Machine Learning in Bioinformatics

ANN Architectures

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Outline

- Part of this lecture:
  - Embeddings
  - Auto-encoders
  - Convolutions on images and graphs
  - Attention mechanism
- Other important architectures not covered here:
  - Generative adversarial networks (GANs)
  - Deep tensor factorization
  - Recurrent neural networks (LSTM/GRU)

Embeddings

One-hot encoding

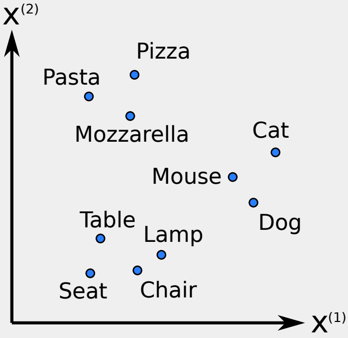
- Assume we want to work with categorical data, e.g.
  - DNA or protein sequences
  - Text (vectors of words)
- Traditionally, we would use one-hot encoding, which use a dimension for each category
- For example, a DNA sequence ACGTTA could be represented as

$$\begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 1 \\ 1 & 0 & 0 & 0 \end{bmatrix}$$

One-hot encoding

- One-hot encodings have several problems
- For data with many categories, we obtain very high-dimensional feature vectors, e.g.
  - Protein sequences would already require 20 dimensions
  - Text would require one dimension per word type
- One-hot encodings should be used for purely categorical data, where we have no similarity between categories
- However, for most data we have certain similarities, e.g.
  - Amino acid replacements have different effects, which suggests that some amino acids are more similar in function than others

Embeddings



- We assign each category *k* a feature vector $x_k \in \mathbb{R}^p$
- The representations x_k are randomly initialized and optimized during training
- After training we often observe that similar categories cluster together

Convolutional Neural Networks for Images

Image pattern detection

Conway's Game of Life - glider gun:

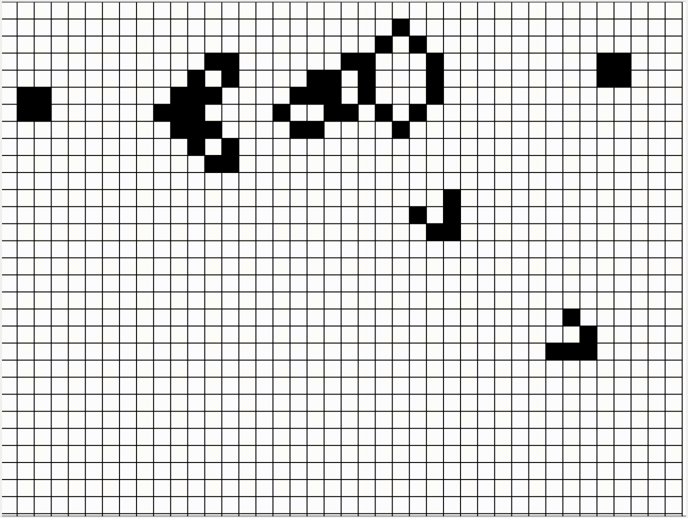
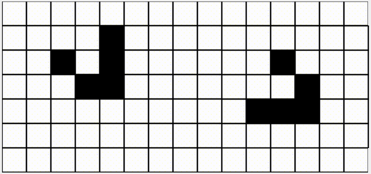


Image pattern detection

Glider gun detector:



Glider pattern:

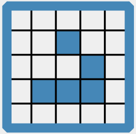


Image pattern detection

Glider gun detector:

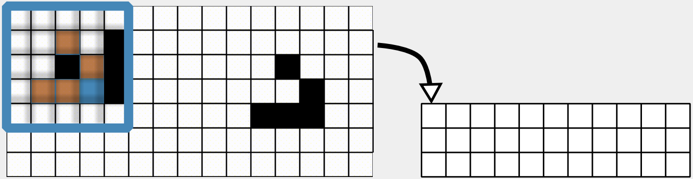
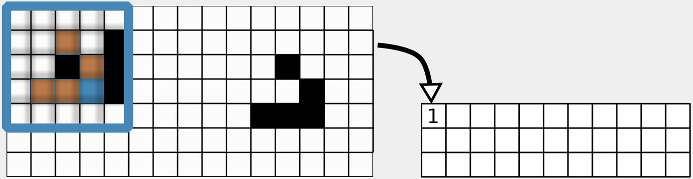
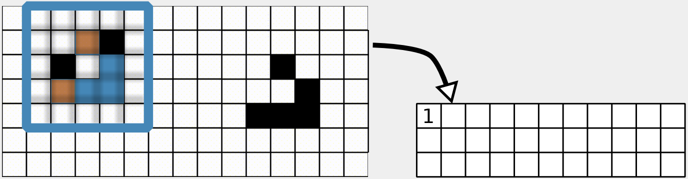


Image pattern detection

Glider gun detector:



Glider gun detector:



Glider gun detector:

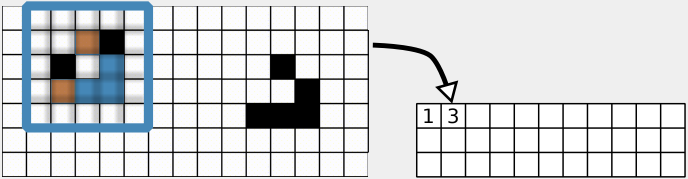
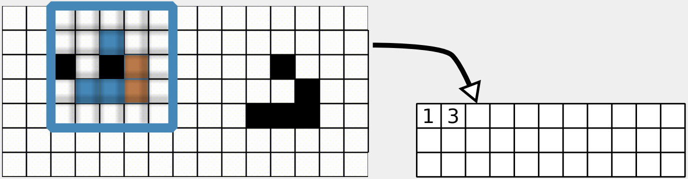


Image pattern detection

Glider gun detector:



Glider gun detector:

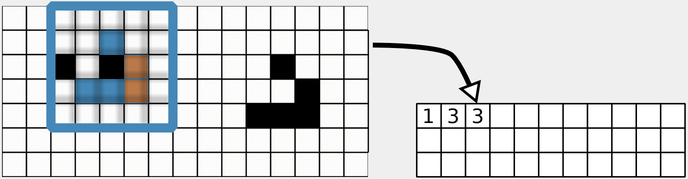
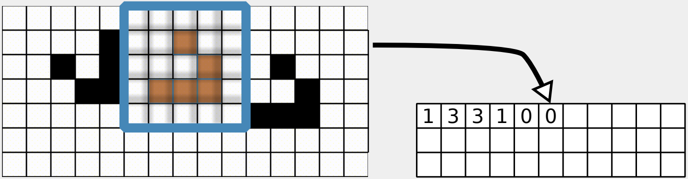


Image pattern detection

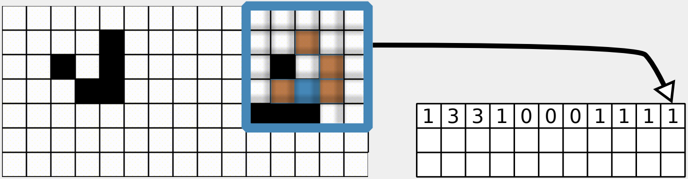
Glider gun detector:



1	3	3	1	0	0					

Image pattern detection

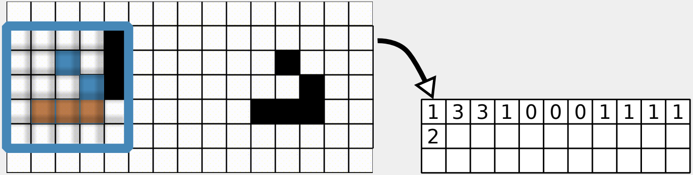
Glider gun detector:



1	3	3	1	0	0	0	1	1	1	1

Image pattern detection

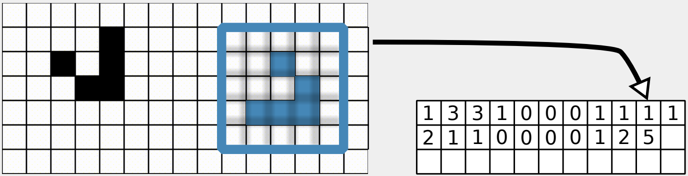
Glider gun detector:



1	3	3	1	0	0	0	1	1	1	1
2										

Image pattern detection

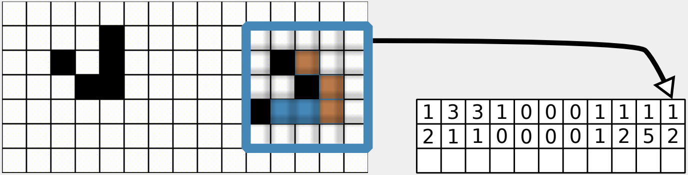
Glider gun detector:



1	3	3	1	0	0	0	1	1	1	1
2	1	1	0	0	0	0	1	2	5	

Image pattern detection

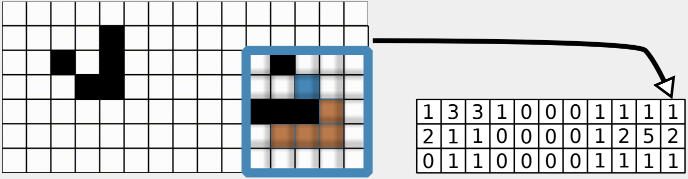
Glider gun detector:



1	3	3	1	0	0	0	1	1	1	1
2	1	1	0	0	0	0	1	2	5	2

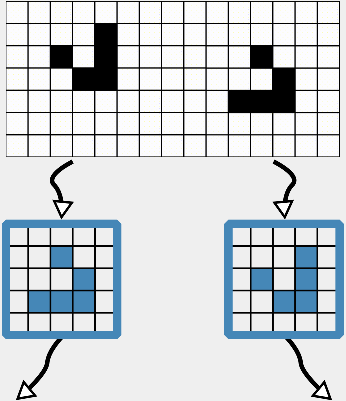
Image pattern detection

Glider gun detector:



1	3	3	1	0	0	0	1	1	1	1
2	1	1	0	0	0	0	1	2	5	2
0	1	1	0	0	0	0	1	1	1	1

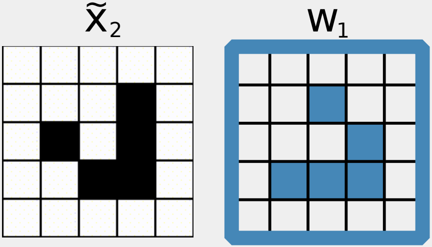
Image pattern detection



1	3	3	1	0	0	0	1	1	1	1
2	1	1	0	0	0	0	1	2	5	2
0	1	1	0	0	0	0	1	1	1	1

1	5	1	1	0	0	0	0	1	1	2
1	2	1	1	0	0	0	1	3	3	1
1	1	0	0	0	0	0	1	1	3	1

Image pattern detection - Convolution



- Let $\tilde{x}_j \in \mathbb{R}^r$ denote the j-th image patch of image X, e.g.

$$\tilde{x}_2 = (0, 0, 0, 0, 0,\ 0, 0, 0, 1, 0,\ 0, 1, 0, 1, 0, \dots)^\top$$

- Let $w_k \in \mathbb{R}^r$ denote the k-th glider pattern or kernel, e.g.

$$w_1 = (0, 0, 0, 0, 0,\ 0, 0, 1, 0, 0,\ 0, 0, 0, 1, 0, \dots)^\top$$

- The output y_j at position j is given by

$$y_j = \tilde{x}_j^\top w_k$$

Image pattern detection - Convolution

- Let $\tilde{X} \in \mathbb{R}^{q \times r}$ denote the matrix of q image patches from image X and $W \in \mathbb{R}^{r \times p}$ the matrix of kernels, i.e.

$$\tilde{X} = \begin{bmatrix} \tilde{x}_1^\top \\ \tilde{x}_2^\top \\ \vdots \\ \tilde{x}_q^\top \end{bmatrix}, \quad W = [w_1, w_2, \ldots, w_p]$$

- The result $Y \in \mathbb{R}^{q \times p}$ of applying the kernel matrix W to image X is given by

$$Y = \tilde{X}W = X * W$$

  where "$*$" is called *convolution*[1]

[1] Technically, we are computing a cross-correlation and not a convolution

Equivariance

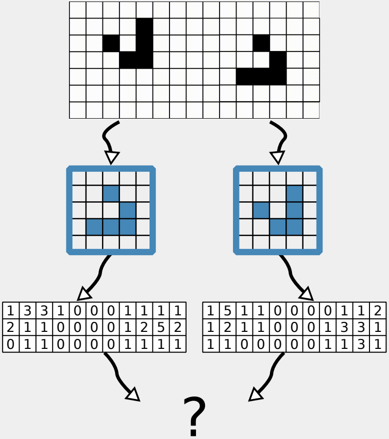
- Let X be an image and W a filter
- $\varphi(X) = X * W$ denotes a convolution with W
- $\tau(X)$ is a translation of an image
- The following diagram shows that φ is *equivariant* with respect to τ

$$\begin{tikzcd}
X \arrow[r, "\varphi"] \arrow[d, "\tau"'] & Y \arrow[d, "\tau"] \\
X' \arrow[r, "\varphi"] & Y'
\end{tikzcd}$$

- Exception are the borders of images

Why equivariance and not invariance?

Image pattern detection



1	3	3	1	0	0	0	1	1	1	1
2	1	1	0	0	0	0	1	2	5	2
0	1	1	0	0	0	0	1	1	1	1

1	5	1	1	0	0	0	0	1	1	2
1	2	1	1	0	0	0	1	3	3	1
1	1	0	0	0	0	0	1	1	3	1

- Stack multiple convolutions

- Case 1: All images have the same dimension

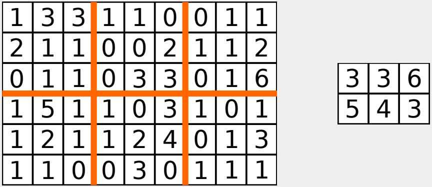
⇒ Feed into neural network

- Case 2: Images have variable dimension

⇒ Compute summary statistics (*global pooling*)
  - mean
  - max

Pooling layers

- Applying kernels leads to *translation-equivariant* features
- Pooling layers add (limited amount of) translation invariance
- Average pooling
- Max pooling

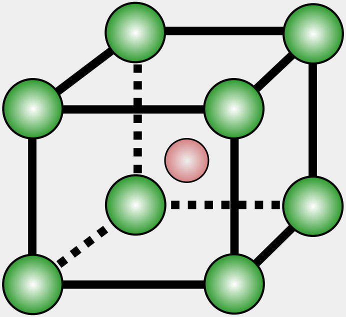


1	3	3	1	1	0	0	1	1
2	1	1	0	0	2	1	1	2
0	1	1	0	3	3	0	1	6
1	5	1	1	0	3	1	0	1
1	2	1	1	2	4	0	1	3
1	1	0	0	3	0	1	1	1

3	3	6
5	4	3

Graph Convolutional Neural Networks (GCNNs)

Graph data



Graph convolutions

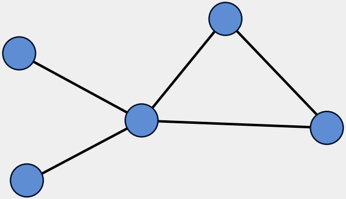
- Convolutions are not only restricted to image and time-series data
- Graph convolutions are used to model the interaction between nodes
- Let $G = (N, E)$ denote a graph with nodes N and edges E
- How could we implement a convolution of G with a weight matrix W?
- The result of a convolution is again a graph[2], i.e.

$$G' = G * W$$

[2] Remember that convolution on images also returns an image

Graph convolutions

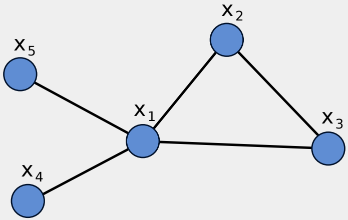
- Graph G with 5 nodes and 5 edges:



- We assign a feature vector $x_i \in \mathbb{R}^p$ to the i-th node
- The feature vector can depend on the type of the node
- Nodes of the same type might share the same feature vector

Graph convolutions

- Graph G with 5 nodes and 5 edges:



- We assign a feature vector $x_i \in \mathbb{R}^p$ to the i-th node
- The feature vector can depend on the type of the node
- Nodes of the same type might share the same feature vector

Graph convolutions

- Let $A = (a_{ij})_{ij} \in \mathbb{R}^{k \times k}$ denote the adjacency matrix of a graph with k nodes
- The strength of the connection between node i and j is given by a_{ij}
- Self-connections $a_{ii} \neq 0$ allow to incorporate the features of the nodes itself
- The convolution operation updates the feature vector of node i by summing over the contributions of all neighbor nodes, i.e.

$$x'_i = \sigma\left(\sum_{j \neq i} a_{ij} W x_j\right)$$

where $W \in \mathbb{R}^{p \times p}$ and σ is the activation function[3]

[3] Graph convolutions are *permutation equivariant*

Graph convolutions

- For the full graph we obtain

$$\underbrace{X'}_{k\times p} = \sigma(\underbrace{A}_{k\times k}\underbrace{X}_{k\times p}\underbrace{W^\top}_{p\times p})$$

  where $X \in \mathbb{R}^{k\times p}$ is the matrix of k feature vectors

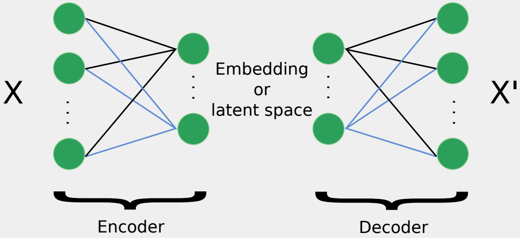
- Note that the weight matrix W does not depend on the size and connectivity of the graph
- W can be applied to multiple graphs and optimized during training of the graph convolutional neural network (GCNN)
- GCNNs typically apply multiple convolutions and afterwards compute summary statistics of the feature vectors, the result can then be used in a conventional neural network

[3] Many extensions and generalizations exist [Battaglia et al., 2018, Dwivedi et al., 2020]

Auto-encoders

Auto-encoders

- Embeddings implicitly group categories by their similarity
- Auto-encoders [Kramer, 1991] learn hidden representations for non-categorical data:



- During training, the error between X and X' is minimized
- The embedding or latent space should have lower dimension than the input space

Auto-encoders - Formal definition

- The encoder $f_W : \mathbb{R}^p \to \mathbb{R}^q$ is a neural network with weights W that maps a sample $x \in \mathbb{R}^p$ into a q-dimensional feature space
- The decoder $g_V : \mathbb{R}^q \to \mathbb{R}^p$ takes a point in feature space and maps it back to input space
- Given a set of training points $\{x_i\}_i$ we train the auto-encoder by minimizing the error between the input and output of the network, i.e.

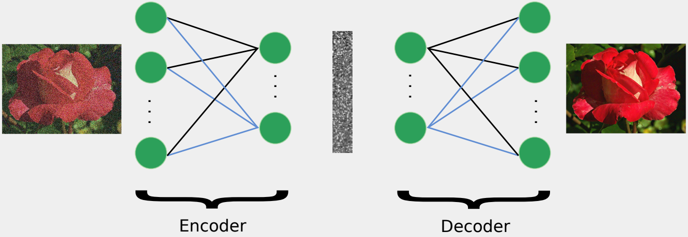
$$W, V = \arg\min_{W,V} \|x_i - (g_v \circ f_W)(x_i)\|_2^2$$

Auto-encoders - Purpose

- Dimensionality reduction and visualization (similar to PCA and t-SNE)

- Compression to most important features (encoder output)

- Denoising and image restauration (decoder output), by adding noise to images before sending it to the encoder

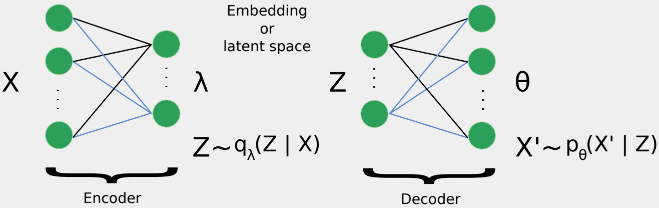


- Clustering and outlier detection on the latent space

Variational auto-encoders (VAEs)

- Can we use auto-encoders for generating data? I.e. we could sample a point from the latent space and decode the corresponding data point
- Practice has shown that this appproach does not work
- The latent space has many *holes* where the decoder generates garbage
- Variational auto-encoders (VAEs) [Kingma and Welling, 2013] are a probabilistic formuation of auto-encoders, that regularize the latent space

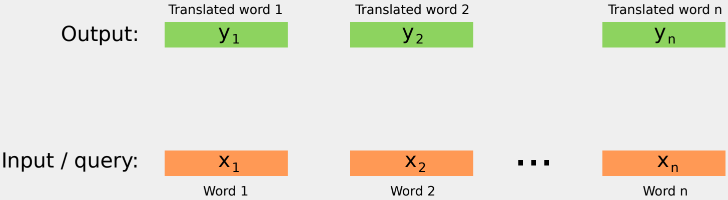
Variational auto-encoders (VAEs)



- Instead of learning latent representations directly, VAEs learn the parameters of given distributions
- The encoder learns the parameters λ of the distribution $q_\lambda(z \mid x)$
- The decoder learns the parameters θ of the distribution $p_\theta(x \mid z)$
- Training is more complicated, i.e. minimize the KL-divergence

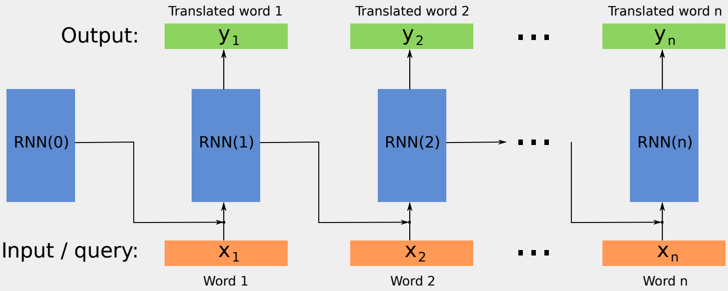
Attention

Sequential data



- Translations require special architectures that can deal with:
  - Variable sentence lengths, i.e. variable *n*
  - Long-range dependencies

Recurrent neural Networks

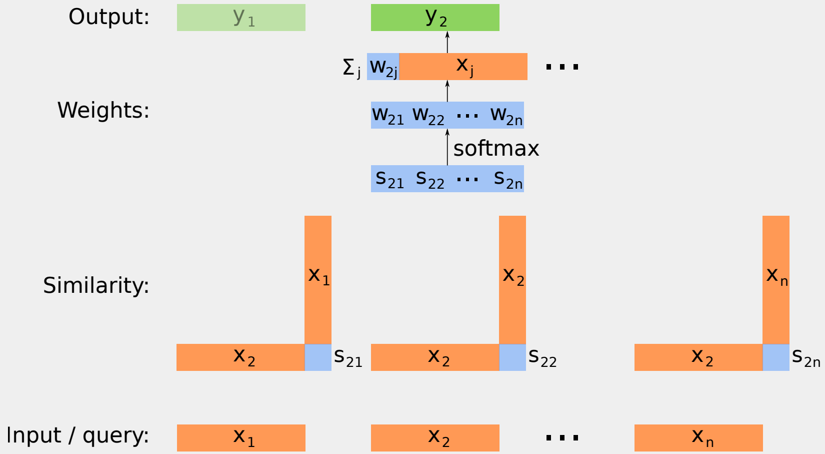


- Recurrent neural networks (RNNs) are sequentially applied to each input x_i
- The architecture and weights are the same for all steps i.e. for RNN(0), RNN(1), . . . , RNN(n)
- At each step i, RNNs take the input x_i and the state of the previous step $i - 1$ as input

Attention is all you need

- Recurrent neural networks (RNNs) were traditionally used for sequence data and to model long-range interactions
- Traditional RNNs have extreme vanishing / exploding gradient problem
- Long-short term memory (LSTM) [Hochreiter and Schmidhuber, 1997] solved this problem, but is still difficult to train
  - On a large input sequence it corresponds to a very deep neural network
  - Transfer learning never worked for LSTM
- Transformers with attention layer [Bahdanau et al., 2014, Vaswani et al., 2017] are an alternative to RNNs and show better performance

Self-attention layer



Self-attention layer

- Let $X = [x_1^\top, x_2^\top, \ldots, x_n^\top] \in \mathbb{R}^{n \times p}$ denote the data matrix, i.e. the embeddings of the input sequence

- The self-attention layer computes the i-th output $y_i \in \mathbb{R}^p$ as follows:

$$\begin{aligned} s_i &= x_i^\top X^\top \\ w_i &= \mathrm{softmax}(s_i) = \left(\frac{e^{s_{ij}}}{\sum_{k=1}^n e^{s_{ik}}} \right)_{j=1,2,\ldots,n} \\ y_i &= w_i X \end{aligned}$$

- The self-attention layer computes the entire output $Y \in \mathbb{R}^{n \times p}$ as follows:

$$Y = \mathrm{softmax}\underbrace{(XX^\top)}_{\text{kernel}} X$$

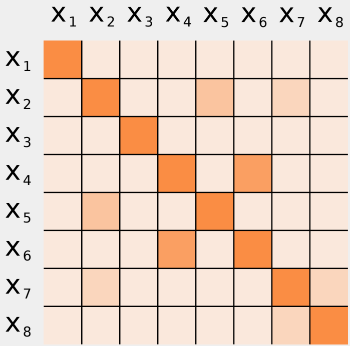
where the softmax is applied independently to each row

Self-attention maps

- The self-attention map is defined as

$$A = \mathrm{softmax}(XX^\top)$$

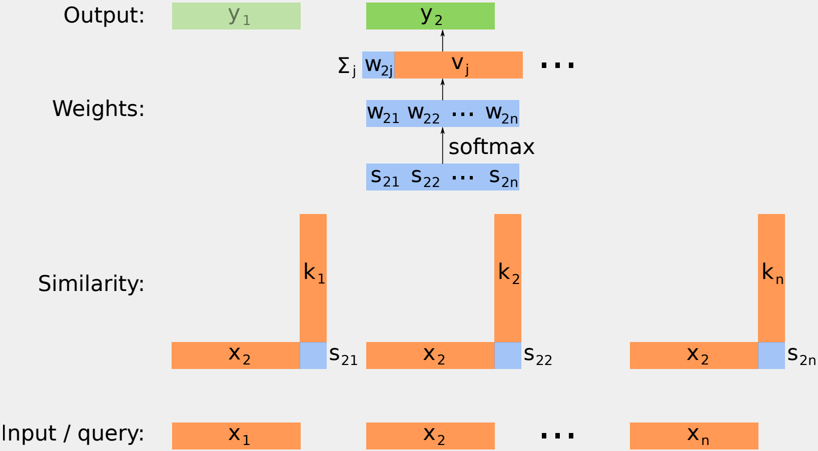
- The matrix A can be visualized to inspect attention



Attention layer

- Except for the embeddings $(x_i)_i$, the self-attention layer has no parameters that can be optimized
- For self-attention, the input sequence focuses attention on the input sequence itself and a linear combination of the input sequence $x_1, x_2, \ldots, x_n$ is returned
- The attention layer is a generalization of the self-attention layer, where
  - attention is focused on a set of m keys $k_1, \ldots, k_m$, with $k_j \in \mathbb{R}^p$
  - a linear combination of m values $v_1, \ldots, v_m$ is returned, where $v_j \in \mathbb{R}^p$
- The attention layer implements a differentiable data retrieval method for a database of m keys and values

Attention layer



Attention layer

- Let $K \in \mathbb{R}^{m \times p}$ and $V \in \mathbb{R}^{m \times p}$ denote a set of m keys and values

- The attention layer computes the entire output $Y \in \mathbb{R}^{n \times p}$ as follows:

$$Y = \mathrm{softmax}(XK^\top)V$$

- Remarks:
  - There exist several variants of the attention layer
  - Transformers use a both attention and self-attention layers
  - The sequential order is lost for self-attention and attention layers
  - Transformers use another encoding for restoring relative word positions
  - Multiple *attention heads* are commonly used

Transfer learning

- Some of the most successful deep learning models:
  - Protein folding: AlphaFold [Jumper et al., 2021]
  - Vision: GoogLeNet [Szegedy et al., 2015], Squeeze-and-Excitation Networks (SENet) [Hu et al., 2018]
  - Translation: BERT [Devlin et al., 2018], Text-to-Text Transfer Transformer (T5) [Raffel et al., 2019]
- Training T5 (11B-parameter variant) costs well above $1.3 million [Sharir et al., 2020]
- True deep neural networks are not affordable for most academics
- Transfer learning allows to adapt pre-trained models

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