Introduction to deep learning in computational biology

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Overview

- Introduction to deep learning
  - History and motivation
  - Activations functions
  - Cost functions
  - Backpropagation
  - Regularization
  - Optimization
- Multi-Layer Perceptron (MLP)
- Auto-enconders (AE)
- Convolutional Neural Networks (CNN)
- Recurrent Neural Networks (RNN)

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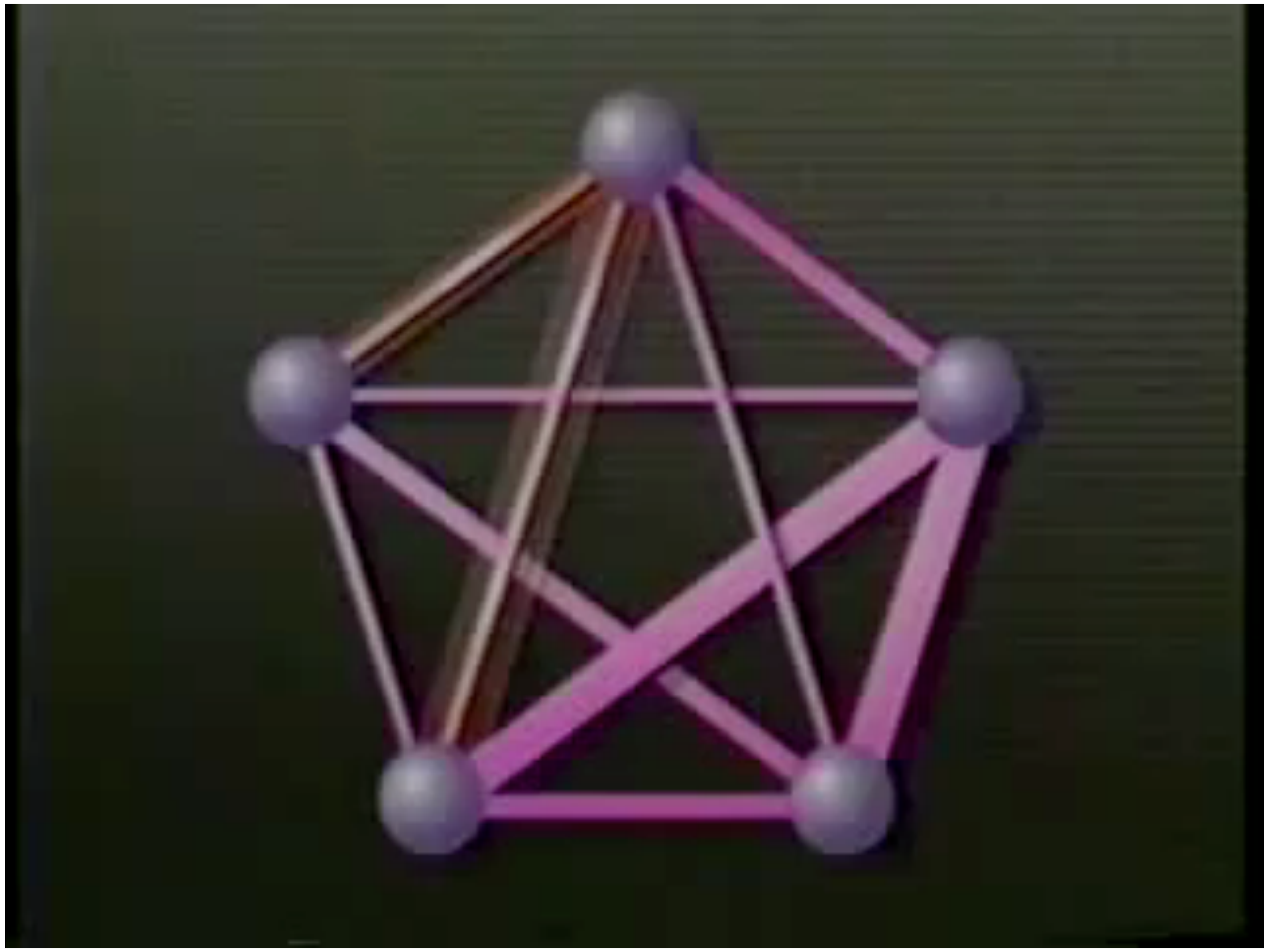
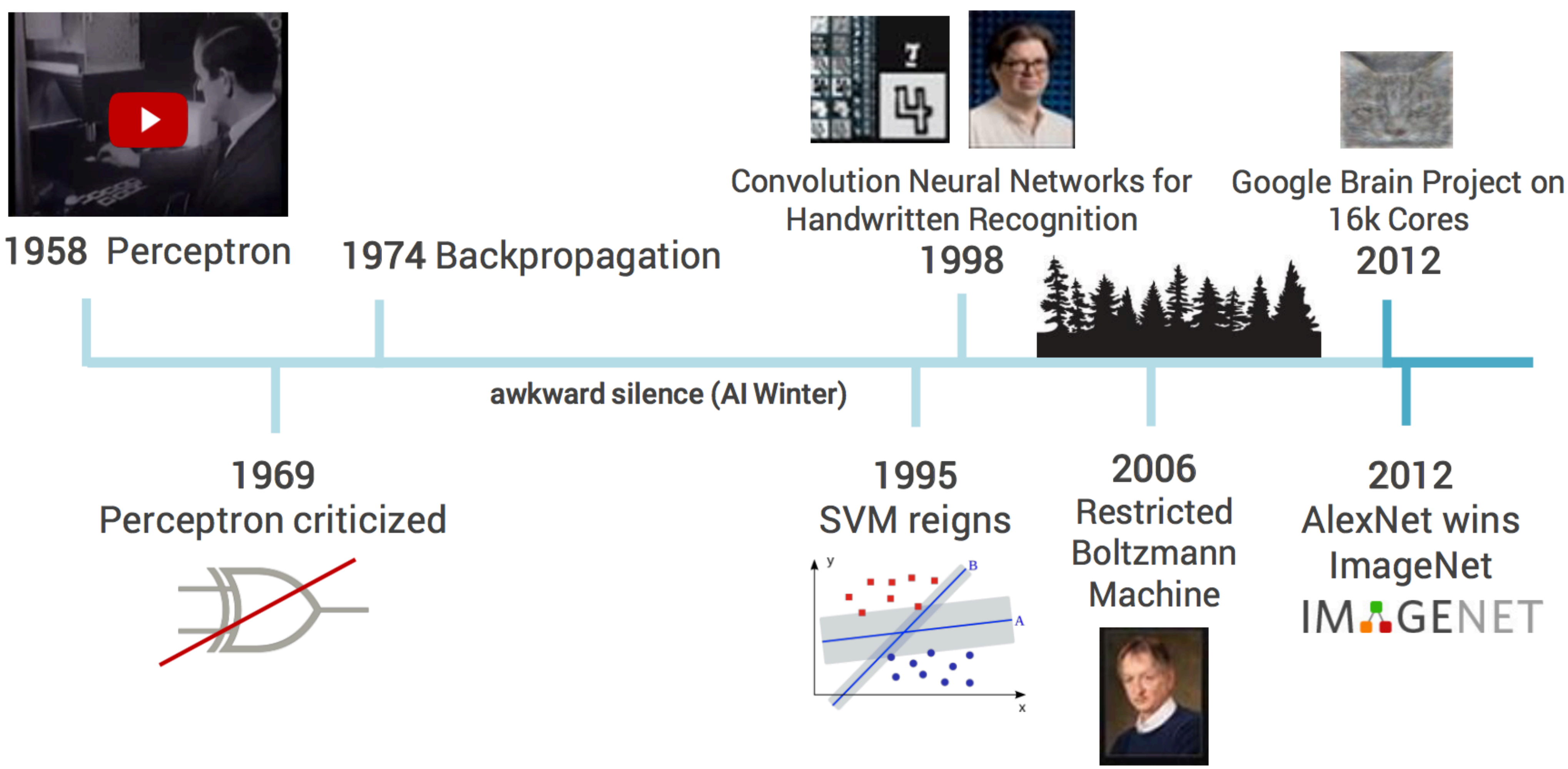
The beginnings: perceptron.



https://www.youtube.com/watch?v=cNxadbrN_aI

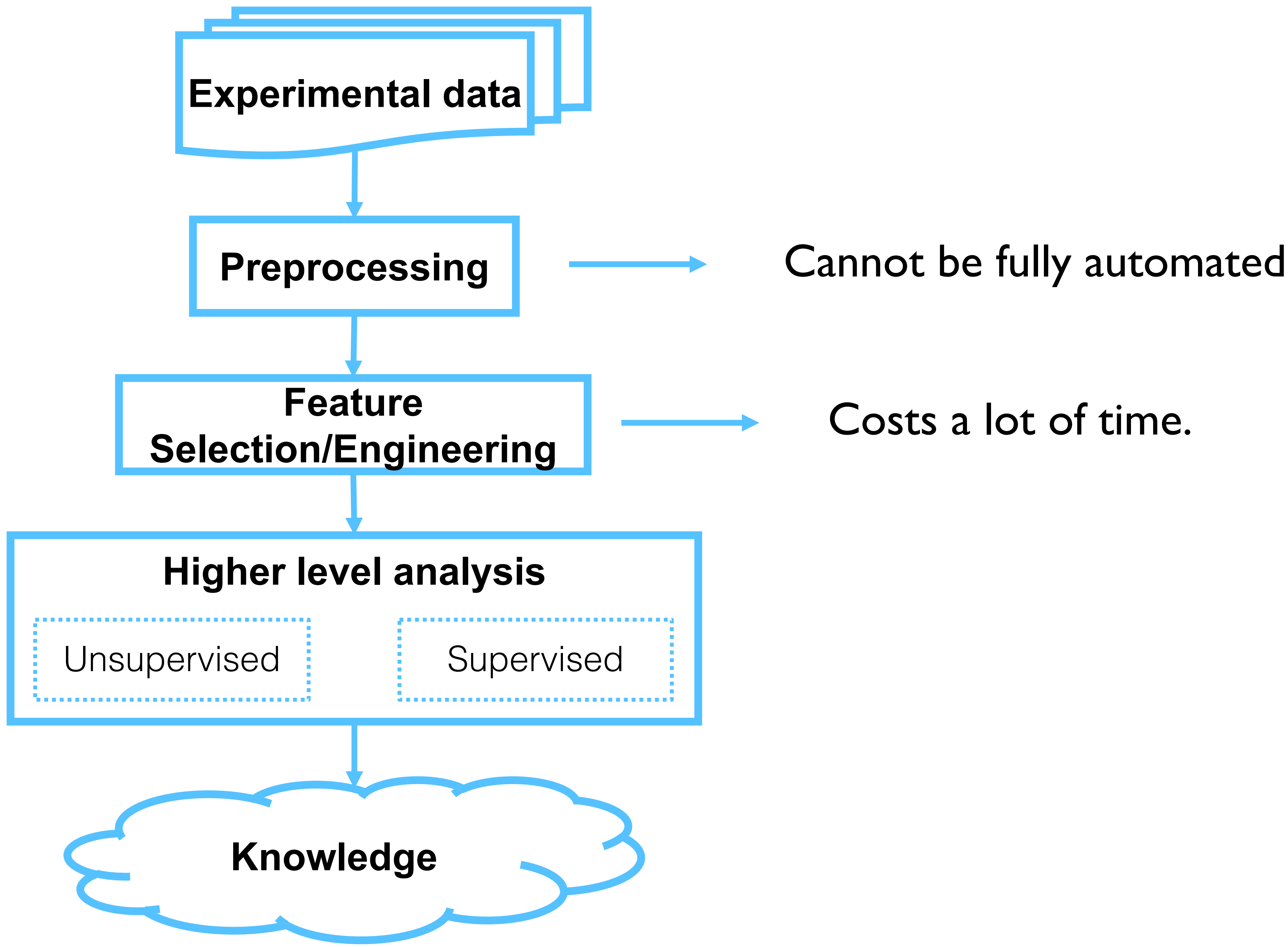
A brief history of deep learning



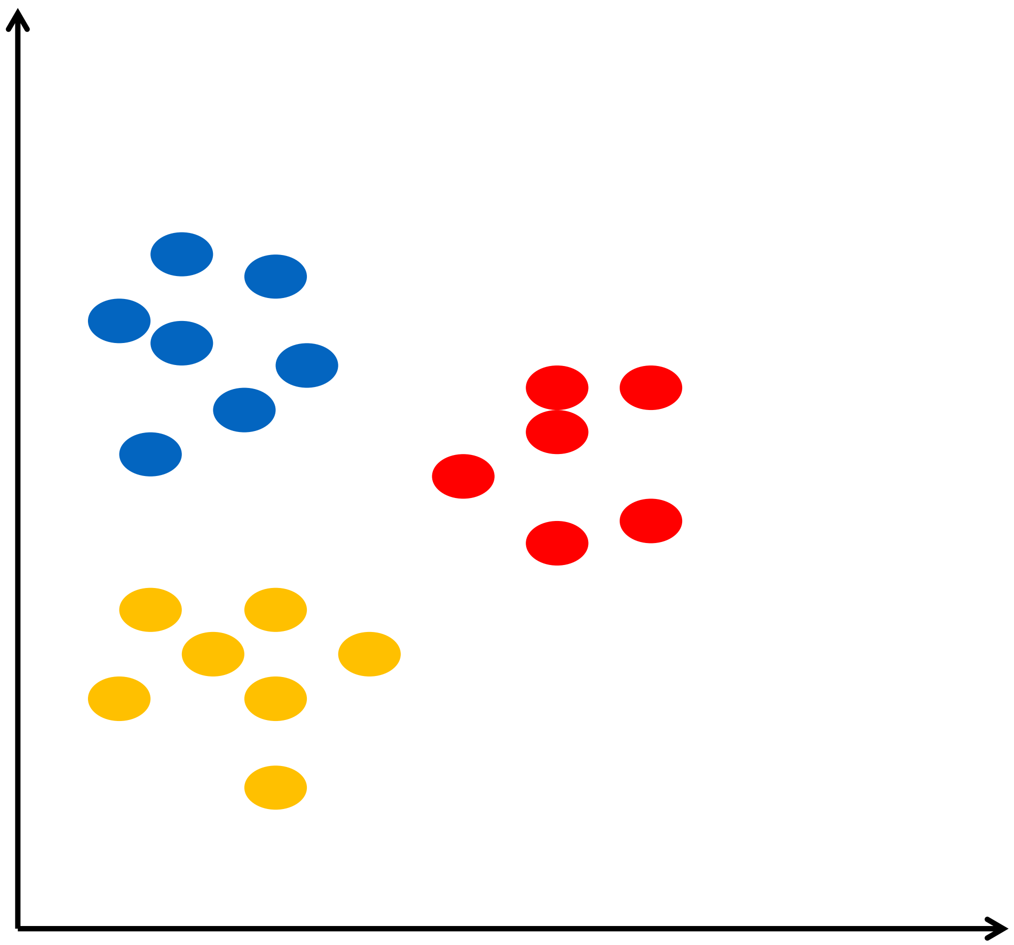
https://www.slideshare.net/LuMa921/deep-learning-a-visual-introduction

Machine learning

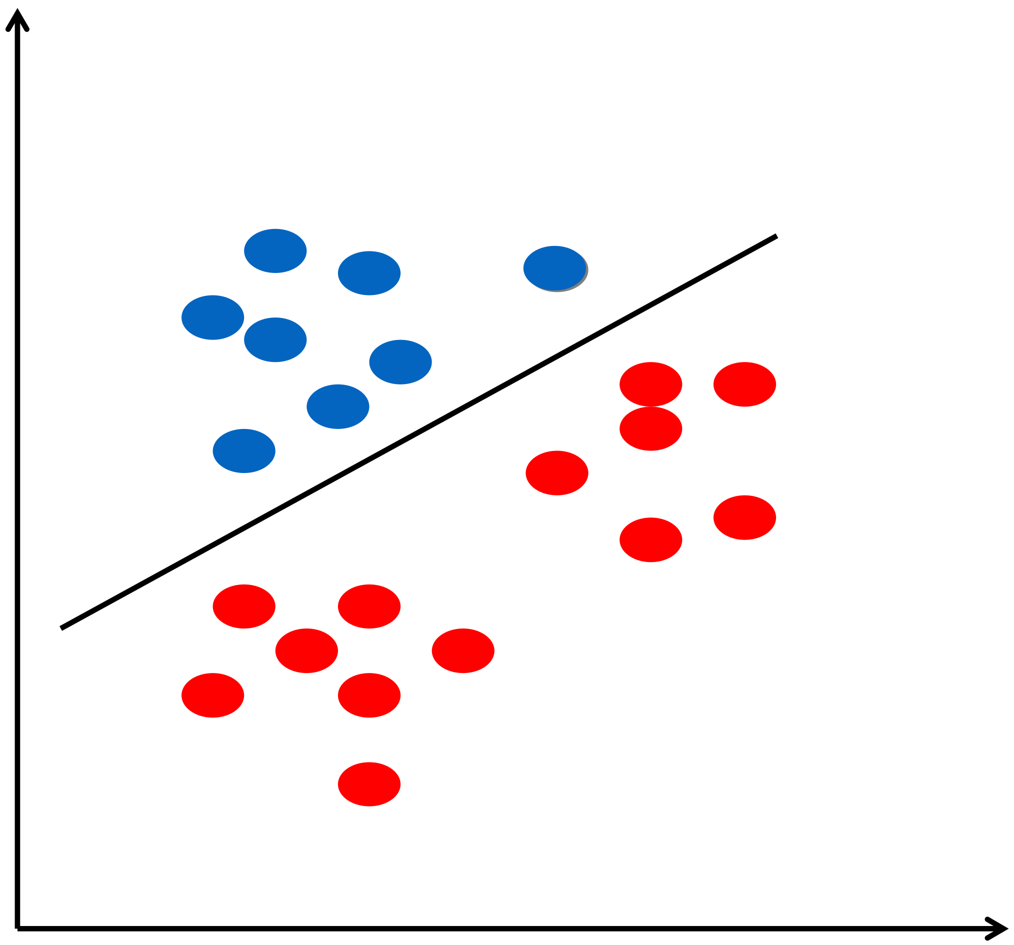
Machine Learning is a type of Artificial Intelligence that provides computers with the ability to learn without being explicitly programmed.



Learning approaches



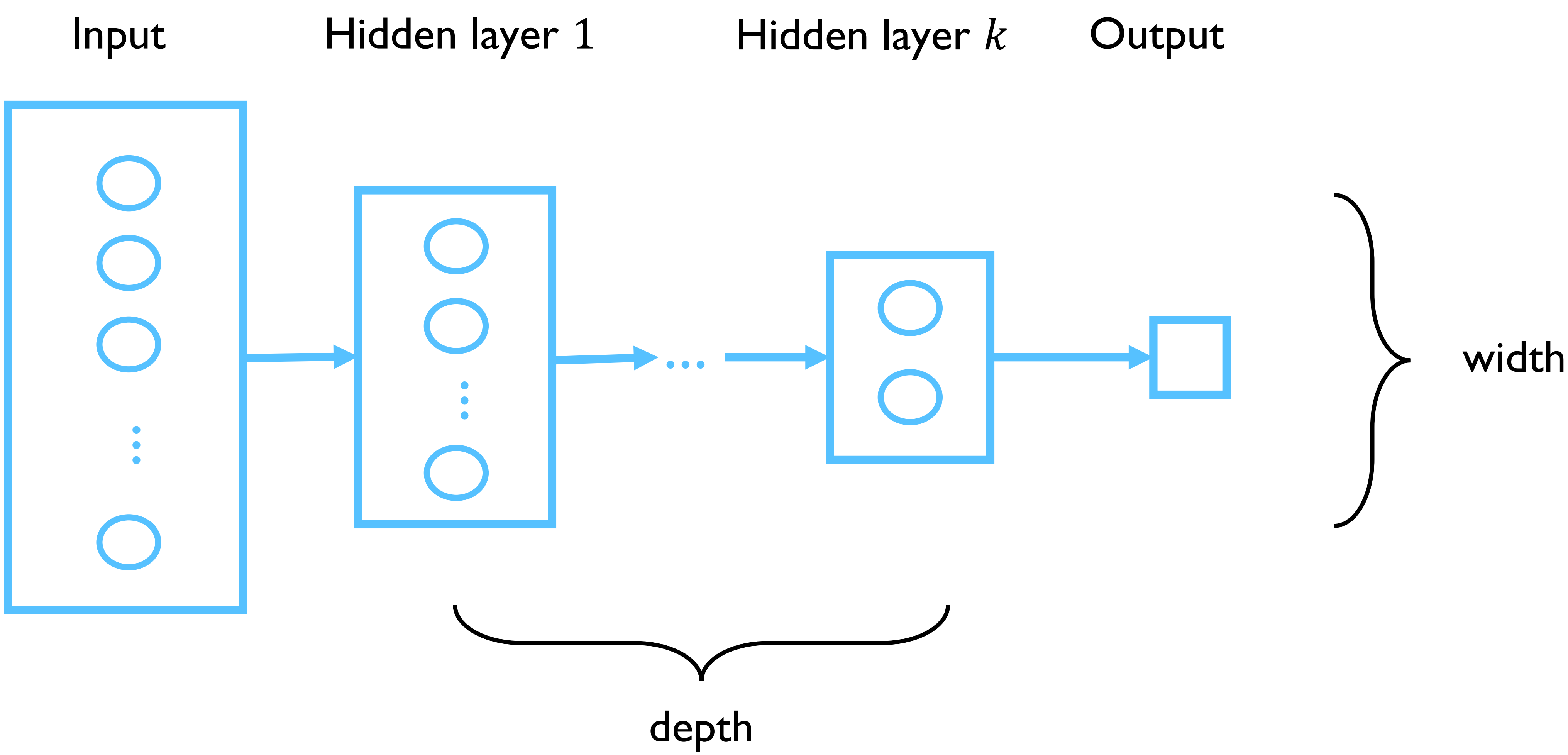
Dimensionality reduction: e.g. PCA, tSNE
Clustering: e.g. Phenograph, FlowSOM



Classification: SVMs, Random Forests

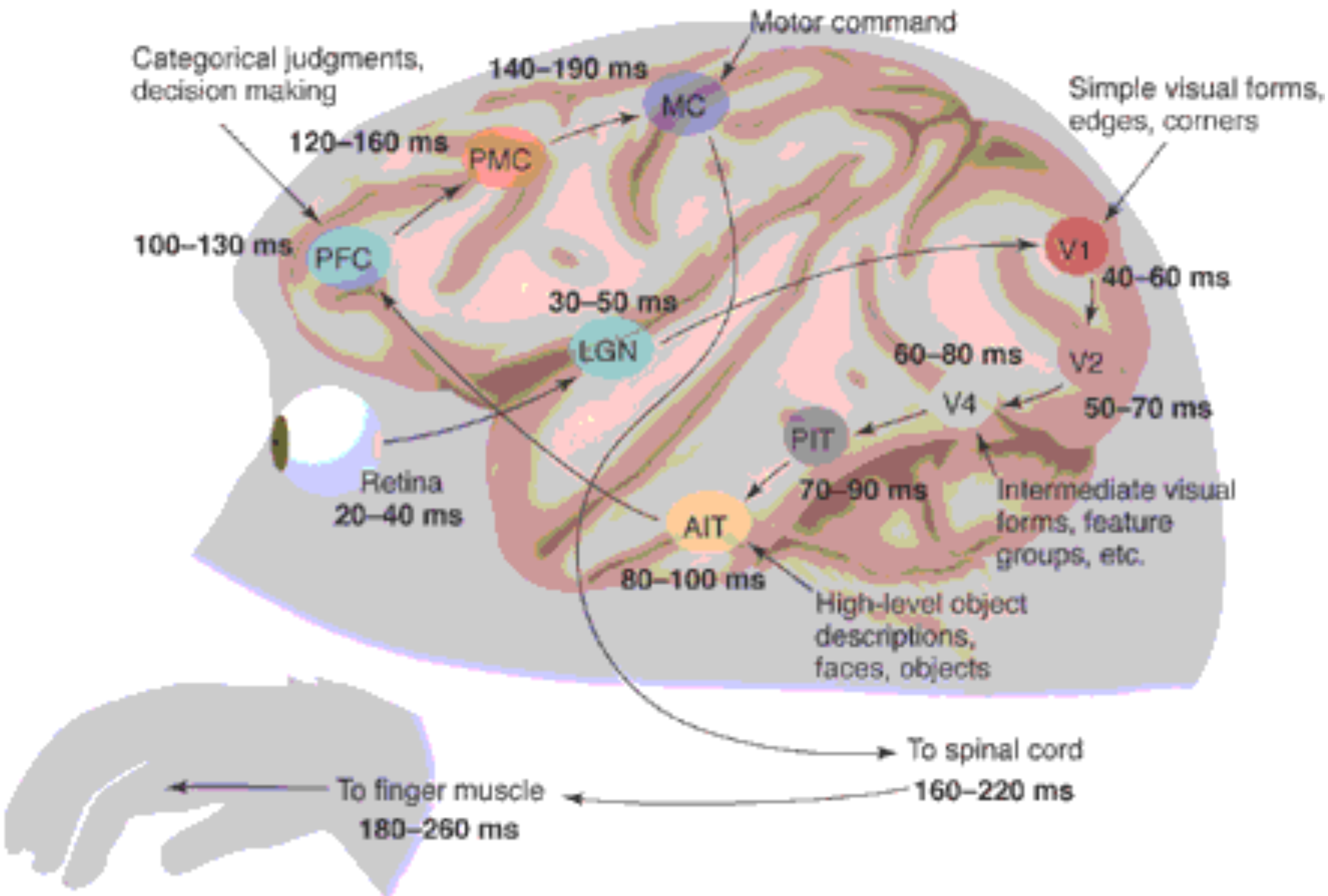
Supervised Learning: Learning with a labeled training set.
E.g. email spam detector with training set of already labeled emails.
Unsupervised Learning: Discovering patterns in unlabeled data.
E.g. cluster similar documents based on the text content .
Reinforcement Learning: learning based on feedback or reward.
E.g. learn to play chess by winning or losing.

Neural networks



- Learn data representations. Exceptional effective at learning patterns.
- Use a hierarchy of layers that mimic the neural networks of our brain.
- Can learn highly complex patterns if sufficient data is available for training.

The mammalian visual cortex is hierarchical

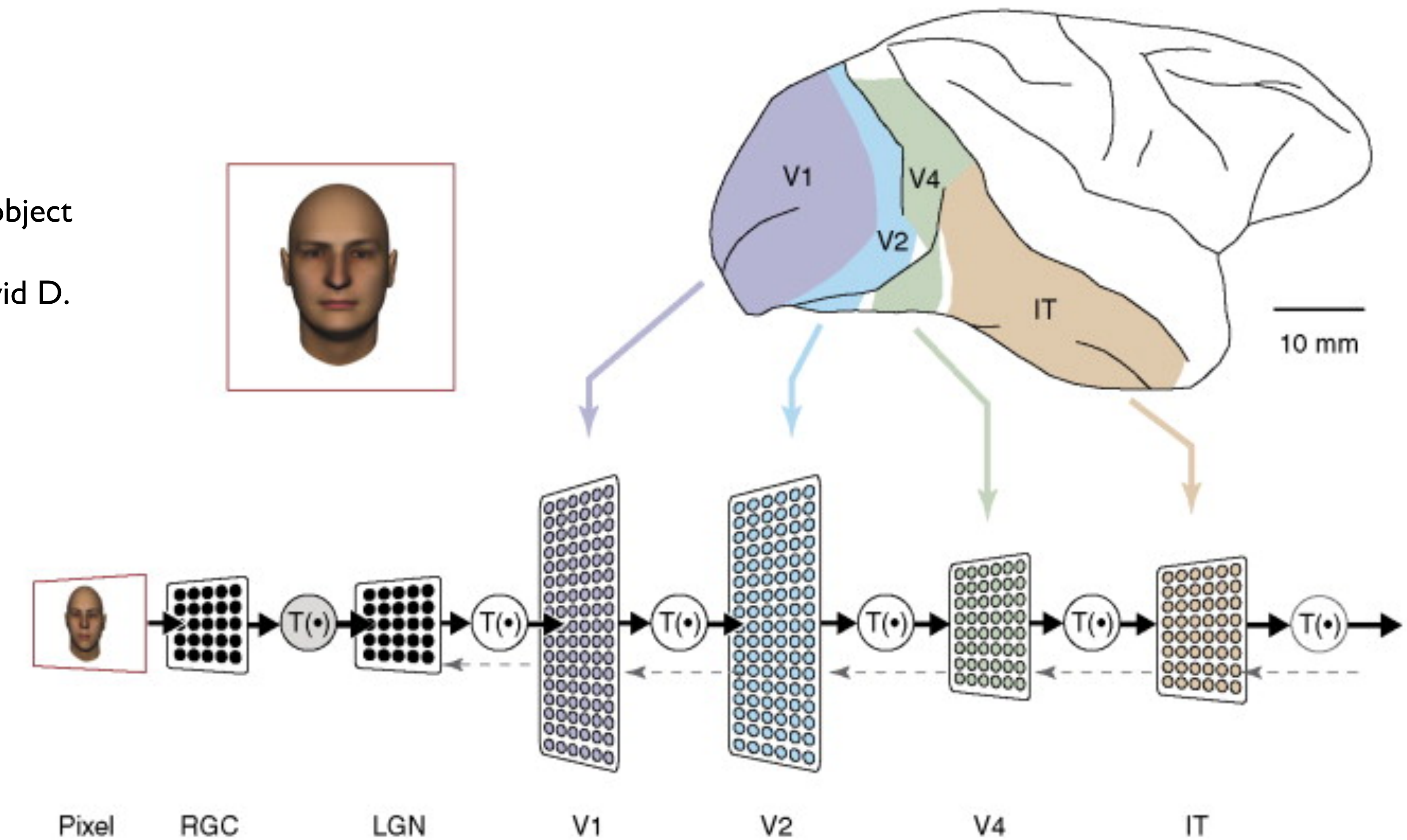


Simon J. Thorpe, Michèle Fabre-Thorpe, *Science* 2001

- First hierarchy of neurons are sensitive to edges.
- Brain regions further down the visual pipeline are sensitive to more complex structures (e.g. faces).
- The strength of the connections between neurons represents long term knowledge.

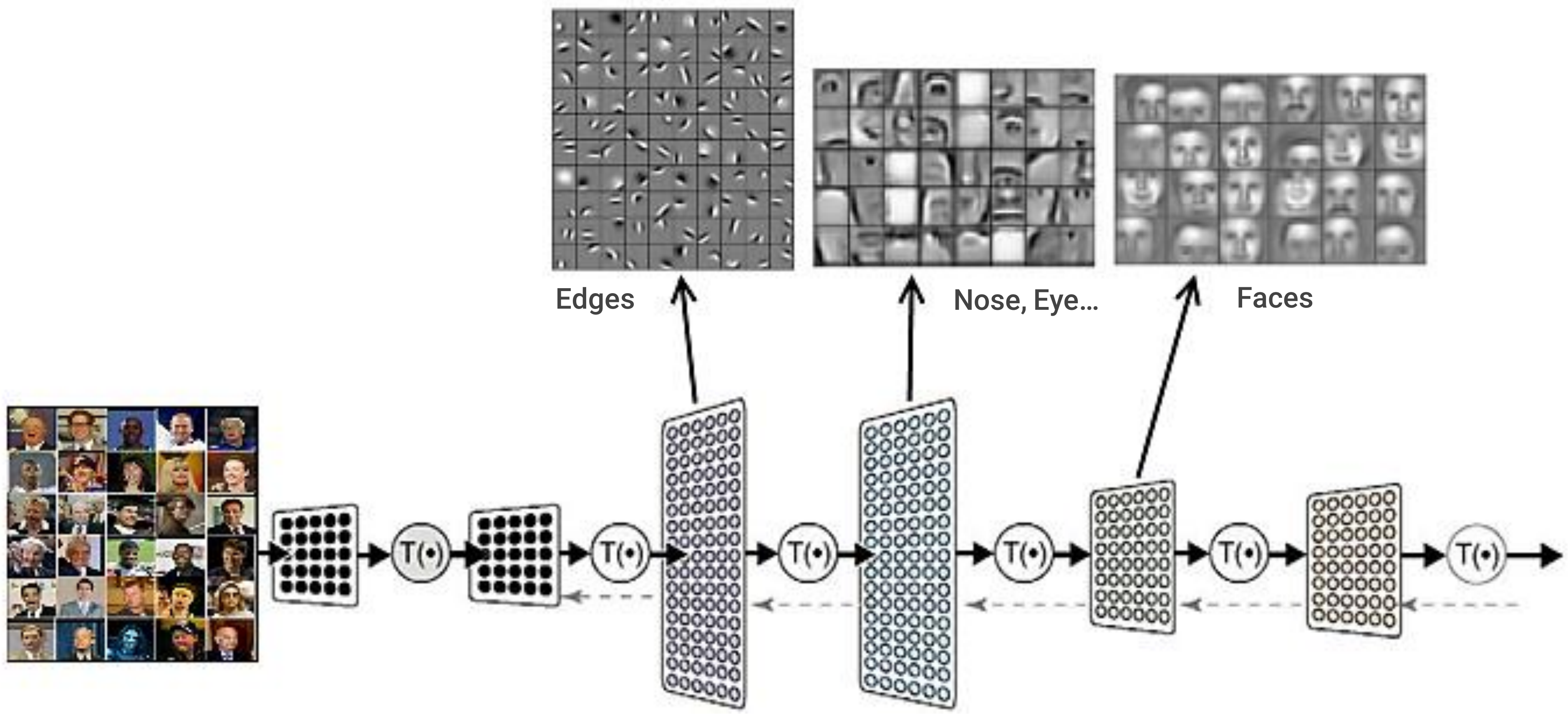
DNNs mimic the neuronal hierarchical connectivity.

Untangling invariant object recognition
James J. DiCarlo, David D. Cox, 2007



- Deep neural networks (DNNs) consists of a hierarchy of layers.
- Each layer transforms the input data into more abstract representations:
  e.g. edge -> nose -> face.
- The output layer combines those features to make predictions.

DNNs mimic the neuronal hierarchical connectivity.



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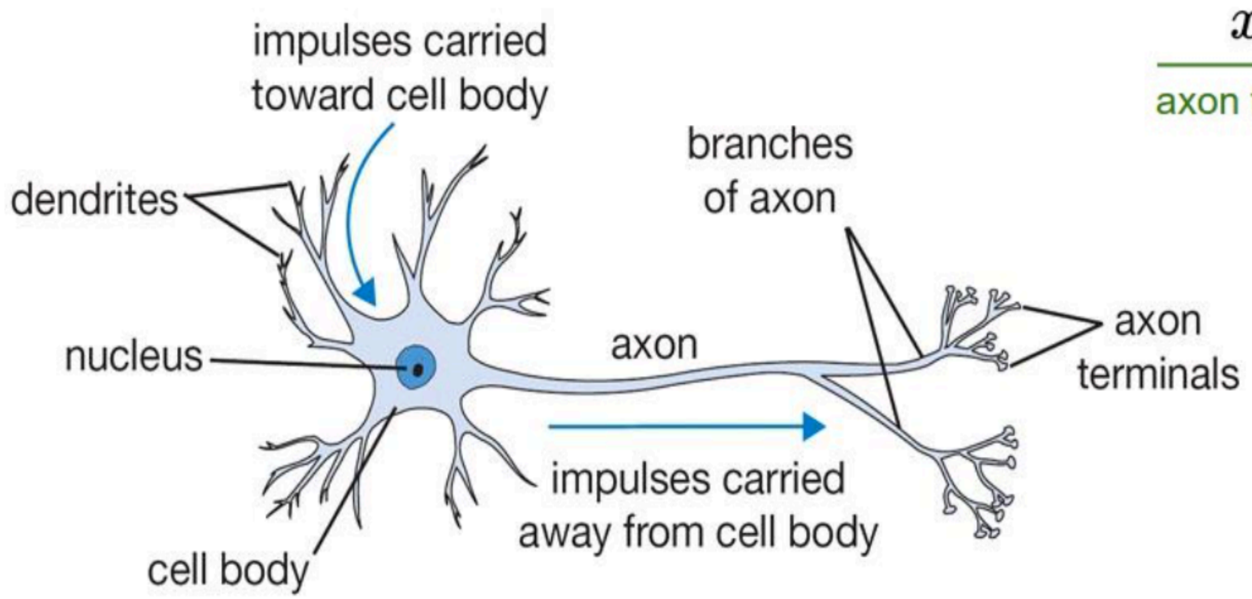
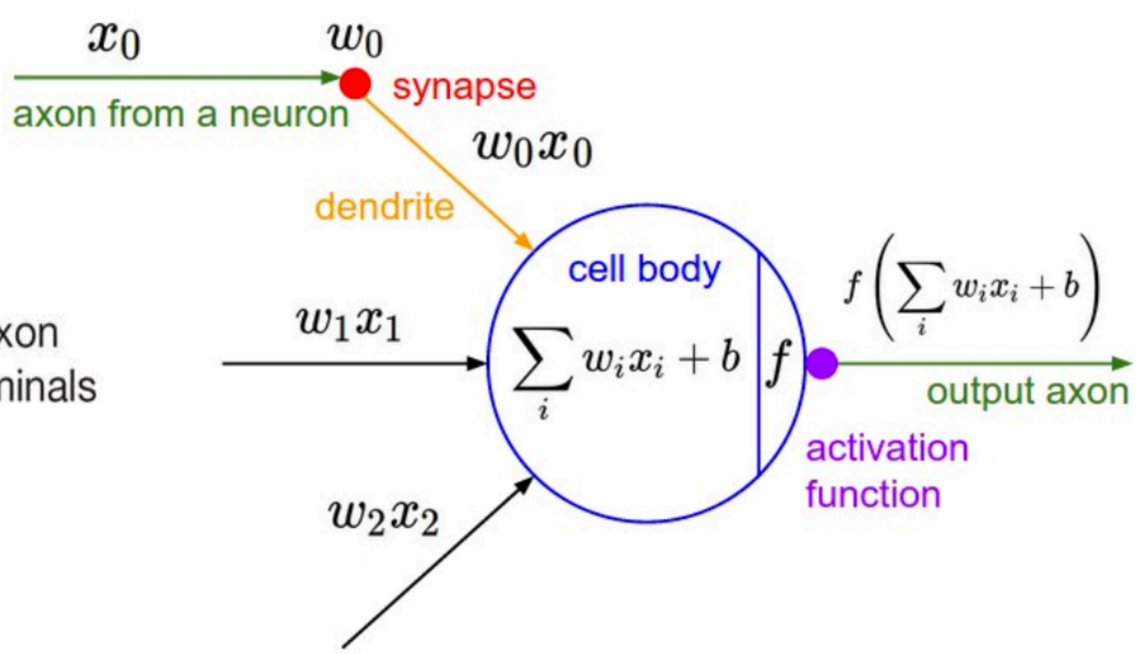
Biological vs. artificial neurons

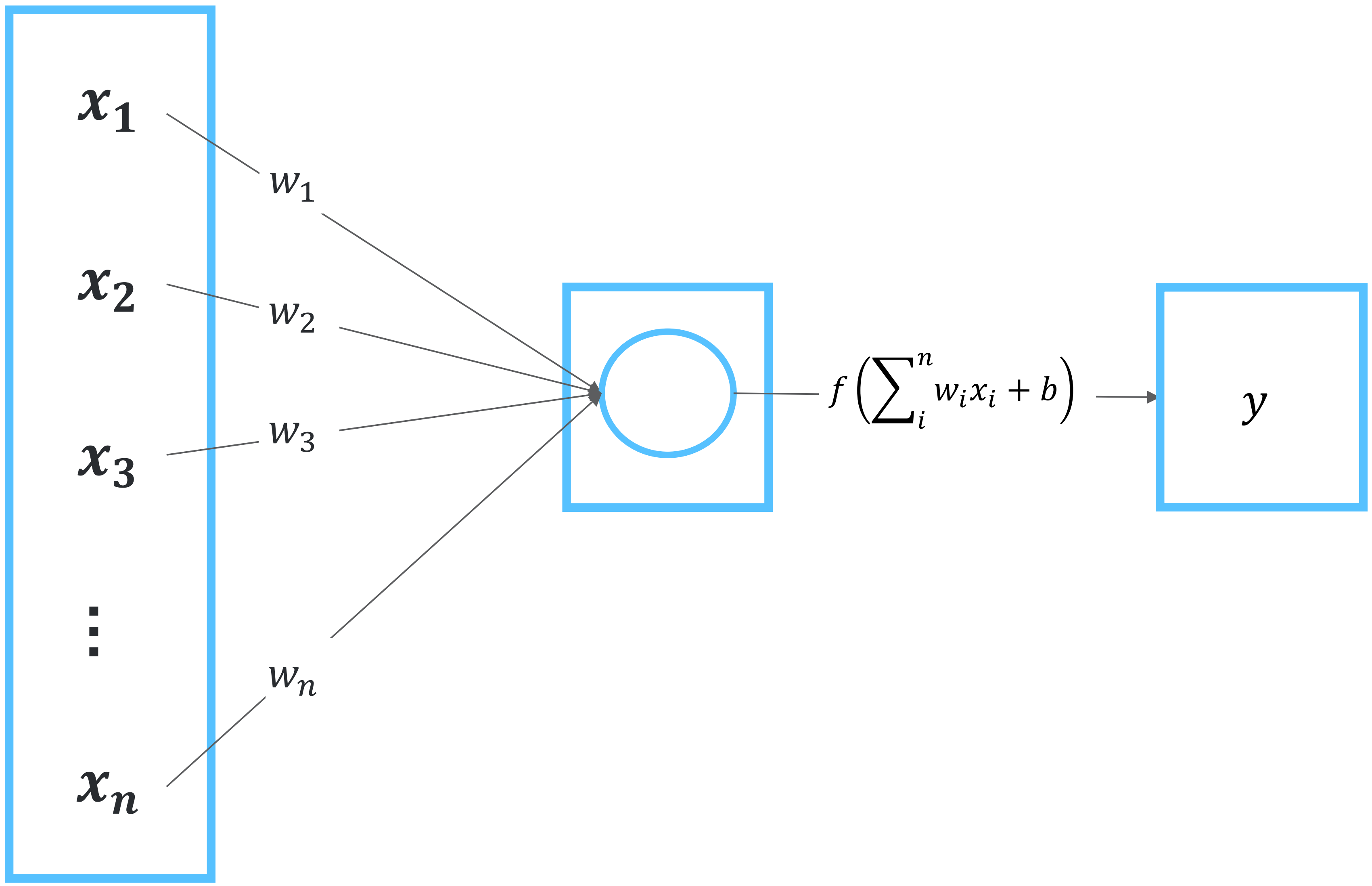




http://cs231n.github.io/neural-networks-1/

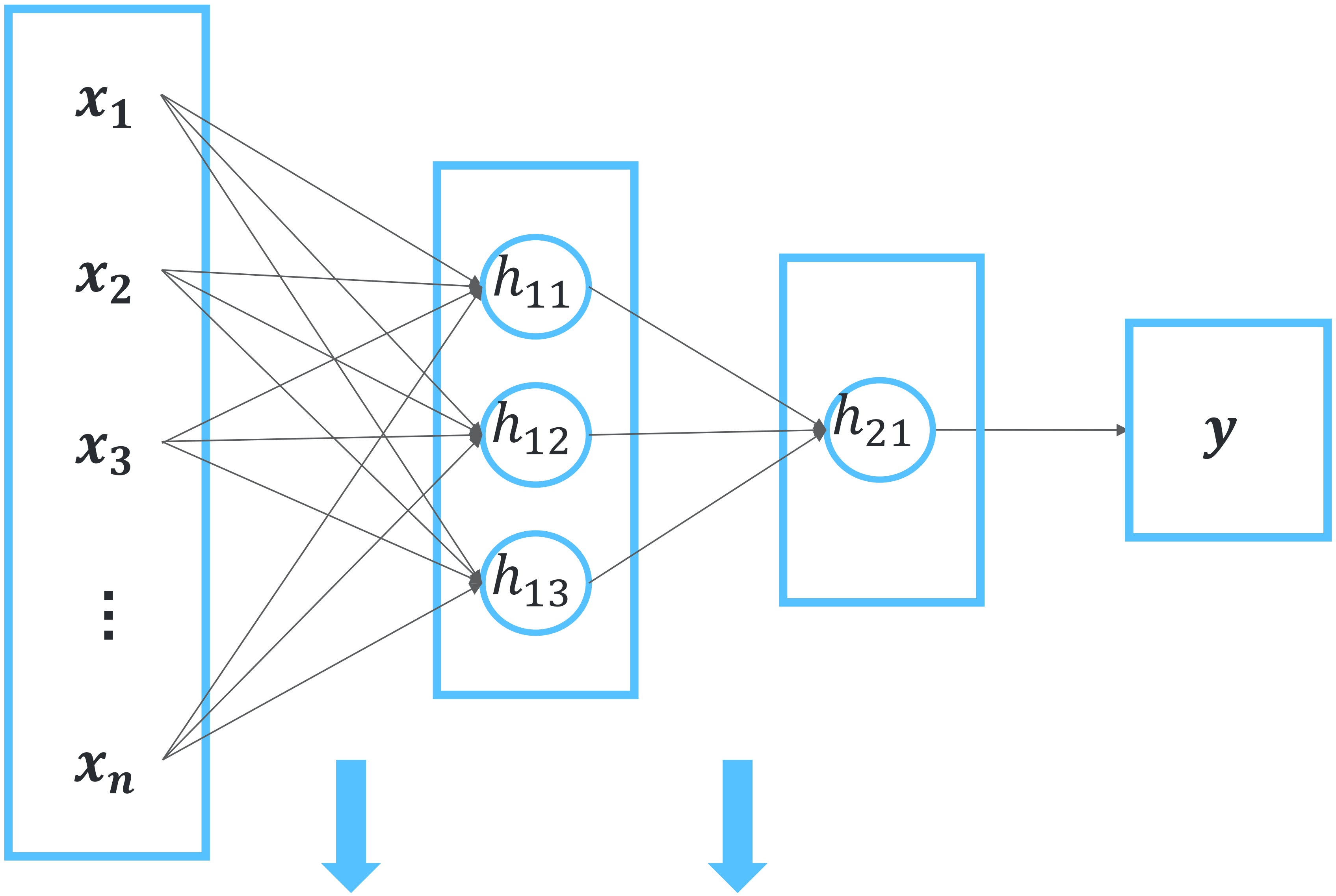
- Neurons filter and detect specific features or patterns (e.g. edge, nose) by receiving a weighted input, transforming it with the activation function and passing it to the outgoing connections.
  - Each neuron performs a dot product with the input and its weights, adds the bias and applies the activation function.
- Artificial neurons mimic brain neurons.

Simplest neural network



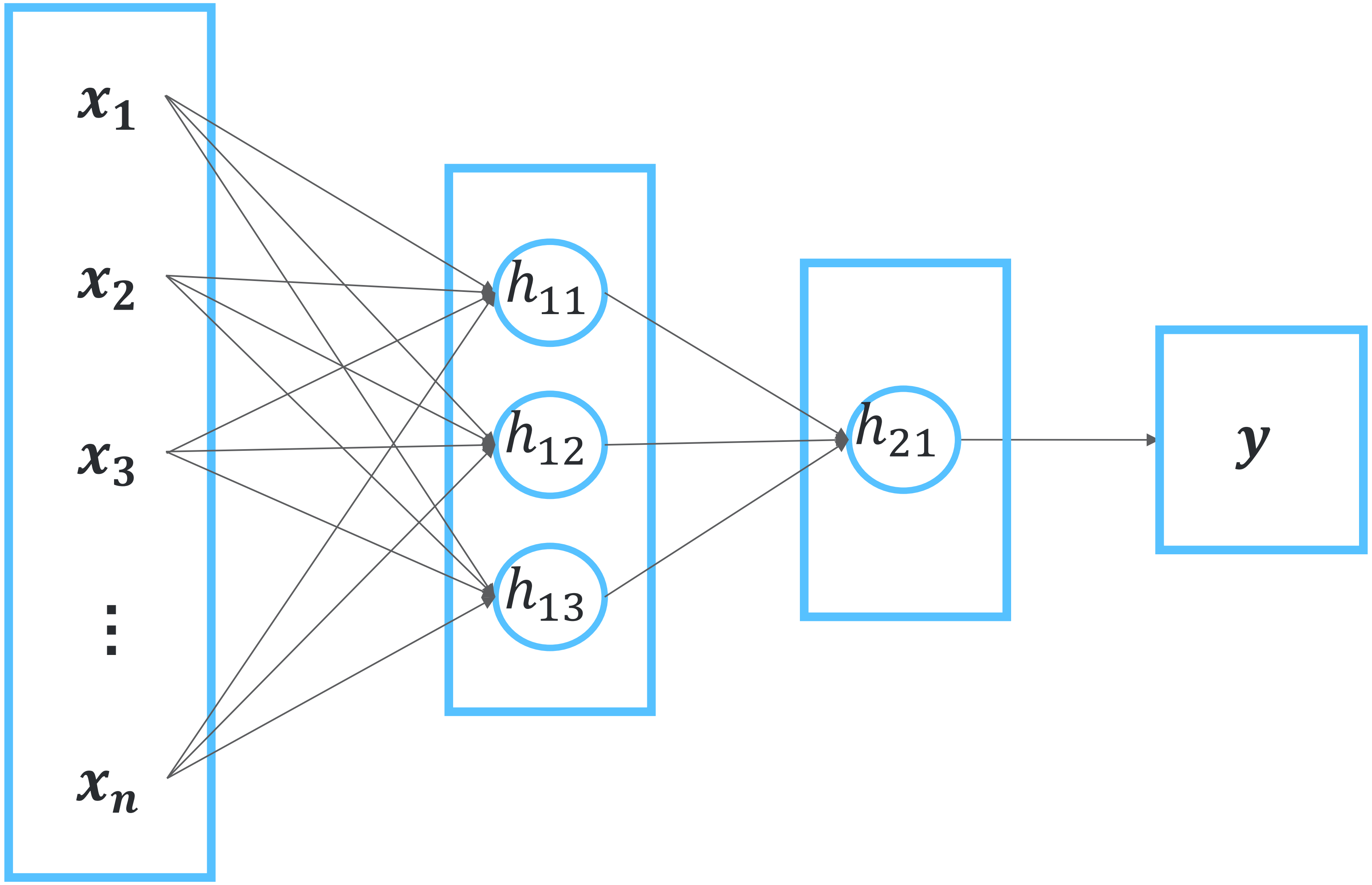
- Weights and biases are the learnable parameters.
- **Weight**: controls the strength of the connection. Weights near zero mean changing this input will not change the output.
- **Bias**: measure of how easy it is to get a node to fire. A node with a large bias will tend produce large positive outputs.

A more realistic example



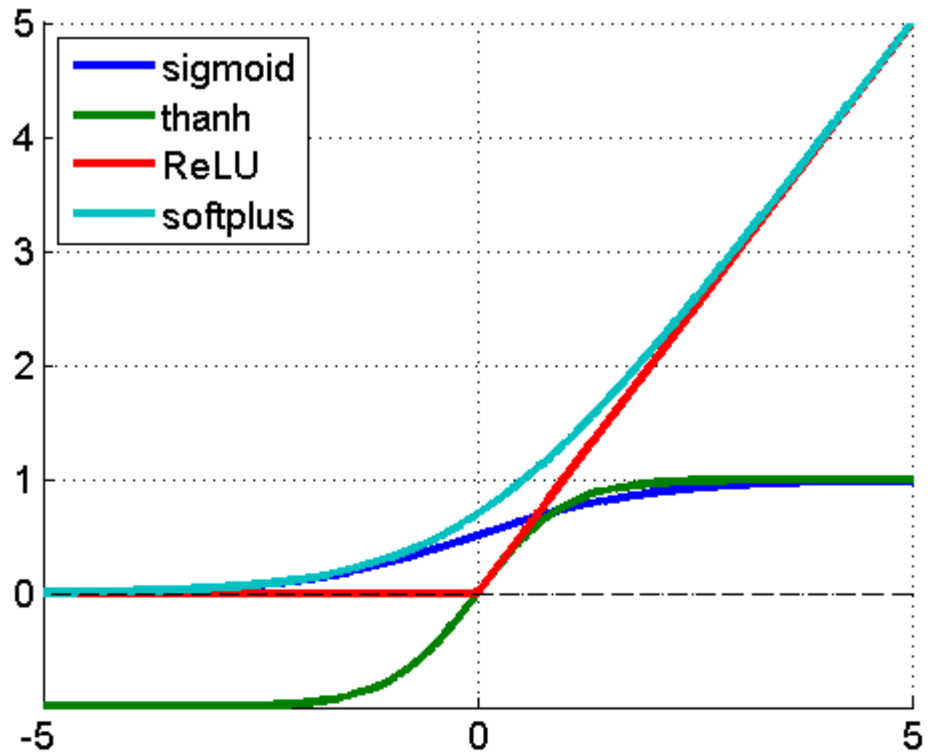
$$W^1 = \begin{bmatrix} w_{11}^1 & w_{12}^1 & w_{13}^1 \\ w_{21}^1 & w_{22}^1 & w_{23}^1 \\ \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot \\ w_{n1}^1 & w_{n2}^1 & w_{n3}^1 \end{bmatrix}, b = \begin{bmatrix} b_1^1 \\ b_2^1 \\ b_3^1 \end{bmatrix} \qquad W^2 = \begin{bmatrix} w_{11}^2 \\ w_{12}^2 \\ w_{13}^2 \end{bmatrix}, b = [b_1^2]$$

A more realistic example



- Each DNN consists of one input, one output and multiple fully-connected hidden layers in between.
- Each layer is represented as a series of neurons that progressively extract higher-level features of the input until the final layer makes a decision about what the input shows.
- The more layers the network has, the more abstract features it can learn.

Commonly used activation functions



https://imiloainf.wordpress.com/2013/11/06/rectifier-nonlinearities/

$$\mathrm{Sigmoid(x)} = \frac{1}{1 + e^{-x}}$$

$$\mathrm{Tanh(x)} = \frac{e^{x} - e^{-x}}{e^{x} + e^{-x}}$$

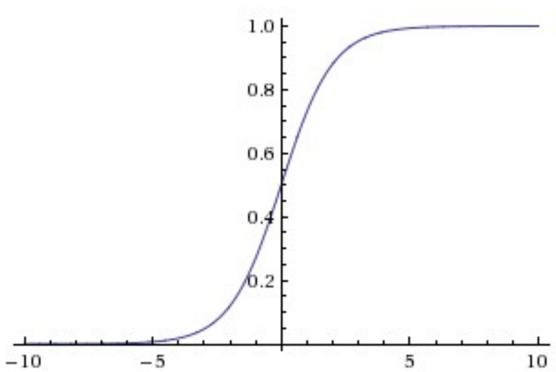
$$\mathrm{ReLU(x)} = \max(0, \mathrm{x})$$

$$\mathrm{Softplus(x)} = \log(1 + e^{x})$$

- Activations functions are non-linear. Non-linearity is needed to learn complex representations of data, otherwise the DNN would be just a linear function (analogous to PCA).
- Most deep networks use ReLU in hidden layers:
  - it trains much faster (constant derivative),
  - improve discriminative performance,
  - prevents the gradient vanishing problem.

Activation functions

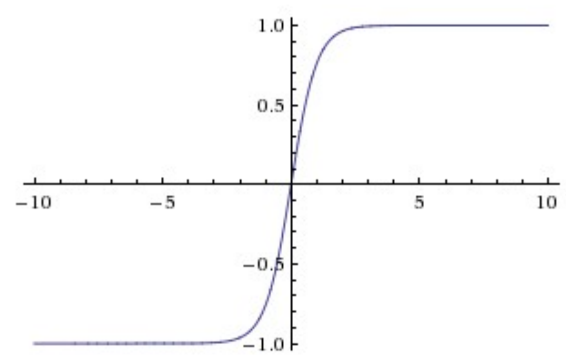
Sigmoid



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

+	Resembles neuronal firing
—	Saturation → zero gradients
—	Sigmoid outputs are not zero-centered

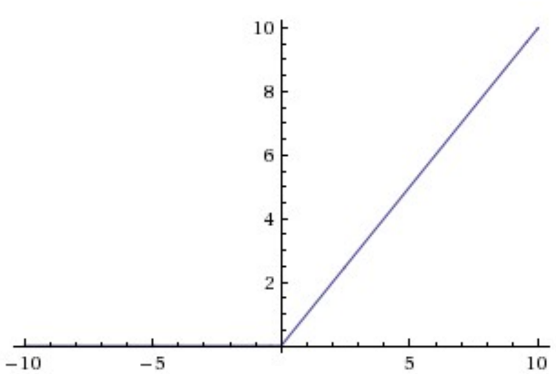
Hyperbolic Tangent (tanh)



$$\tanh(x) = \frac{1 - e^{-2x}}{1 + e^{-2x}} = 2\sigma(2x) - 1$$

+	Outputs are zero-centered
—	Saturation → zero gradients

Rectified Linear Unit



$$\mathrm{ReLU}(x) = \max(0, x)$$

+	Cheap operation
+	Accelerates convergence
—	Large gradients → Dying ReLUs

Additional activation functions

- **Leaky ReLUs**: solves the dying ReLUs issue, results are not consistent
- **Maxout:** generalization of ReLUs, no saturation, no dying, very expensive to compute

Examples of cost functions

- A cost function measures how well a neural network predicts the expected outputs given the training samples.
- A cost function is single valued function:

$$C_i(W, B, S_i, O_i)$$

Weights Biases Sample i Expected output of sample i

- **Cost function requirements:**
  - The cost function C must be able to be written as an average over individual training samples:

$$C(W, B, S, O) = \frac{1}{n}\sum_{i=1}^{n} C_i(W, B, S_i, O_i)$$

  - The cost function C must not depend on any network activation value besides the activation value of the output layer, a_j^L.

- $C(W, B, S, O) \approx 0$ means the DNN is well trained.

Cost functions

- **Mean square error** (aka maximum likelihood and sum squared error):

$$C(W, B, S, O) = \frac{1}{n}\sum_{i=1}^{n}\sum_{j=1}^{m}\left(a_j^L - O_{ij}\right)^2$$

- **Cross-entropy** (aka Bernoulli negative log-likelihood and binary cross-entropy):

$$C(W, B, S, O) = -\frac{1}{n}\sum_{i=1}^{n}\sum_{j=1}^{m}\left[O_{ij}\log a_j^L + \left(1 - O_{ij}\right)\log\left(1 - a_j^L\right)\right]$$

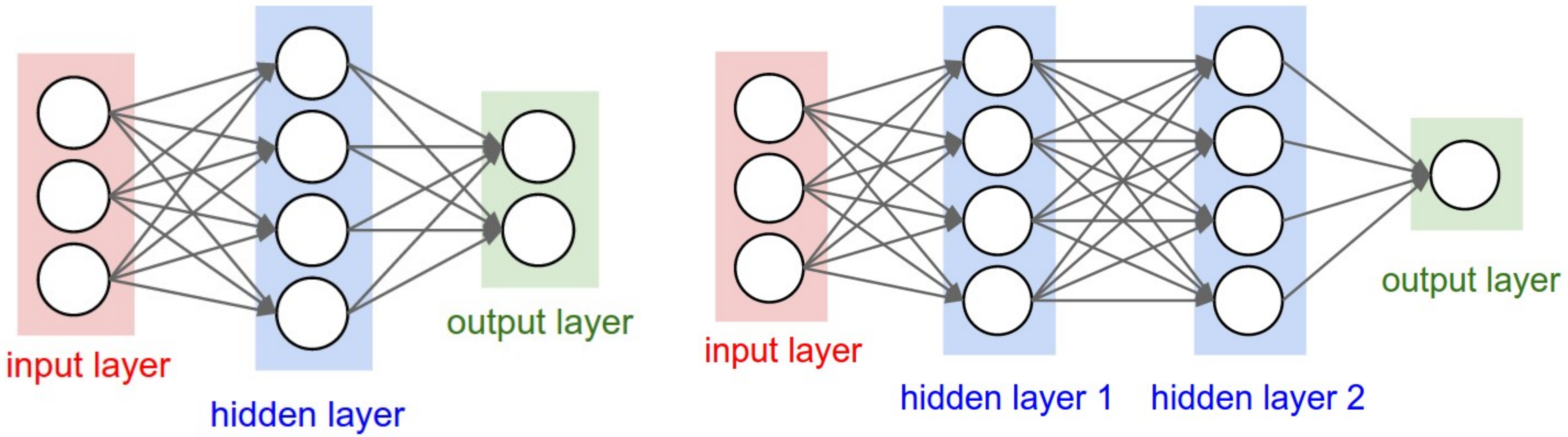
- **Kullback–Leibler divergence** (aka information divergence, information gain and relative entropy):

$$C(W, B, S, O) = \frac{1}{n}\sum_{i=1}^{n}\sum_{j=1}^{m} O_{ij}\log\frac{O_{ij}}{a_j^L}$$

- **Hellinguer distance**

$$C(W, B, S, O) = \frac{1}{n\sqrt{2}}\sum_{i=1}^{n}\sum_{j=1}^{m}\left(\sqrt{a_j^L} - \sqrt{O_{ij}}\right)^2$$

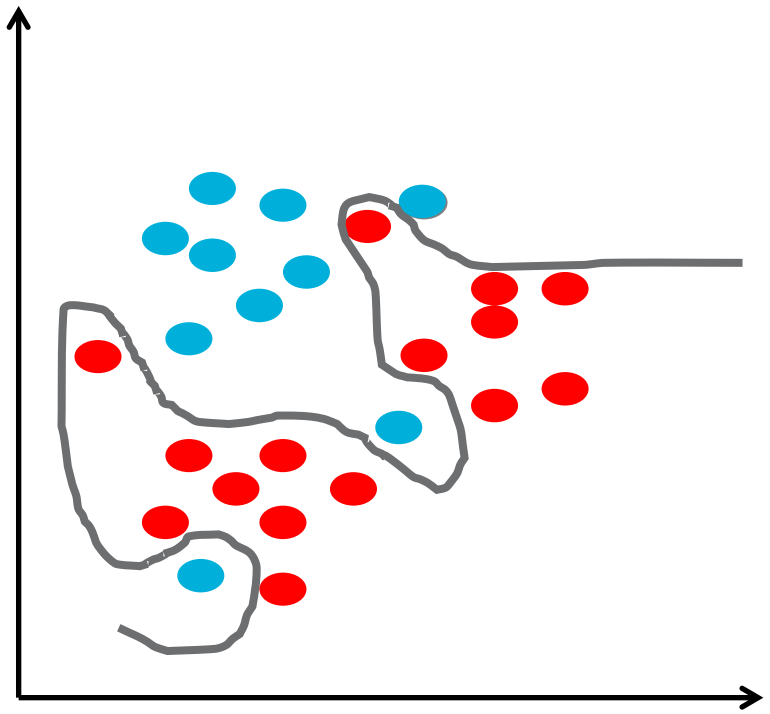
The importance of network architecture

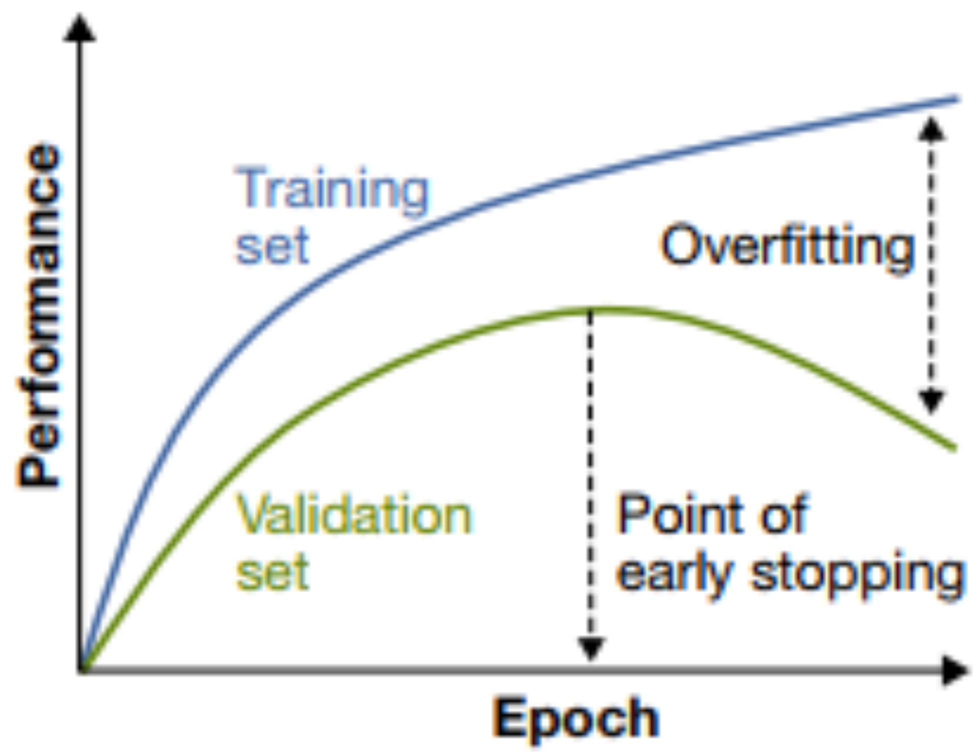


- The capacity of a network can be increased with the number of layers and units per layer.
- As a rule of thumb, going deeper results in more expressive networks, while going wider may lead to overfitting
    - more layers lead to more nested functions and non-linearities that increase the abstraction power, while more units in the same layer usually add features of the same complexity, which might lead to redundancy.

http://cs231n.github.io/neural-networks-1/#bio

Overfitting

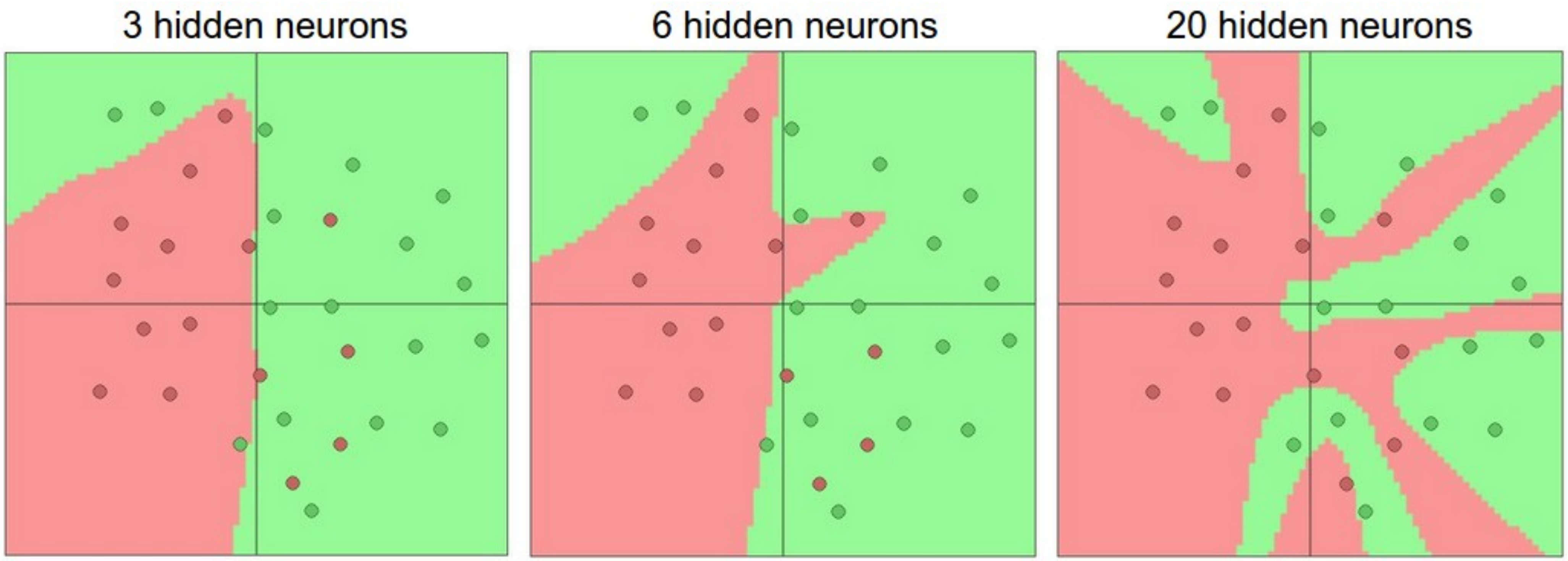




- **Overfitting** occurs when a model with high capacity fits the noise in the data instead of the (assumed) underlying relationship.

Source: https://livingthing.danmackinlay.name/deep_learning.html

Overfitting



- Larger DNNS can represent more complicated functions. Should therefore we go always very deep?
  - No, DNNs with more neurons can express more complicated functions, however, large networks trained on scarce data might lead to overfitting.
- When data is scarce, it is essential to implement methods to prevent overfitting (L2 regularization, dropout, input noise, etc).
- In practice, it is always better to use methods to control overfitting instead of reducing the number of neurons.

http://cs231n.github.io/neural-networks-1/#bio

How to prevent overfitting.

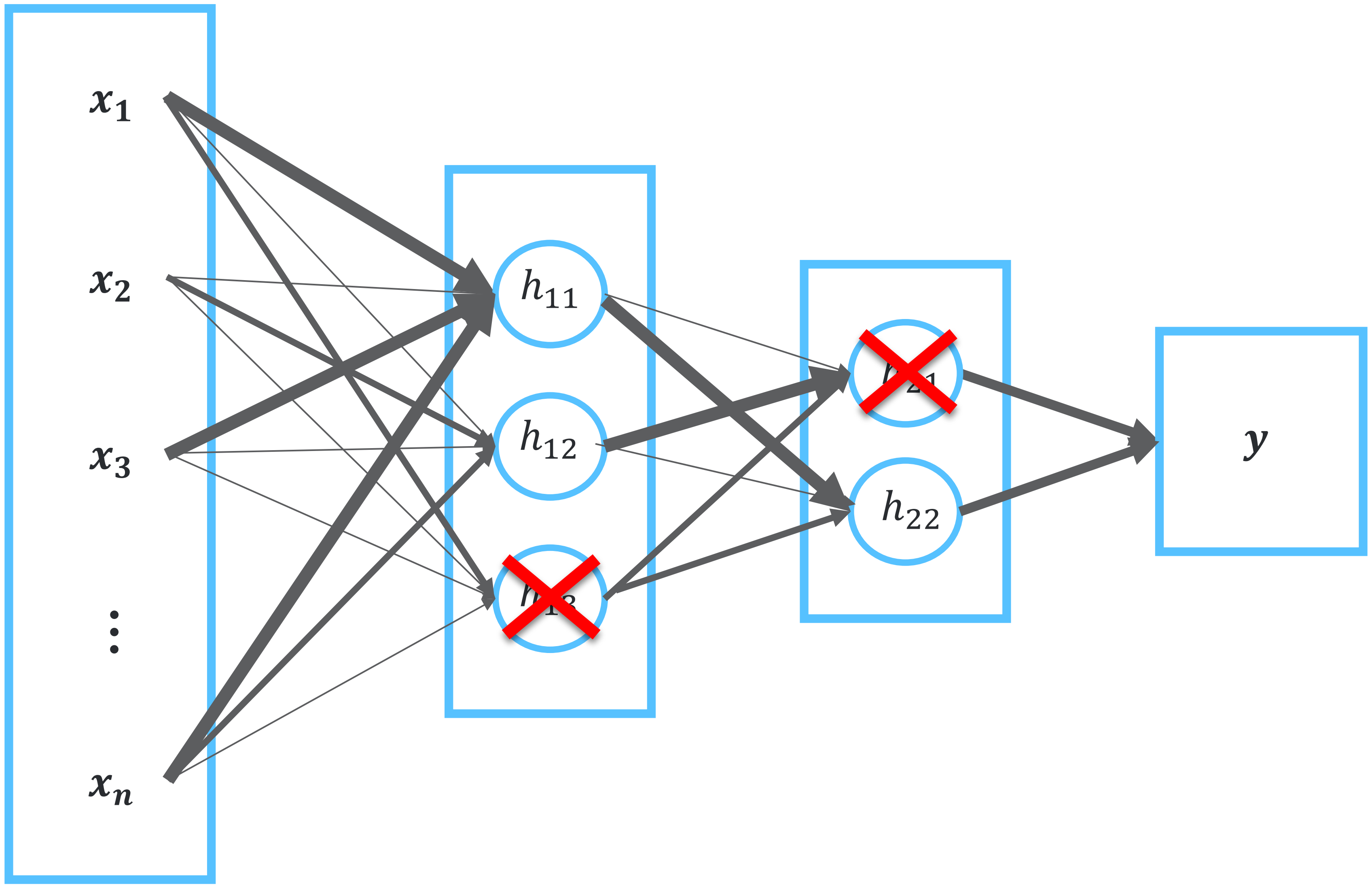
- Early stopping:
  - Stop training as so on as the error on the validation set is higher than it was the last time it was checked.

- Noise addition:
  - Dropout: dropping out units (both hidden and visible) in a neural network.
  - Add noise to data (e.g. denoising autoencoders): we train the network to reconstruct the input from a corrupted version of it.

- Regularization penalties :
  - Create weight penalties L1 and L2.

- Dataset augmentation:
  - Create fake data and add it to the training set.

Dropout



- At each training iteration a dropout layer randomly removes some nodes in the network with probability p along with all of their incoming and outgoing connections.
- Dropout can be applied to hidden or input layer.
- Why it works:
  - Prevents co-adaptation between neurons.
  - Dropout is an example of ensemble technique, where multiple thinned networks with shared parameters are averaged out.

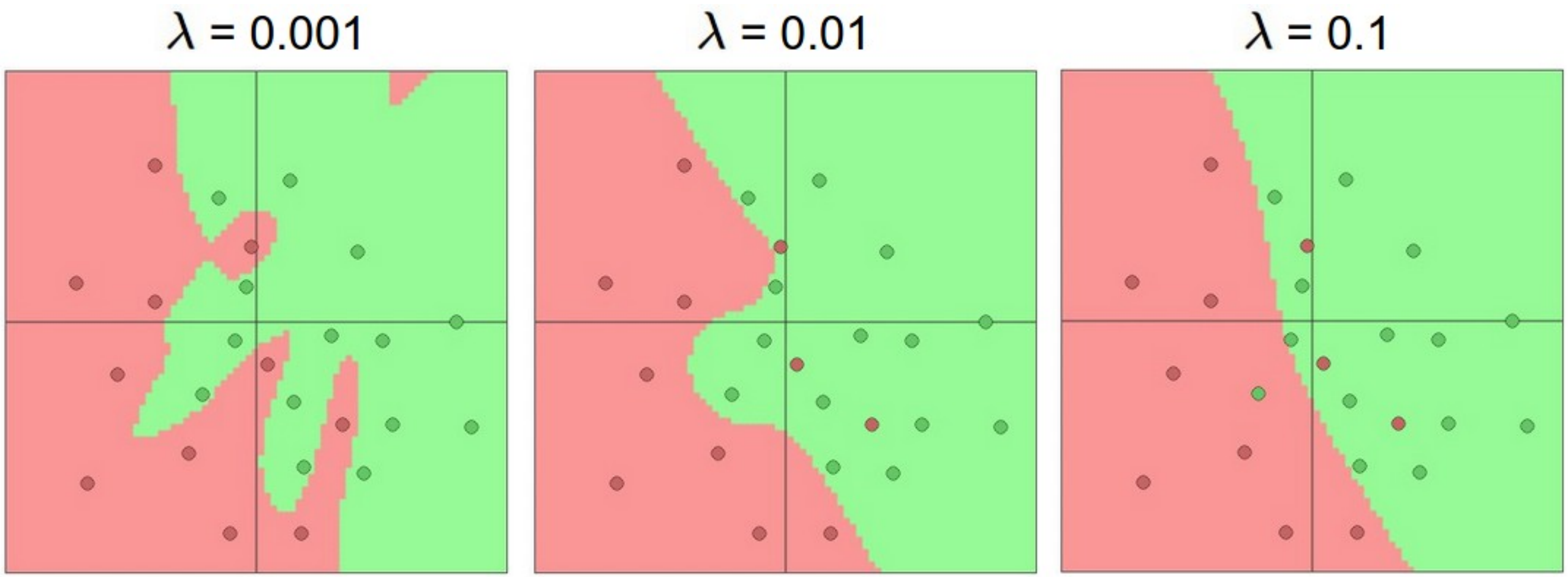
Weight regularization

- L2 norm
  - penalizes the square value of the weight (p = 2).
  - tends to drive all the weights to smaller values.

- L1 norm
  - penalizes the absolute value of the weight (p = 1)
  - tends to drive some weights to exactly zero (introducing sparsity in the model), while allowing some weights to be big.

$$\text{C(W, B, S, O)}_{regularized} = \text{C(W, B, S, O)} + \lambda \sum_{i,j} \left| w_{ij} \right|^{p}$$

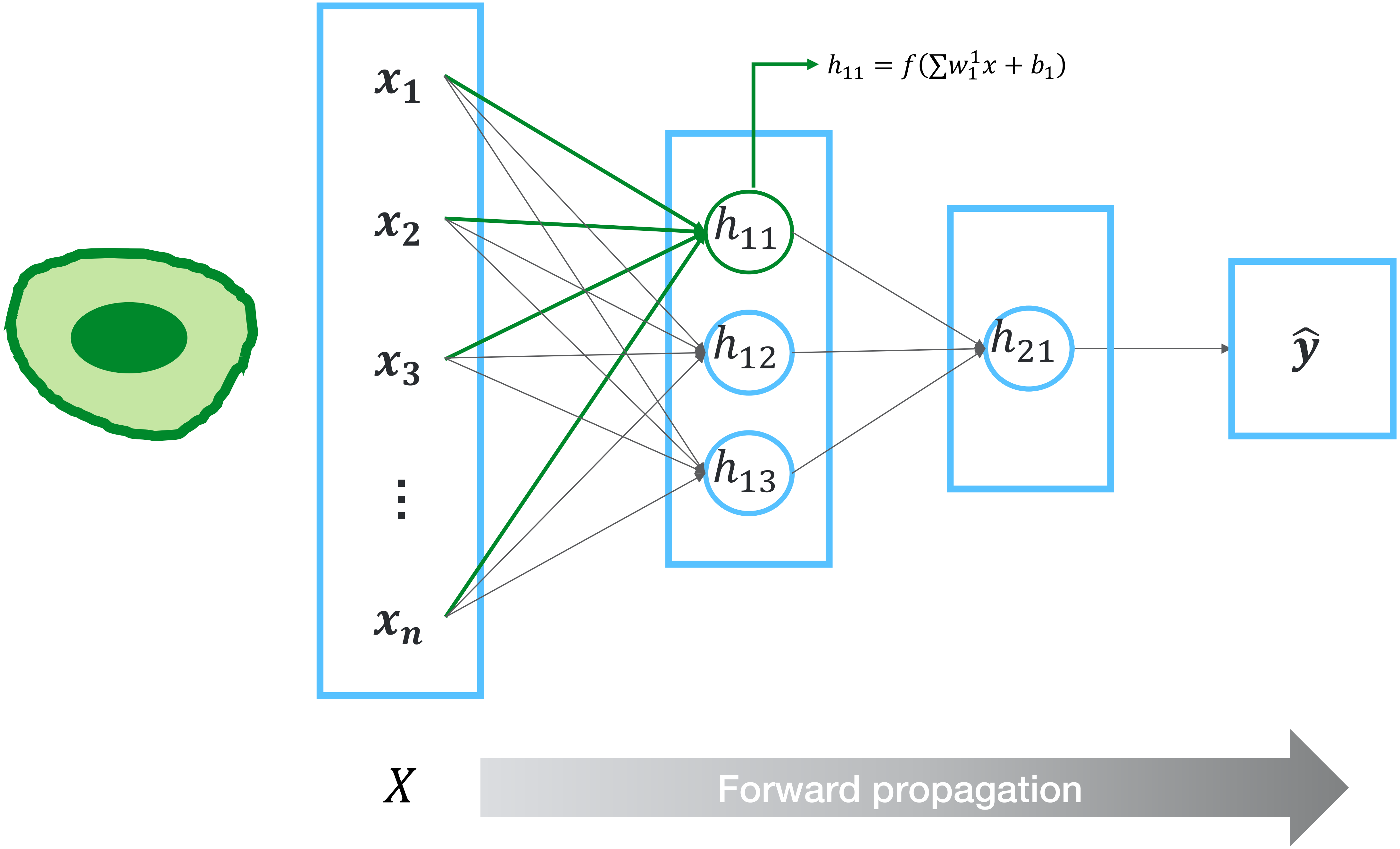
The effect of regularization



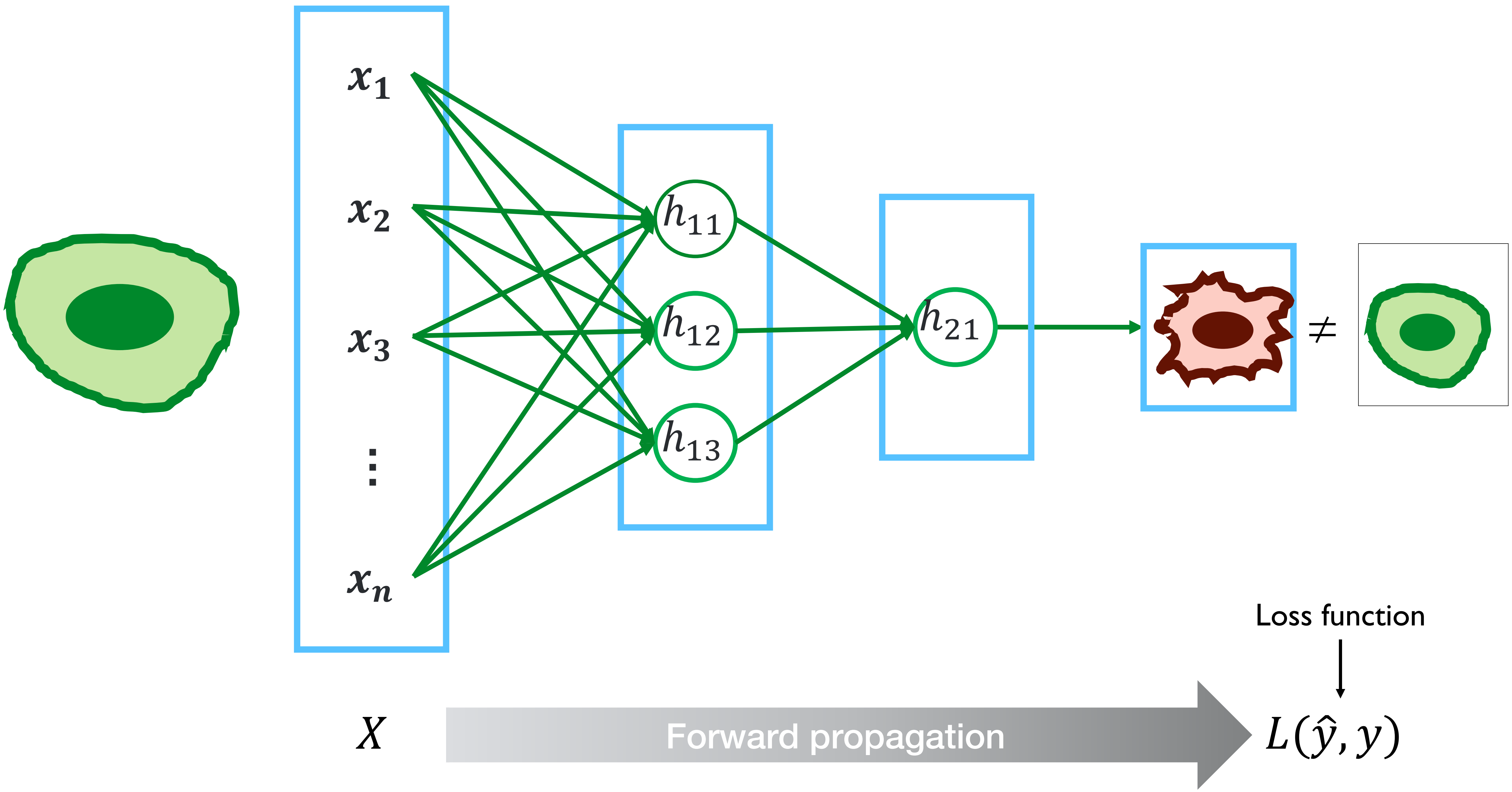
- **The effects of regularization strength**:
  - Each neural network above has 20 hidden neurons, but increasing the regularization strength makes its final decision regions smoother.

http://cs231n.github.io/neural-networks-1/#bio

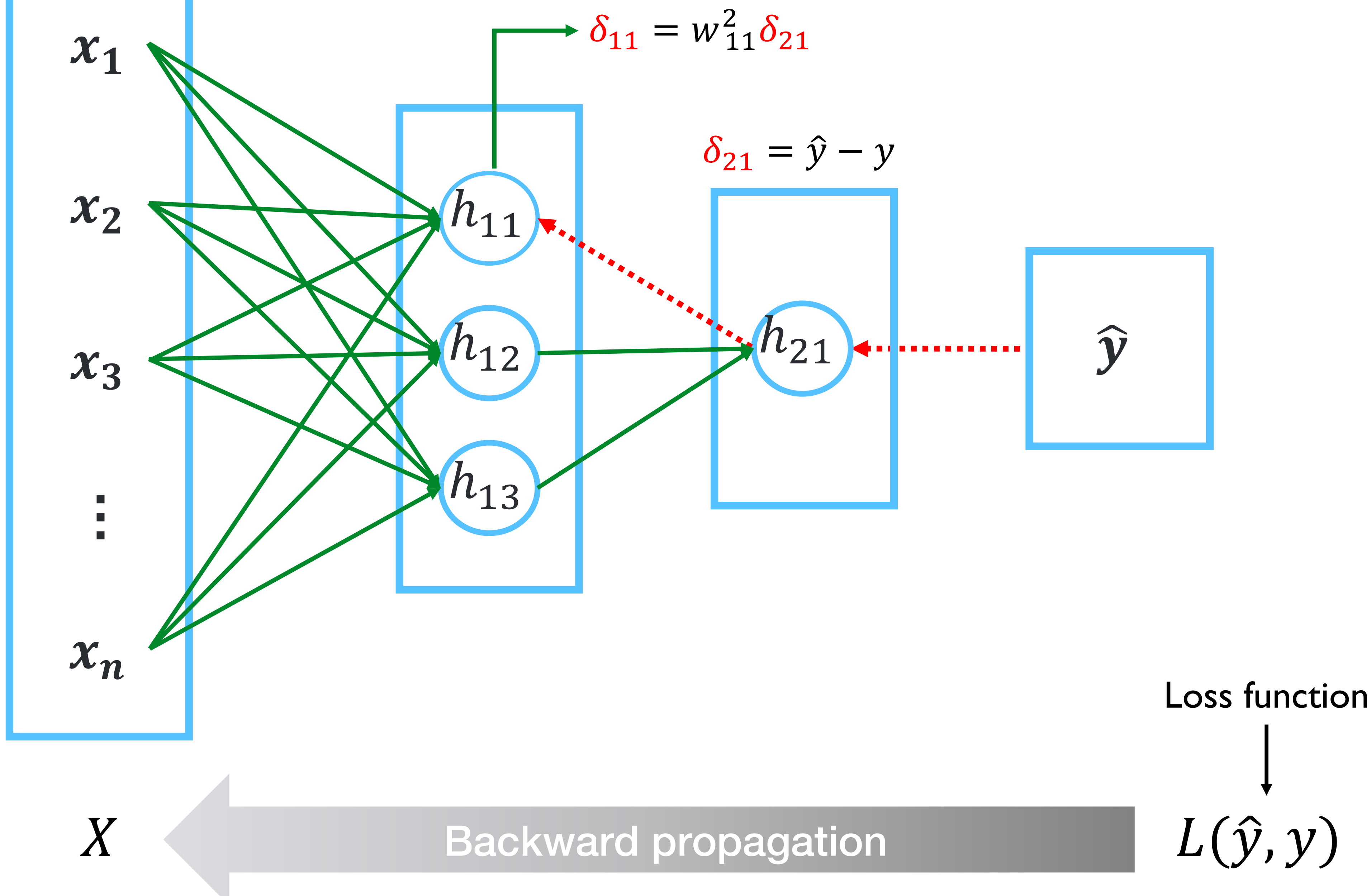
Backpropagation



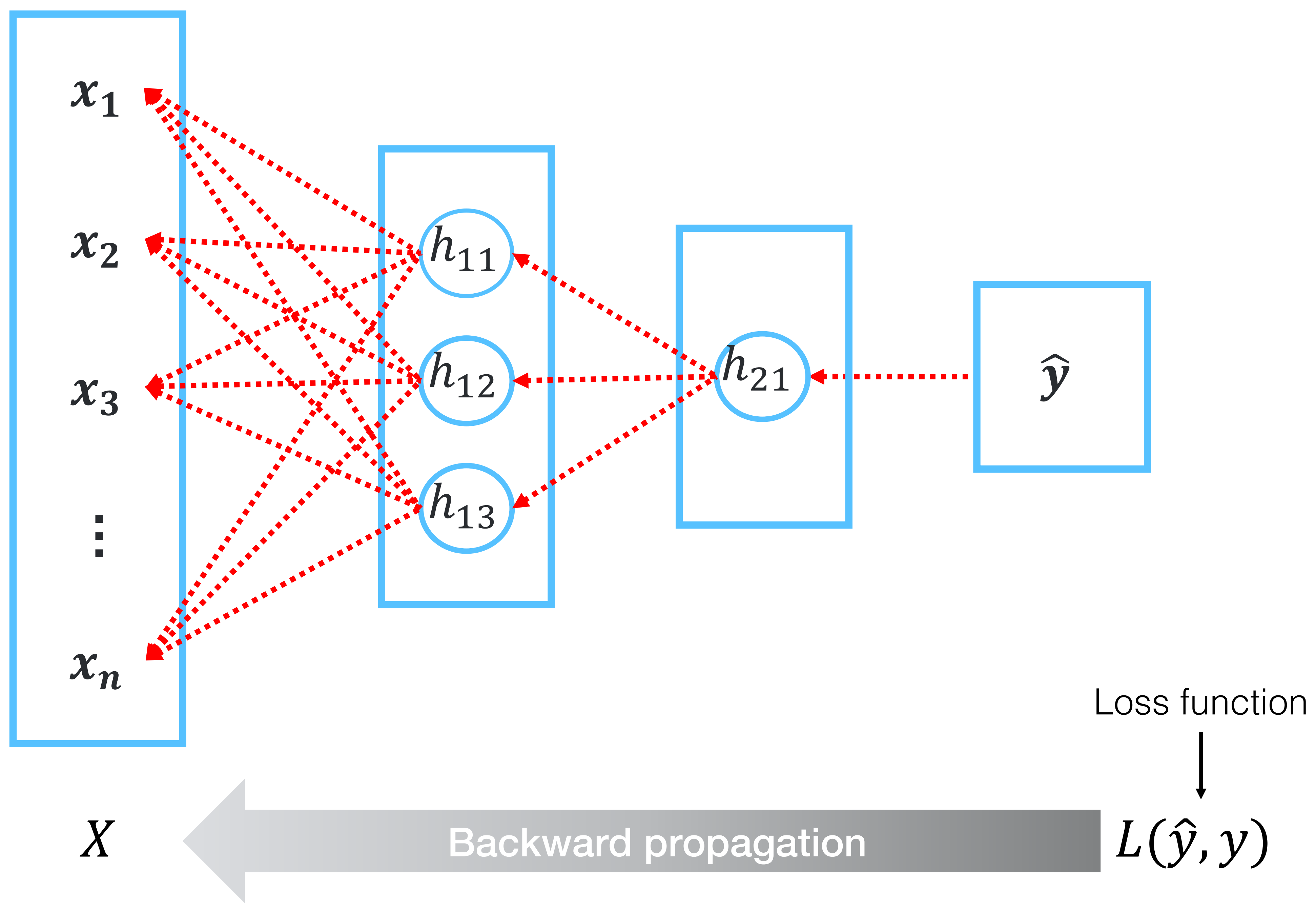
Backpropagation



Backpropagation



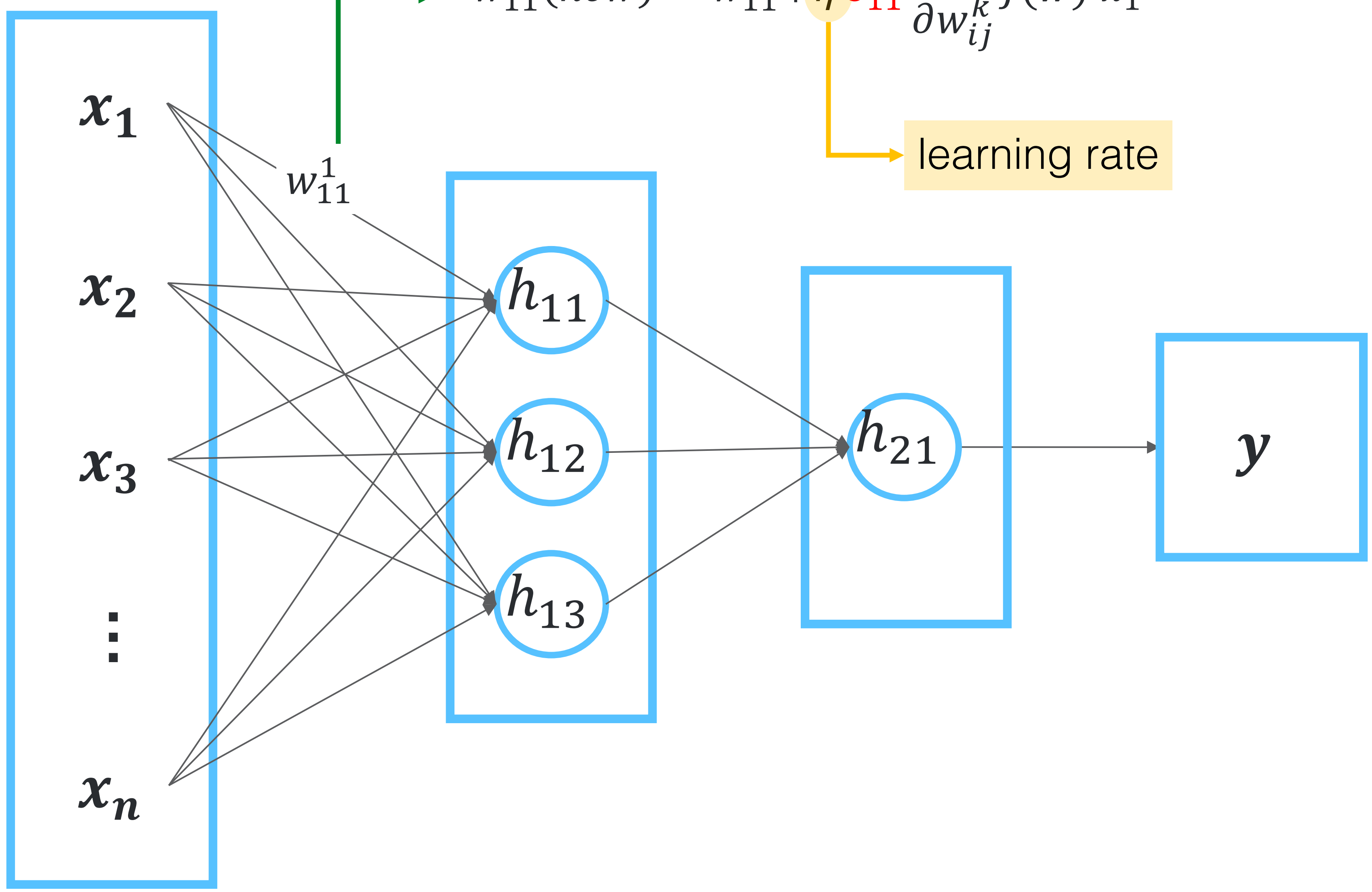
Backpropagation



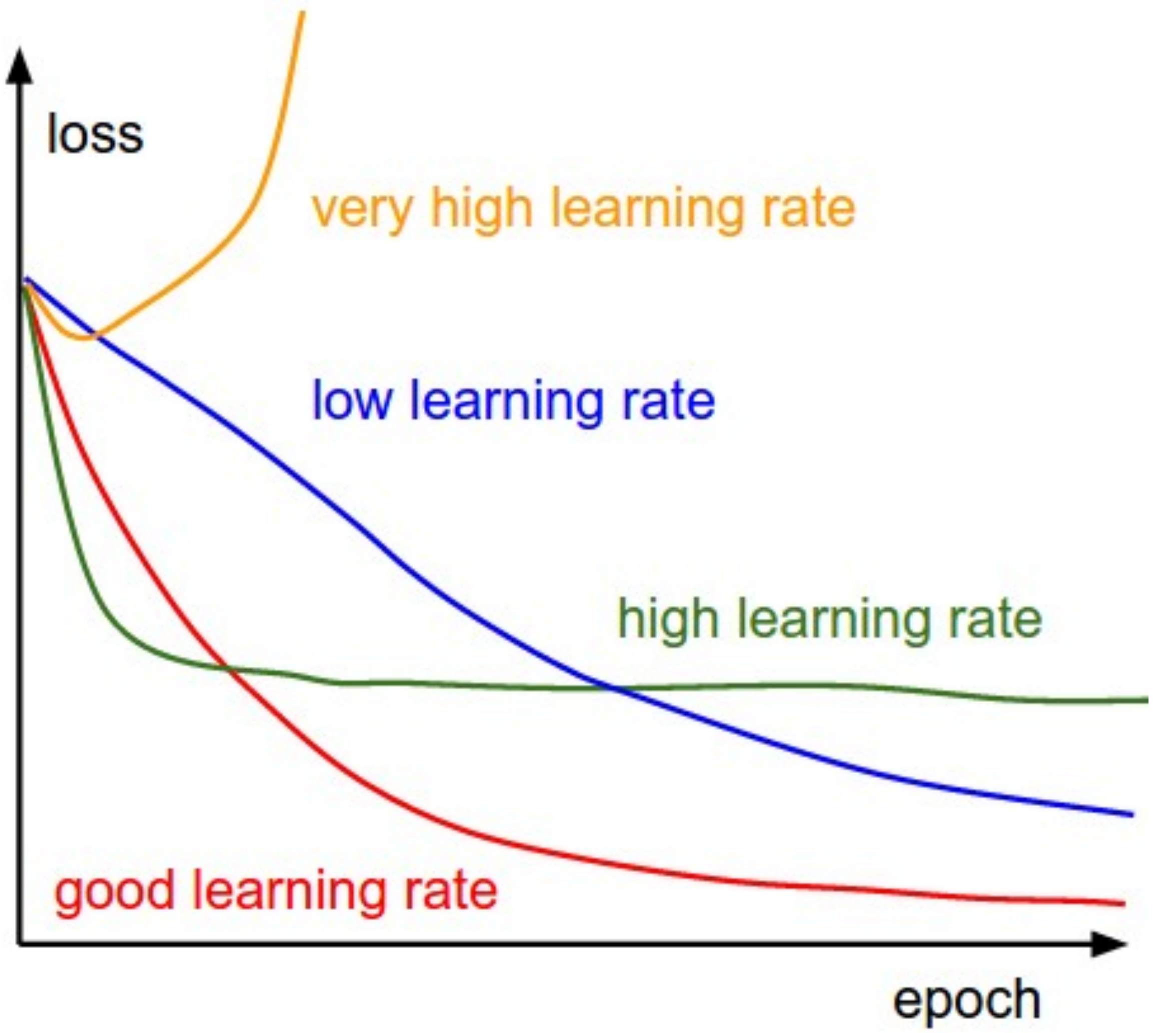
Weight update

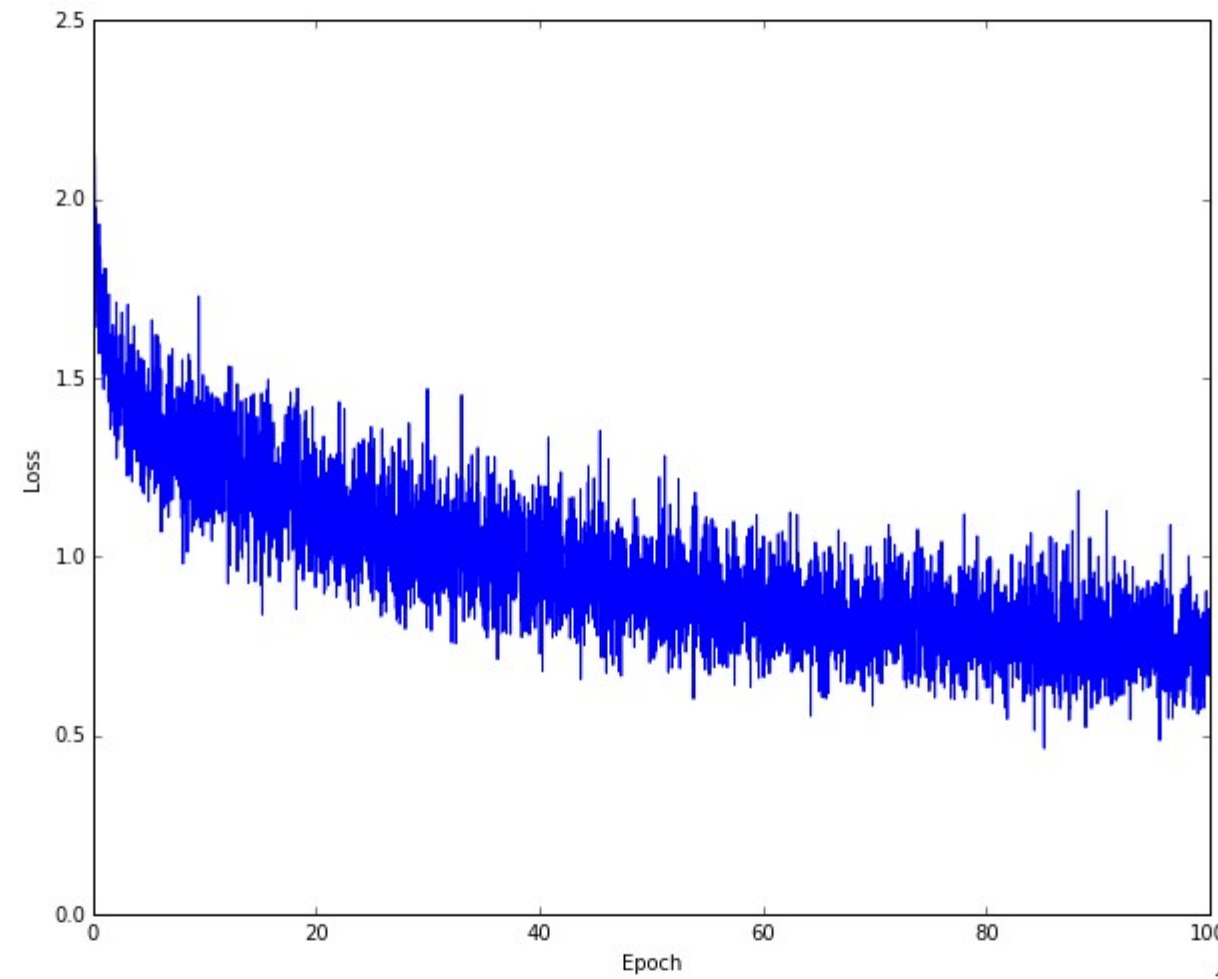
$$w_{11}^{1}(new) = w_{11}^{1} + \eta\, \delta_{11} \frac{\partial}{\partial w_{ij}^{k}} J(\boldsymbol{w})\; x_1$$

learning rate



The effect of different learning rates





- Low learning rates decrease linearly (slow convergence).
- High learning rates initially decrease exponentially, but saturate at higher values: there is too much "energy" in the optimization and the parameters keep bouncing chaotically, unable to settle in a good minimum.

http://cs231n.github.io/neural-networks-3/

Optimizers

Stochastic gradient descent:

1. Choose an initial vector of parameters
2. Repeat until convergence:
- Randomly shuffle training examples
- Move the weight vector towards the direction of steepest descent by learning rate η

Advanced choices:

- **Momentum:** save the update at each iteration, and determine the next update as a linear combination of the gradient and the previous update
- **Adaptive learning rate methods:** RMSprop, Adagrad, Adam

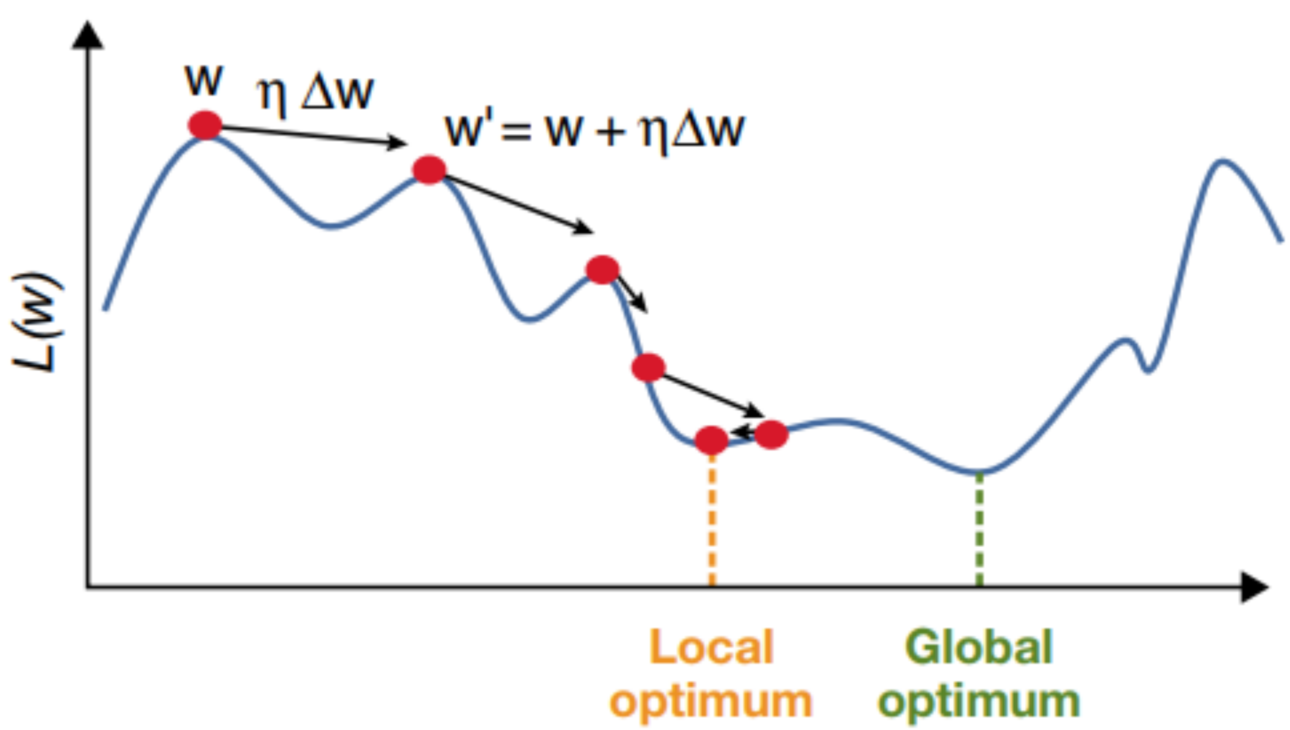
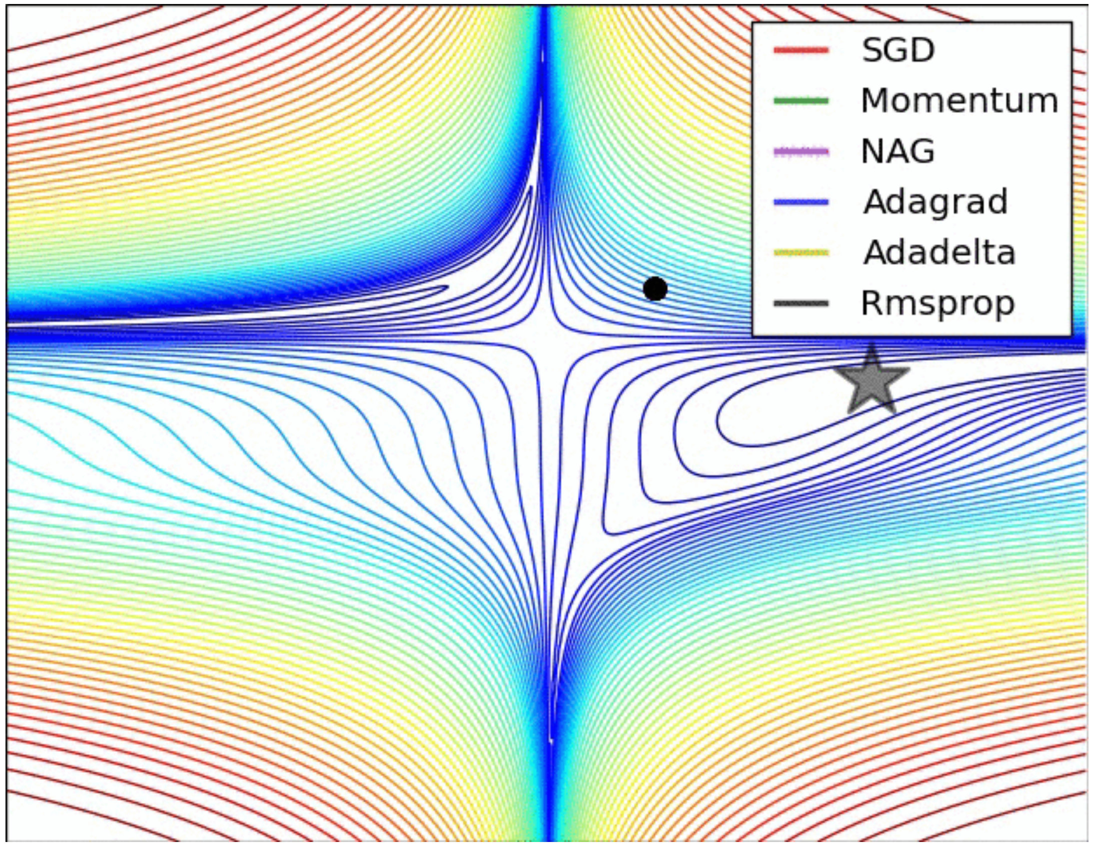
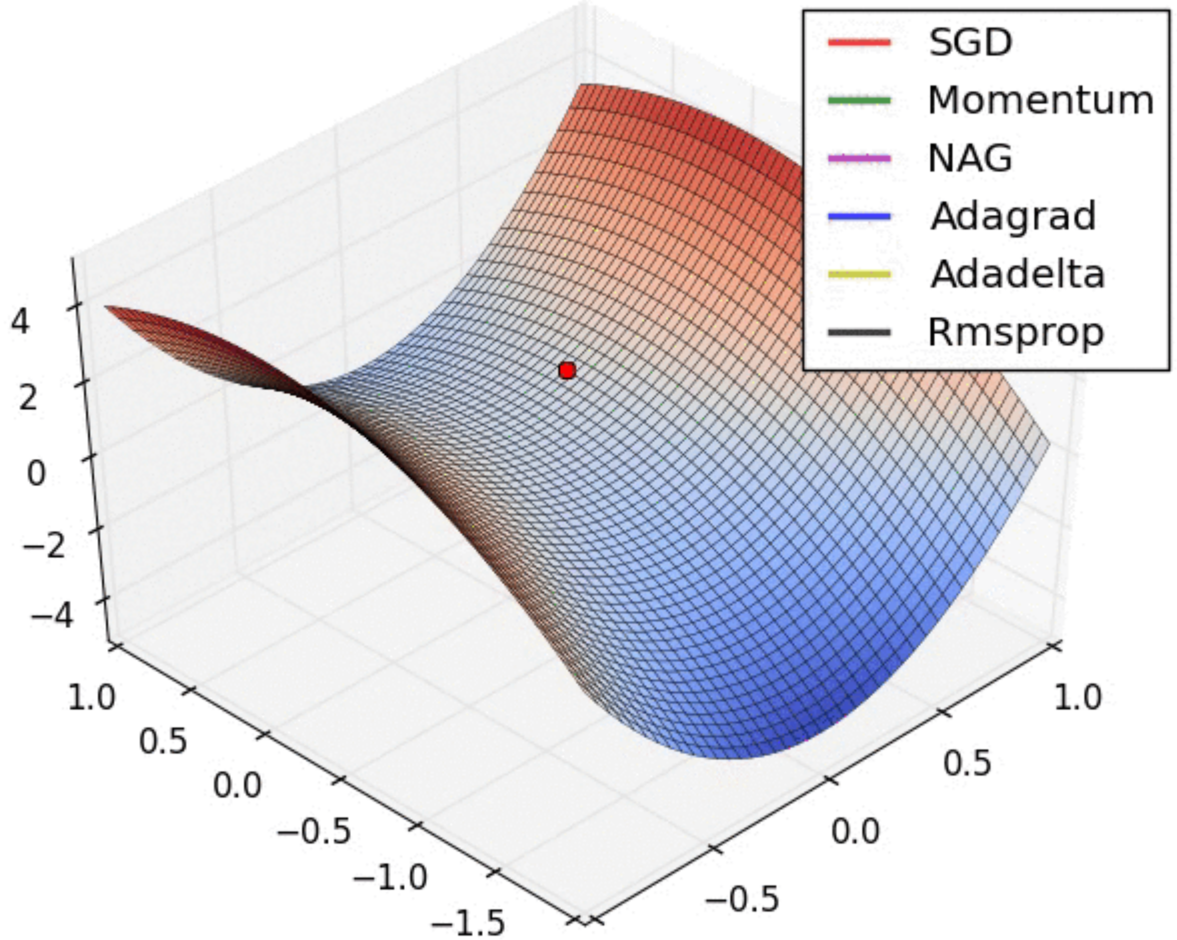


Figure from Angermueller et al., Mol Syst Biol. (2016) 12: 878

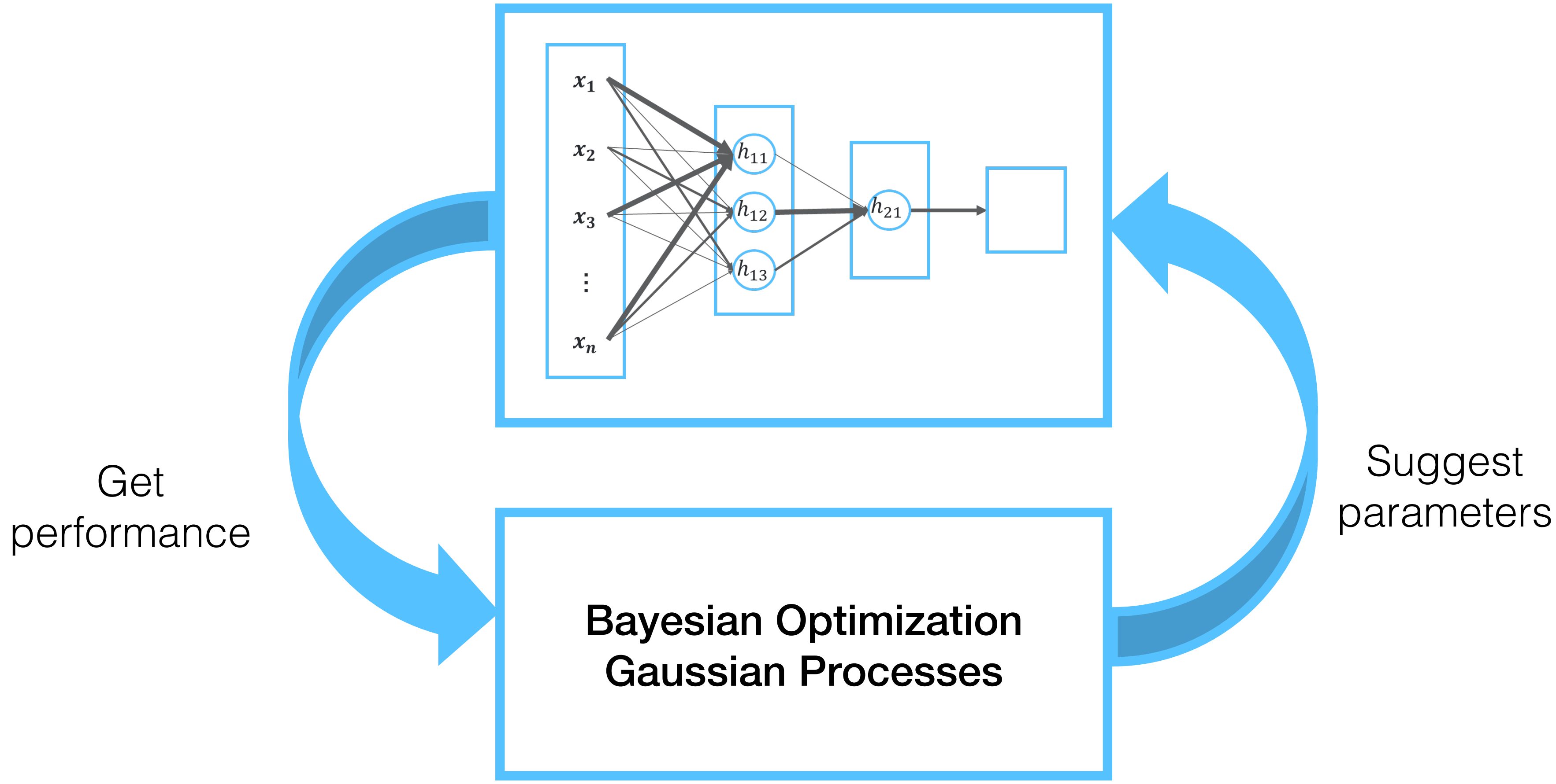
Different optimizers achieve very different convergence rates





Images credit: Alec Radford.

Hyperparameter tuning and reproducibility

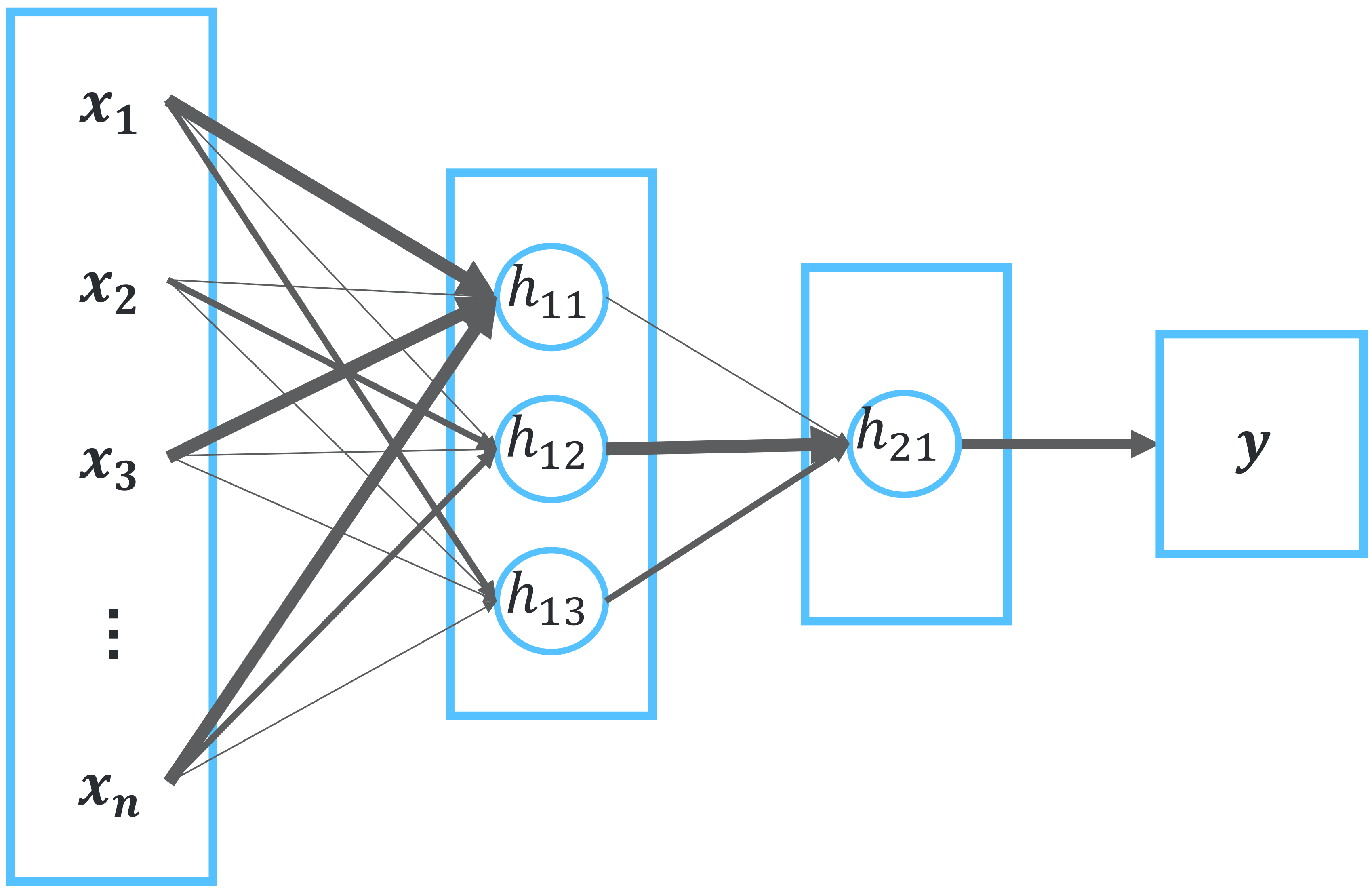


DNNs can involve many hyperparameters. The most common include:

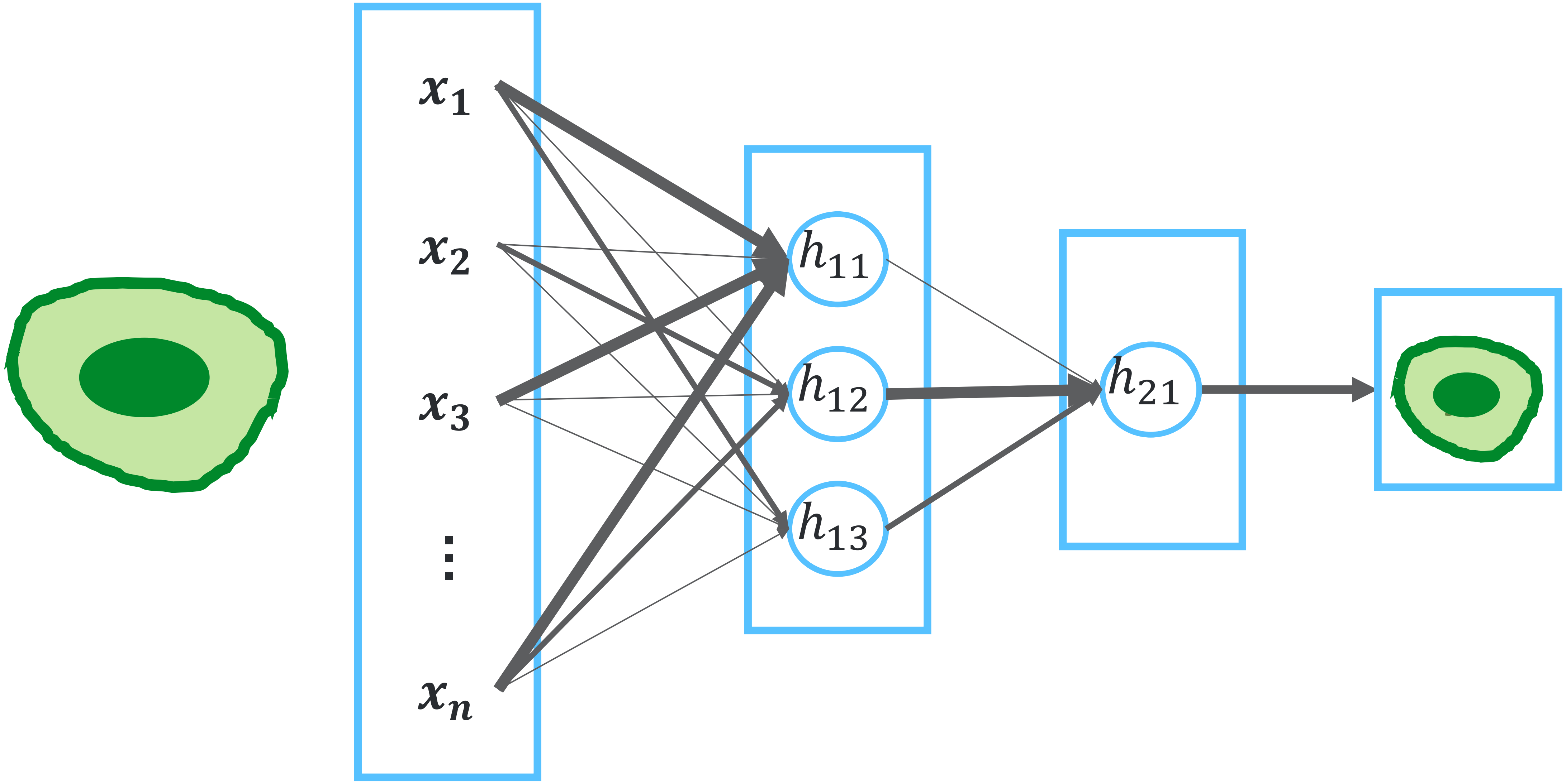
- initial learning rate
- momentum
- regularization strength (L2 penalty, dropout strength, etc)

A grid search exploration of all possible parameter combination might not be the most efficient way of tuning the DNN!

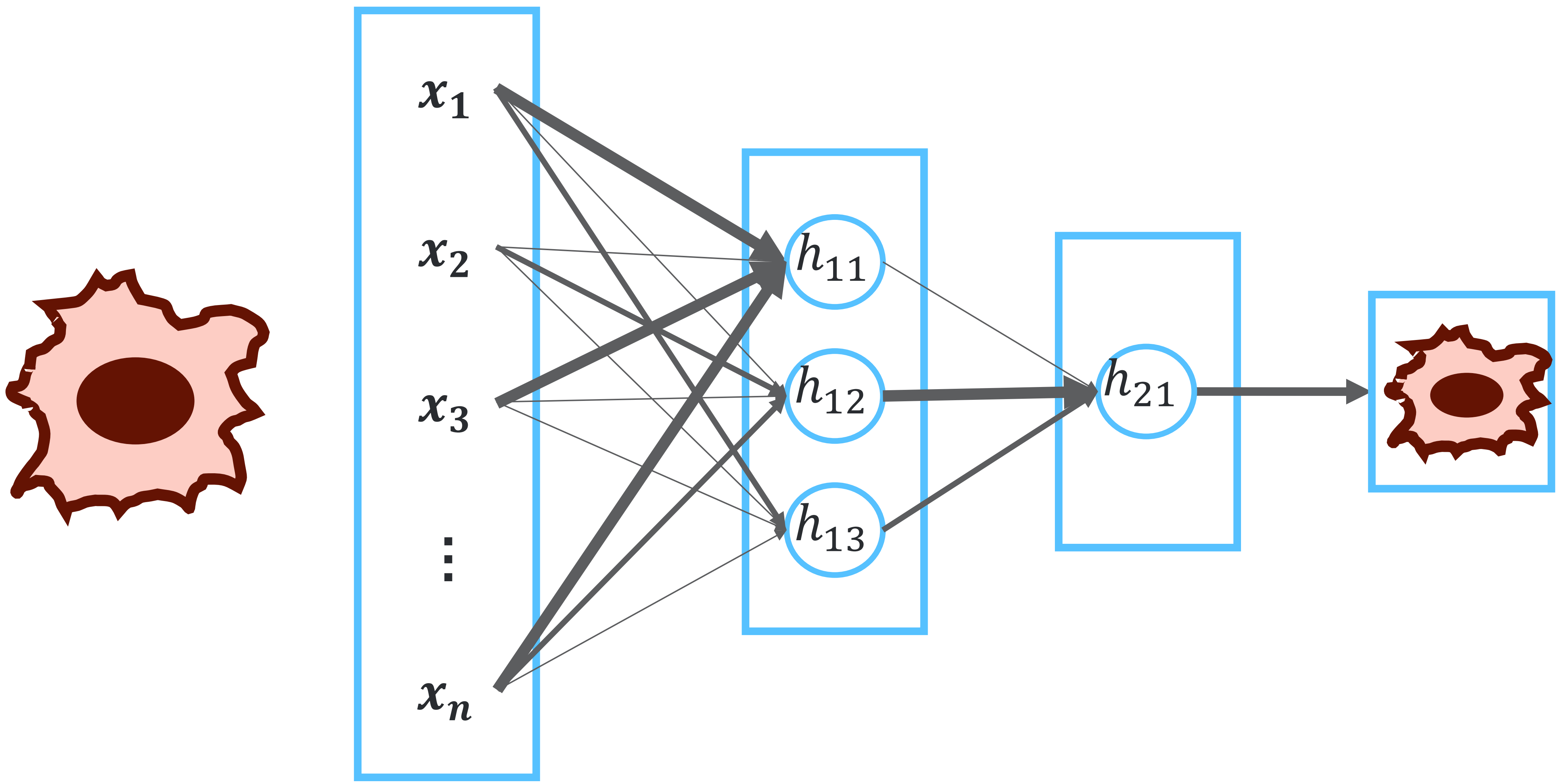
Trained network



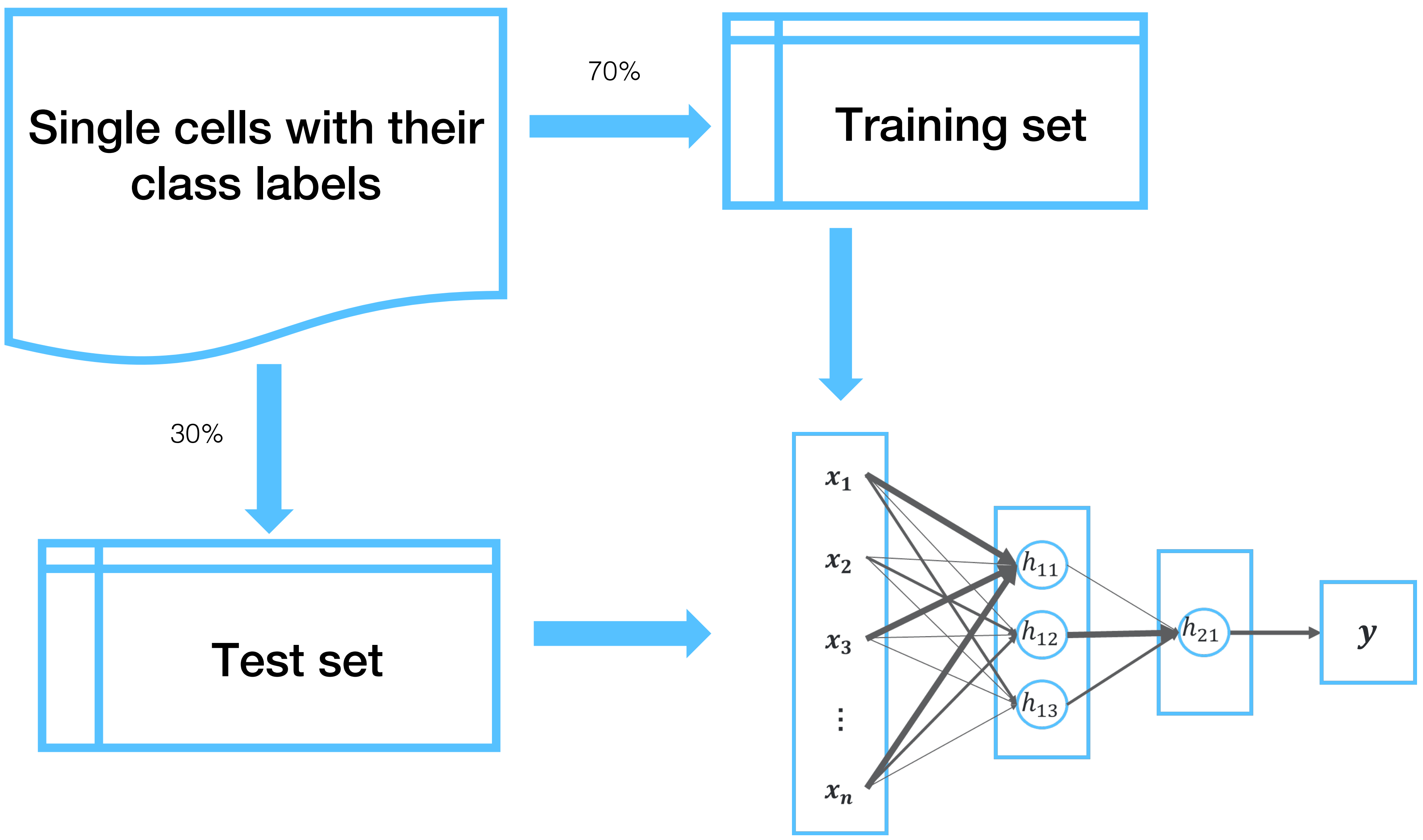
Trained network



Trained network



Training and testing



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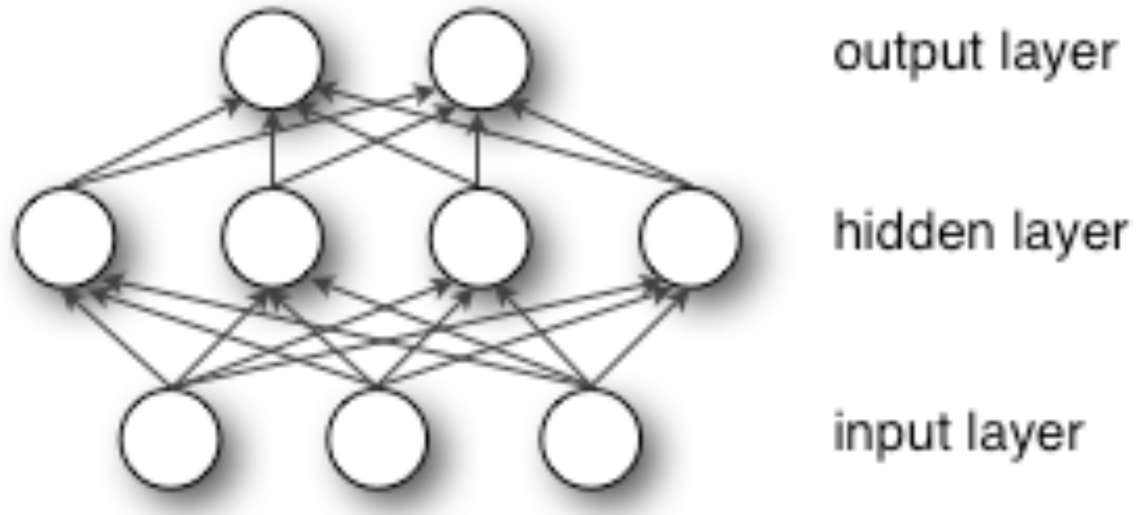
Multi-layer perceptron (MLP)



- An MLP is a DNN that:
  - Consists at least of three layers of nodes (i.e. there is at least one hidden layer).
  - It is always feedforward (no loops are allowed).
  - Consecutive layers are fully connected.

- A single hidden layer is sufficient to make MLPs **a universal approximator**. However usually there are substantial benefits to using more than one hidden layer.

http://deeplearning.net/tutorial/mlp.html

Deep learning in genomics

Article | OPEN

Deep Learning in Label-free Cell Classification

Claire Lifan Chen, Ata Mahjoubfar, Li-Chia Tai, Ian K. Blaby, Allen Huang, Kayvan Reza Niazi & Bahram Jalali

NATURE METHODS | BRIEF COMMUNICATION

Predicting effects of noncoding variants with deep learning–based sequence model

Jian Zhou & Olga G Troyanskaya

RESEARCH ARTICLE

The human splicing code reveals new insights into the genetic determinants of disease

Hui Y. Xiong[1,2,3,*], Babak Alipanahi[1,2,3,*], Leo J. Lee[1,2,3,*], Hannes Bretschneider[1,3,4], Daniele Merico[5,6,7], Ryan K. C. Yuen[5,6,7], Yimin Hua[8], Serge Gueroussov[2,7], Hamed S. Najafabadi[1,2,3], Timothy R. Hughes[2,3,7], Quaid Morris[1,2,3,7], Yoseph Barash[1,2,9], Adrian R. Krainer[8], Nebojsa Jojic[10], Stephen W. Scherer[3,5,6,7], Benjamin J. Blencowe[2,5,7], Brendan J. Frey[1,2,3,4,5,7,10,†]

A deep learning framework for modeling structural features of RNA-binding protein targets

Sai Zhang[1], Jingtian Zhou[2,†], Hailin Hu[2,†], Haipeng Gong[3,4], Ligong Chen[2], Chao Cheng[5,*] and Jianyang Zeng[1,4,*]

Gene expression inference with deep learning

Yifei Chen[1,4,†], Yi Li[1,†], Rajiv Narayan[2], Aravind Subramanian[2] and Xiaohui Xie[1,3,*]

PDF version

Deep biomarkers of human aging: Application of deep neural networks to biomarker development

Evgeny Putin [1,2], Polina Mamoshina[1,3], Alexander Aliper[1], Mikhail Korzinkin[1], Alexey Moskalev[1,4], Alexey Kolosov[5], Alexander Ostrovskiy[5], Charles Cantor[6], Jan Vijg[7], and Alex Zhavoronkov[1,3]

Basset: Learning the regulatory code of the accessible genome with deep convolutional neural networks

David R Kelley[1], Jasper Snoek and John Rinn

Deep learning of the tissue-regulated splicing code

Michael K. K. Leung[1,2], Hui Yuan Xiong[1,2], Leo J. Lee[1,2] and Brendan J. Frey[1,2,3,*]

Deep learning frameworks

High-level frameworks make deep learning easier

Deep Learning Frameworks:

- Keras
- Lasagne
- Caffe

Graph compilers:

- Theano
- Tensor Flow

Linear Algebra Libraries:

- PyCuda (python)
- CUDAMat (python)
- JCuda (java)

Thank you!

CompSysBio team @ IBM Research