematical models of neural networks

Short and incomplete history of neural network models:

- McCulloch-Pitts networks [McCulloch and Pitts, 1943]
- The perceptron [Rosenblatt, 1957]
- Multilayer perceptrons [Werbos, 1974, McClelland et al., 1986]
- Backpropagation algorithm [LeCun et al., 1988]

AlexNet - The breakthrough



- AlexNet [Krizhevsky et al., 2012] is the first neural network that performs better than traditional feature extraction and classification methods on images

From Logistic Regression to ANNs

Logistic regression

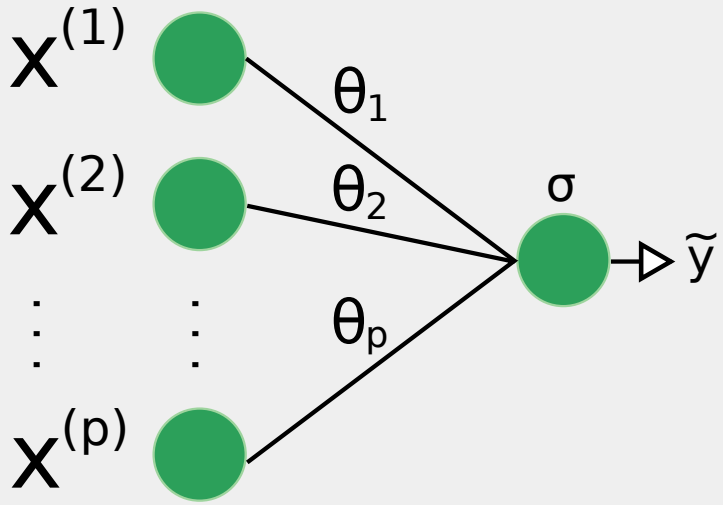
- We convert $x^\top \theta$ to probabilities

$$\mathrm{pr}(Y = 1 \mid \theta) = \sigma(x^\top \theta)$$

- The function σ denotes the sigmoid function

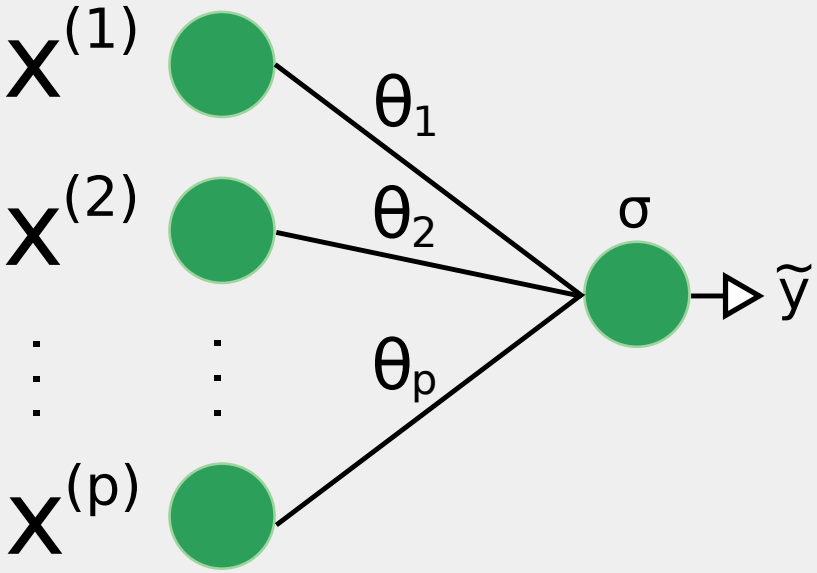
$$\sigma(z) = \frac{1}{1 + e^{-z}}$$

- Visual respresentation of logistic regression:



where $x^{(j)}$ is the j-th value of the input vector $x \in \mathbb{R}^p$

Generalizing logistic regression



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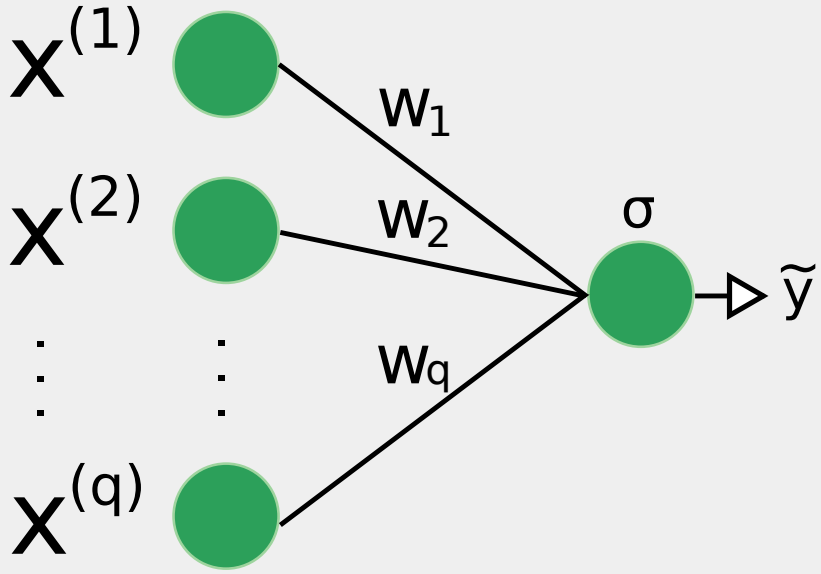
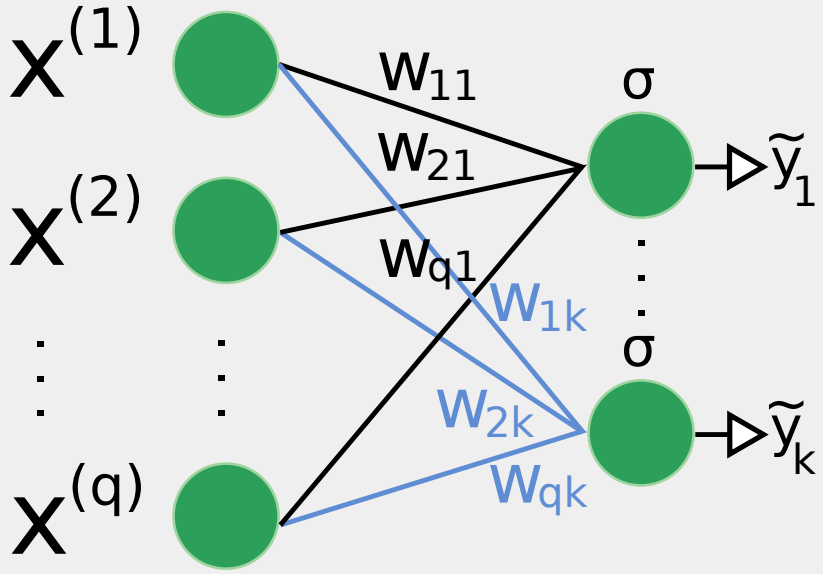


- Instead of θ we use w for weights. In addition, q refers to the number of inputs or features, which for neural networks is much lower than the number of parameters p

Generalizing logistic regression



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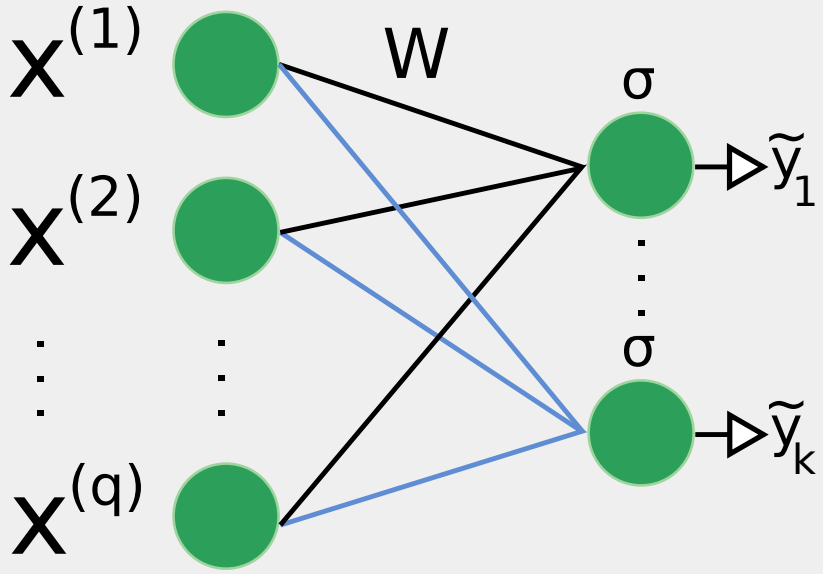

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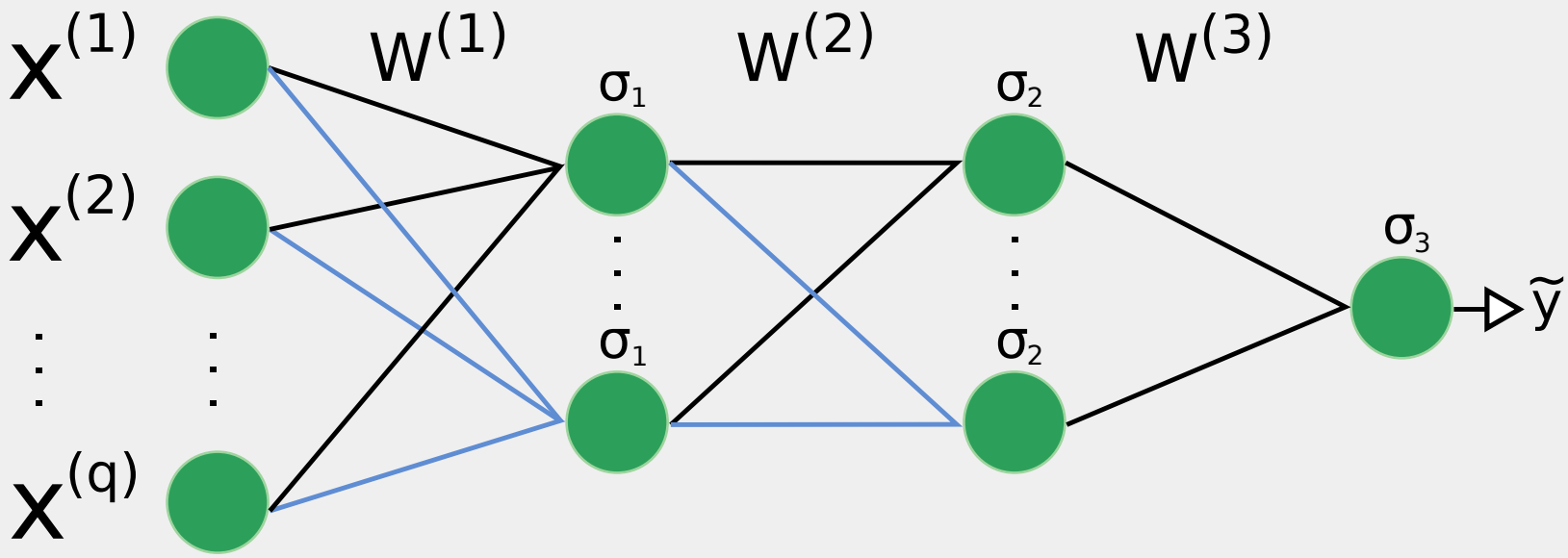
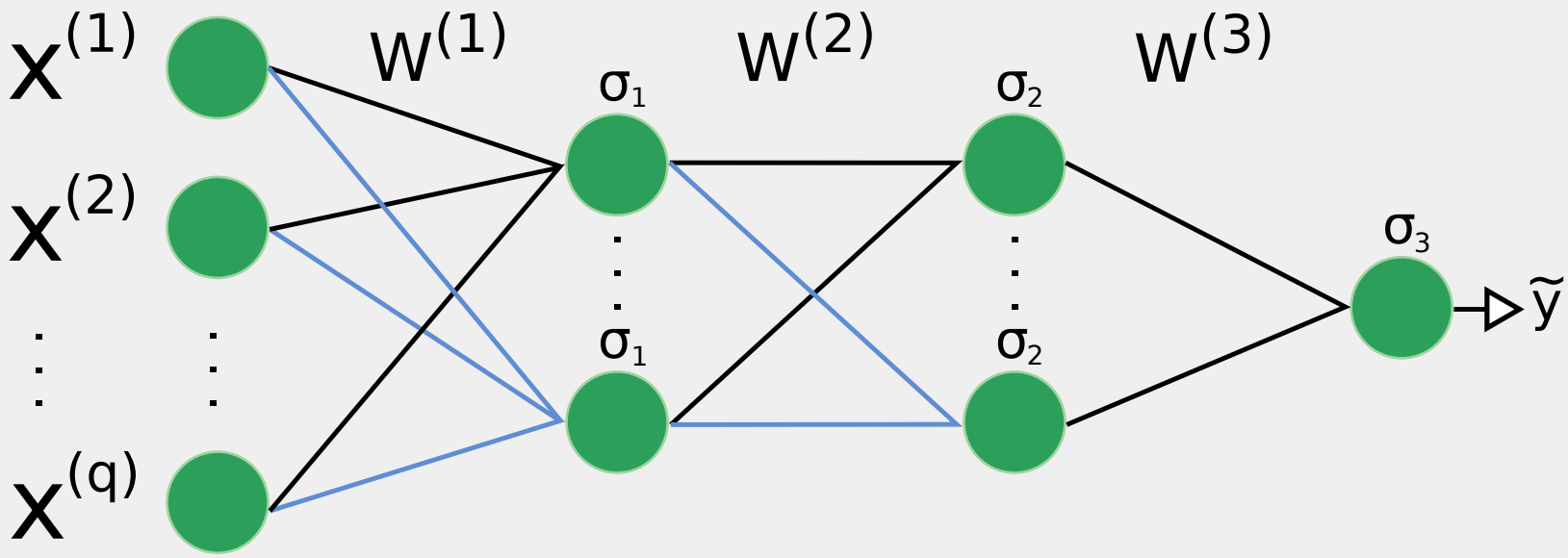
- We introduce multiple output neurons $\tilde{y}_1, \ldots, \tilde{y}_k$
- Weights are compiled into a single weight matrix $W \in \mathbb{R}^{p \times k}$

Generalizing logistic regression



- Instead of θ we use w for weights. In addition, q refers to the number of inputs or features, which for neural networks is much lower than the number of parameters p
- We introduce multiple output neurons $\tilde{y}_1, \ldots, \tilde{y}_k$
- Weights are compiled into a single weight matrix $W \in \mathbb{R}^{p \times k}$
- We stack several layers, where each layer ℓ has its own weight matrix $W^{(\ell)}$ and activation function σ_ℓ

Artificial neural network



Feedforward Artificial Neural Network

A feedforward neural network consists of a variable number of layers. Each layer ℓ has its own weight matrix $W^{(\ell)} \in \mathbb{R}^{k_\ell \times k_{\ell+1}}$, where k_ℓ denotes the number of nodes within layer ℓ. The input layer has weight matrix $W^{(1)} \in \mathbb{R}^{k_1 \times k_2}$, where $q = k_1$ is the dimension of the input data. The activation function σ_ℓ is a layer-specific function and applied independently to each node.

Artificial neural network - Notation

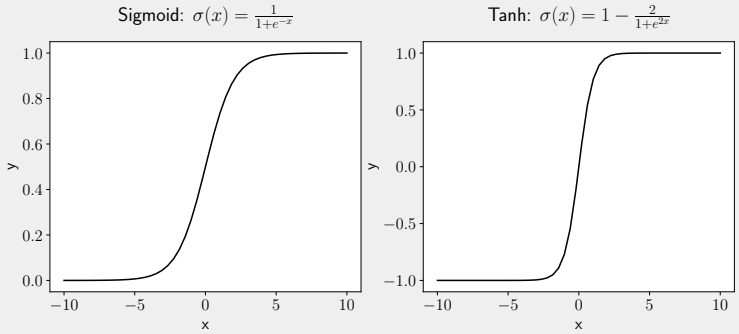
- Let $X = X^{(1)} \in \mathbb{R}^{n \times q}$ denote a data matrix with n samples or observations, each of dimension q
- The output of the ℓ-th layer of a neural network is denoted

$$X^{(\ell+1)} = \sigma_\ell(X^{(\ell)} W^{(\ell)})$$

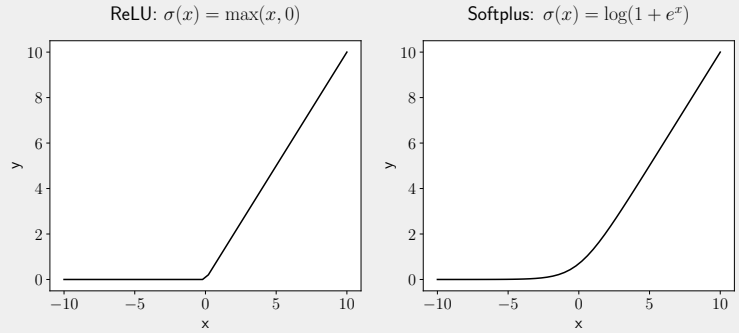
- The activation function σ_ℓ is applied to each cell of the matrix $X^{(\ell)} W^{(\ell)}$
- The prediction $\tilde{y}$ of a neural network with L layers is the output $X^{(L+1)}$ of the last layer
- *Deep neural networks* have a large number of layers L

Activation functions

- Linear functions $\sigma(x) = ax + b$ are not very useful, except for output neurons[1]
- Traditionally there were mainly two activation functions:



- Rectifier linear units (ReLU) [Glorot et al., 2011] and Softplus show better performance for training deep neural networks



[1] Stacking of linear functions results in a linear function

Activation functions

- Especially important is the activation function of the output layer
- Classification:
  - For binary classification problems we use one output node with sigmoid activation
  - The softmax activation $\sigma : \mathbb{R}^k \to (0,1)^k$ is used for multiclass problems

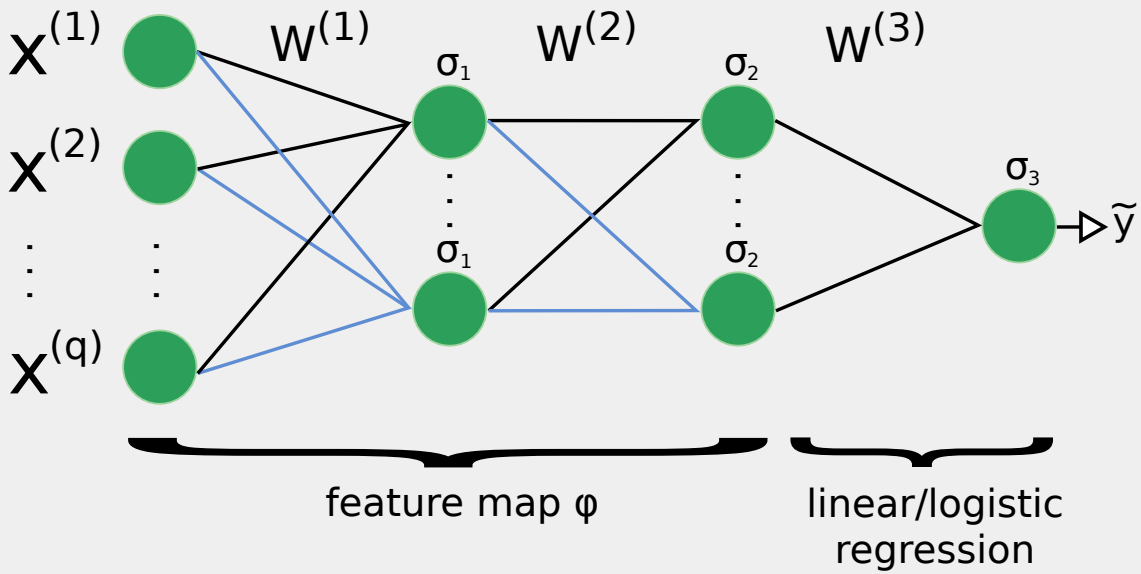
$$\sigma(x)_i = \frac{e^{x_i}}{\sum_{j=1}^{k} e^{x_j}}$$

  - The output of the softmax is interpreted as class probabilities
- Regression:
  - In most cases simply the identity function $\sigma(x) = x$
  - ReLU can be used for only positive targets

Architectures

- How do we choose the architecture? How many hidden layers? How many neurons in each layer?
- Neural networks with one hidden layer and an abritrary amount of neurons are universal approximators [Hornik et al., 1989]
- Deep neural networks seem to perform better in practice than shallow networks with many neurons
- Each application domain has its own Architectures
  - Image processing: convolutional neural networks (CNNs)
  - Materials: Graph neural networks
  - Machine translation: transformers / attention

ANN INTERPRETATION



Training ANNs

Training ANNs

- Similar to logistic regression, the weights of ANNs are computed using gradient descent
- Gradient descent is an iterative algorithm to minimize a given loss function $\mathcal{L}_W$, i.e.

$$\hat{W} = \arg\min_{w} \mathcal{L}_W(X, y)$$

  where (X, y) denotes the training data and $W = (W^{(1)}, W^{(2)}, \ldots, W^{(L)})$ the weights of the neural network
- Logistic regression uses the negative log-likelihood as loss function
- What loss functions do we use for neural networks?

Training ANNs - Loss functions

- Let f_W denote the neural network with weights W and (X, y) a training data set
- Regression:
  - Mean squared error (similar to OLS):

$$\mathcal{L}_W = \frac{1}{n} \|y - f_W(X)\|_2^2$$

  - Mean absolute error:

$$\mathcal{L}_W = \frac{1}{n} \|y - f_W(X)\|_1$$

    Useful when targets y contain outliers

Training ANNs - Loss functions

- Classification:
  - Binary cross-entropy ($y_i \in \{0, 1\}$):

$$\mathcal{L}_W = -\frac{1}{n} \sum_{i=1}^{n} y_i \log(f_W(x_i)) + (1 - y_i) \log(1 - f_W(x_i))$$

    Equivalent to maximum likelihood of logistic regression

  - Multiclass cross-entropy with k classes ($y_i \in \{0, 1\}^k$):

$$\mathcal{L}_W = -\frac{1}{n} \sum_{i=1}^{n} \sum_{j=1}^{k} y_{i,j} \log(f_W(x_i)_j) = -\frac{1}{n} \sum_{i=1}^{n} y_i^\top \log(f_W(x_i))$$

    where $y_{i,j}$ is 1 if the i-th sample belongs to class j and $f_W(x_i)_j$ denotes the output of the j-th node of the last layer of the neural network f_W

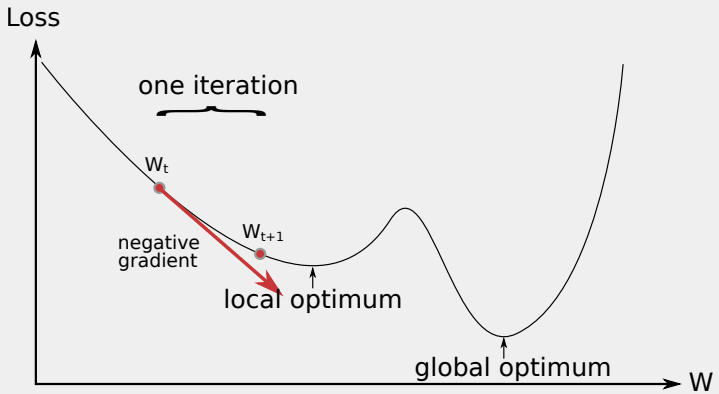
- The loss function is typically not convex!

Gradient descent

Gradient descent updates the weights at each iteration t according to the following update rule:

$$W_{t+1} = W_t - \gamma \nabla_{W_t} \mathcal{L}_{W_t}(X, y)$$

where γ is a parameter that determines the step size



- The larger γ the more likely the algorithm jumps over local optima, but the higher the chance of divergence

Stochastic gradient descent (SGD)

Stochastic gradient descent (SGD) selects at each iteration t a single training sample (x_t, y_t) with $t \in \{1, \ldots, n\}$ at random and updates the weights based on this one sample:

$$W_{t+1} = W_t - \gamma \nabla_{W_t} \mathcal{L}_{W_t}(x_t, y_t)$$

- The stochastic nature of SGD can help to bypass local optima [Masters and Luschi, 2018]
- SGD is slow, because we have to update weights for each sample and cannot utilize parallel computation

Mini-batch SGD

Mini-batch SGD selects at each iteration t a random subset (X_t, y_t) of m samples $X_t = (x_{t_1}, \ldots, x_{t_m})$, $y_t = (y_{t_1}, \ldots, y_{t_m})$ with $t_k \in \{1, \ldots, n\}$ and updates the weights accordingly:

$$W_{t+1} = W_t - \gamma \nabla_{W_t} \mathcal{L}_{W_t}(X_t, y_t)$$

(X_t, y_t) is called a mini-batch and m controls the mini-batch size

- Practice has shown that (mini-batch) SGD seems to improve generalization [Hoffer et al., 2017]
- We typically select $m = 32$ or $m = 64$

Gradient descent with momentum

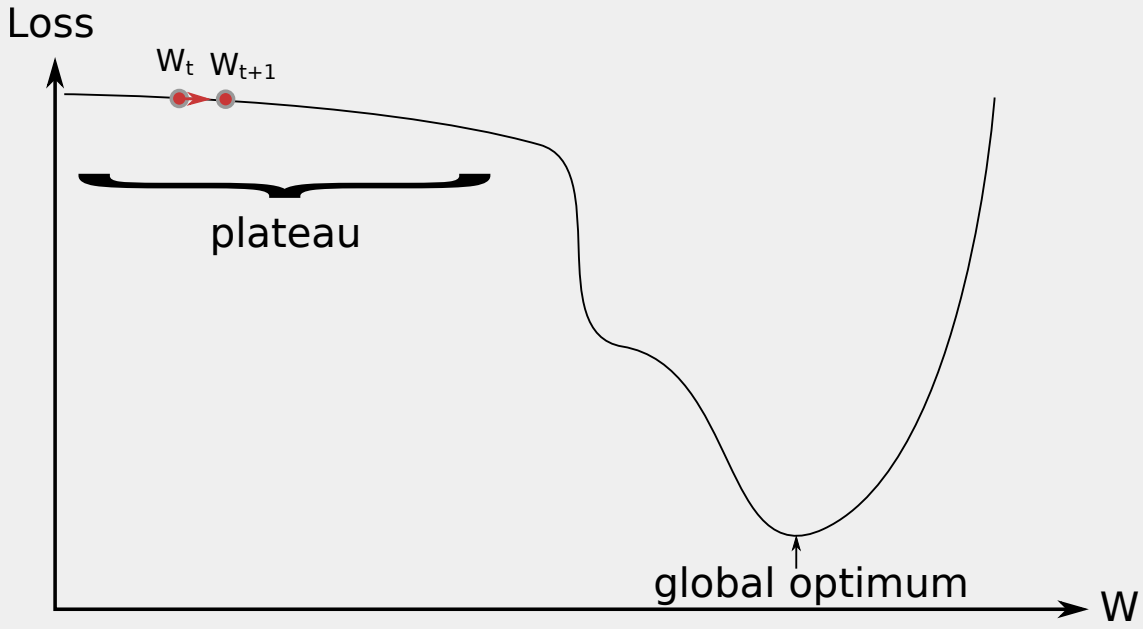
The update rule of gradient descent with momentum is

$$M_{t+1} = \beta M_t + \nabla_{W_t} \mathcal{L}_{W_t}(X_t, y_t)$$
$$W_{t+1} = W_t - \gamma M_{t+1}$$

where γ is the usual step size and β determines the weight of previous updates

- For $\beta = 0$ we obtain vanilla gradient descent
- Intuitive explanation: The mass of a stone rolling downhill adds momentum
- In some cases gradient descent with momentum can help to jump out of local optima
- It makes SGD or mini-batch SGD more stable

Training ANNs - Gradient descent



- Gradient descent converges slowly when being stuck on plateaus
- The gradient itself is not very informative
- Some gradient descent methods only use the sign of the gradient (i.e. Rprop [Riedmiller and Braun, 1992])
- Rprop does not work for mini-batches

Root Mean Square Propagation (RMSProp)

RMSProp uses the following update rule:

$$V_{t+1} = \beta V_t + (1-\beta)\left(\nabla_{W_t}\mathcal{L}_{W_t}(X_t, y_t)\right)^2$$
$$W_{t+1} = W_t - \frac{\gamma}{\sqrt{V_{t+1}}}\nabla_{W_t}\mathcal{L}_{W_t}(X_t, y_t)$$

where γ denotes the step size and β decay rate for averaging over previous gradients

- For $\beta = 0$ we obtain

$$W_{t+1} = W_t - \frac{\gamma}{|\nabla_{W_t}\mathcal{L}_{W_t}(X_t, y_t)|}\nabla_{W_t}\mathcal{L}_{W_t}(X_t, y_t)$$

  i.e. we only consider the sign of the gradient

Adaptive Moment Estimation (Adam)

Adam uses the following update rule:

$$M_{t+1} = \beta_1 M_t + (1-\beta_1)\nabla_{W_t}\mathcal{L}_{W_t}(X_t, y_t) \quad | \text{ momentum}$$

$$V_{t+1} = \beta_2 V_t + (1-\beta_2)\nabla_{W_t}\mathcal{L}_{W_t}(X_t, y_t)^2 \quad | \text{ adaptive } \gamma$$

$$\hat{M}_{t+1} = M_{t+1}/(1-\beta_1^{t+1}), \quad \hat{V}_{t+1} = V_{t+1}/(1-\beta_2^{t+1}) \quad | \text{ bias correction}$$

$$W_{t+1} = W_t - \frac{\gamma}{\sqrt{\hat{V}_{t+1} + \epsilon}}\hat{M}_{t+1}$$

where γ denotes the step size and β decay rate for averaging over previous gradients

- $M_0 = 0$ and $V_0 = 0$, hence early estimates are biased towards zero, $\hat{M}$ and $\hat{V}$ correct this bias

Adaptive Moment Estimation (Adam)

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where γ denotes the step size and β decay rate for averaging over previous gradients

- Adam is the default for training neural networks
- RMSProp with bias-correction and momentum

Vanishing and exploding gradient problem

- Suppose we want the gradient of the first weight matrix of a neural network with L layers
- The derivative of the first weight matrix is defined by the *chain rule*:

$$\frac{\partial}{\partial W^{(1)}} \mathcal{L}_W(X, y) = \frac{\partial \mathcal{L}_W}{\partial \hat{y}} \frac{\partial \hat{y}}{\partial X^{(L)}} \frac{\partial X^{(L)}}{\partial X^{(L-1)}} \cdots \frac{\partial X^{(2)}}{\partial W^{(1)}}(X, y)$$

- We use the partial derivative $\partial / \partial W^{(1)}$ to denote that all other weight matrices

$$W^{(2)}, W^{(3)}, \ldots, W^{(L)}$$

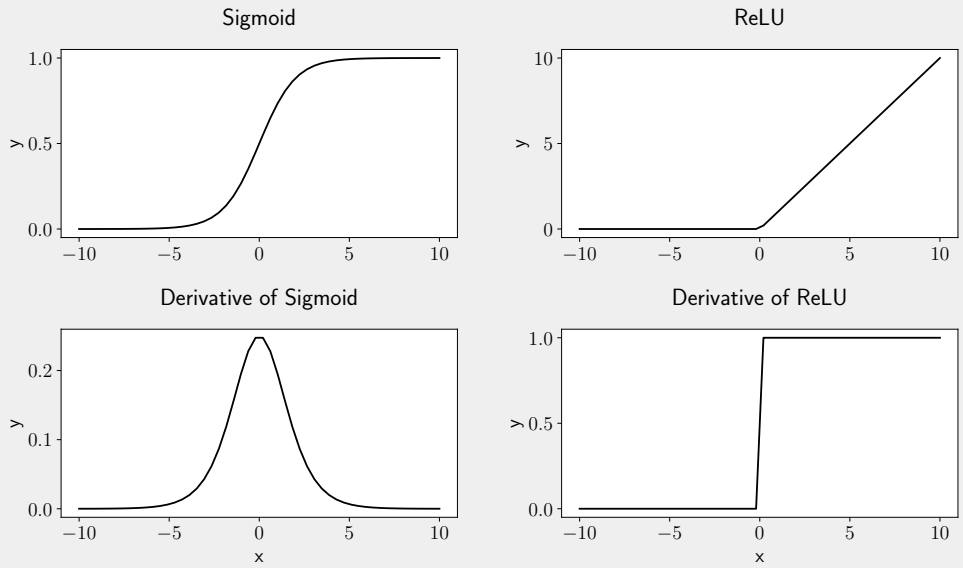
  are treated as constants at their current values
- In deep neural networks, the gradient of the first layers will behave very differently than the gradient of the last layers

Vanishing and exploding gradient problem

- In deep neural networks, the gradient of the first layers will behave very differently than the gradient of the last layers
- For the first layers, the gradient easily vanishes or explodes
- Strategies to counter this problem
  - Normalization of training data
  - Proper weight initialization
  - Activation functions such as ReLU
  - Normalization of layer outputs $X^{(\ell)}$ (batch normalization)
  - Skip connections: $X^{(\ell+1)} = \sigma_\ell(X^{(\ell)}W^{(\ell)}) + X^{(\ell)}$

Vanishing and exploding gradient problem

- Sigmoid and Tanh activations cause vanishing gradients:



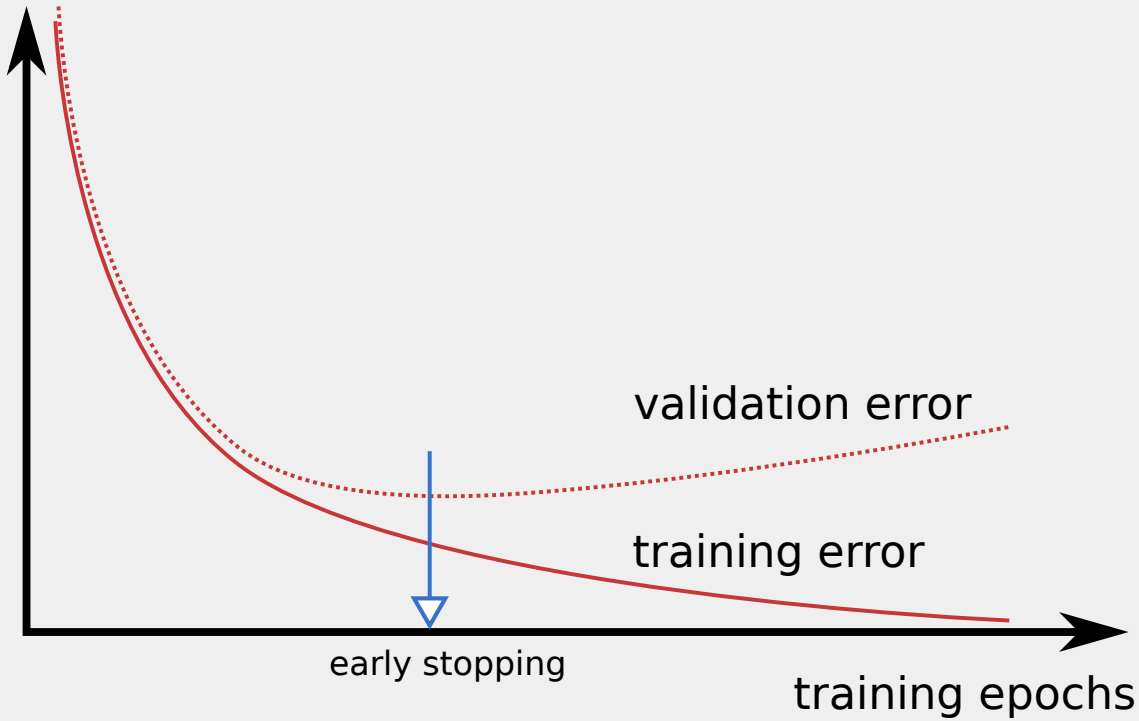
- ReLU is less prone to vanishing gradients
- ReLU often leads to inactive nodes during training (zero gradient)
- LeakyReLU is often used instead

Training ANNs - Remarks

- How do we compute the gradient for training neural networks?
- Backpropagation algorithm for neural networks
- Libraries such as Tensorflow or PyTorch use automatic differentiation (AD)
- With AD it is possible to compute the gradient of arbitrary functions, including neural networks
- Developing deep neural networks requires much testing (watch the gradient!)
  - Weights must stay within a reasonable range
  - Training data must be normalized
  - Local optima must be bypassed using SGD
  - Overfitting must be prevented

Training ANNs - Remarks

- Early stopping prevents overfitting
- We use a small portion of the training data for validation



Training ANNs - Remarks

- Statistics:
  - Define the optimization problem (e.g. maximum likelihood)
  - Use explicit regularization, especially for overparameterized models
  - Check that there is a unique solution
  - Develop numerical methods for finding the solution
- Modern machine learning:
  - Define the optimization problem (e.g. minimize MSE) using an overparameterized model
  - Use a variety of tricks to compute solutions that generalize well
  - The gradient method itself is considered a method for regularization

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