

# Unsupervised Deep Learning and Spatial Transcriptomics

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Lecture 12, 1000-719bMSB

# Unsupervised learning

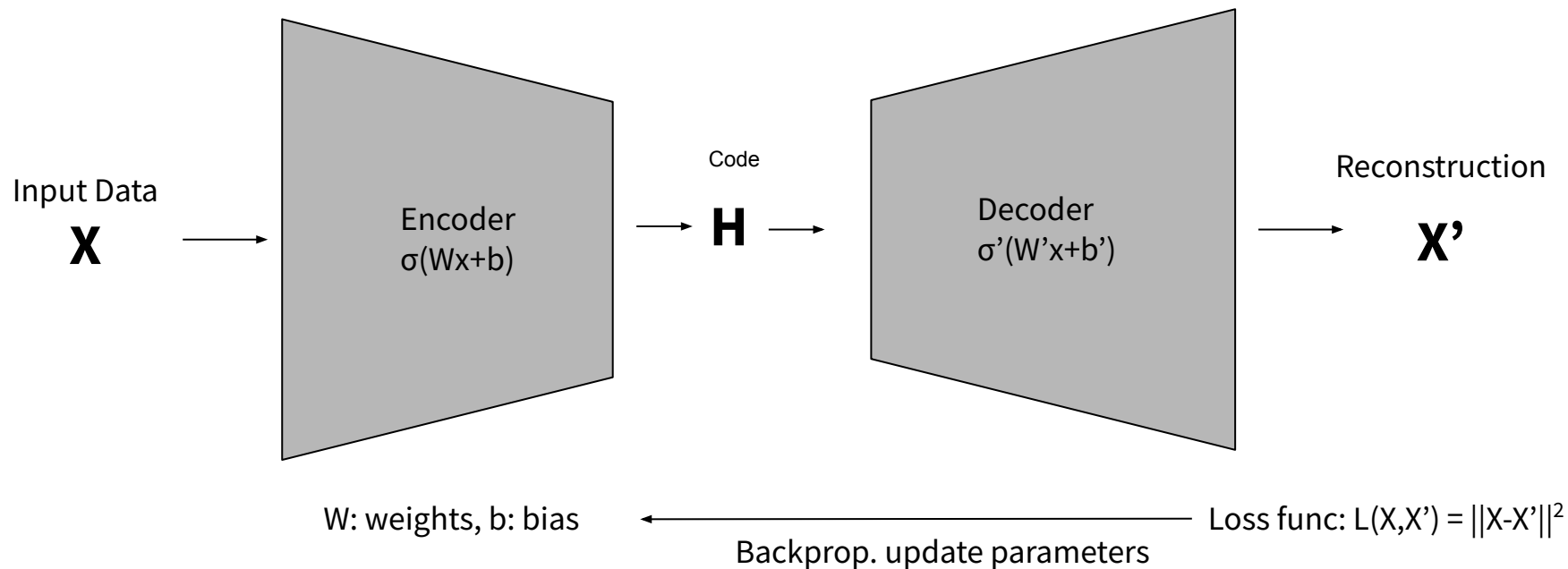
- Labels are not available or not used
- Discover patterns or internal/compact representation
- Identify the latent space or latent variables underlying the data
- Self-supervised learning may be fall under unsupervised learning
- Clustering and principal component analysis are two major techniques

# Previously

- Clustering (k-means, hierarchical, etc)
- Principal component analysis, independent component analysis, factor analysis
- Latent variable models

# Autoencoder

Non-linear generalization of PCA (Kramer, 1991)



# Autoencoder

**H** contains encoding vectors, that represent learned attributes

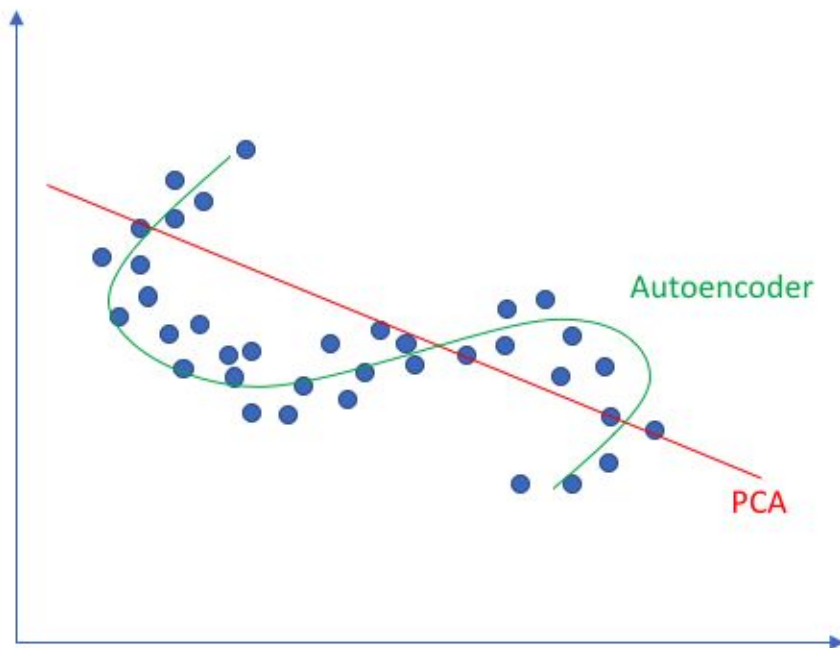
Encoder network converts the input data into numeric values for **H**

Decoder network knows how to take that numeric values in **H** to reconstruct

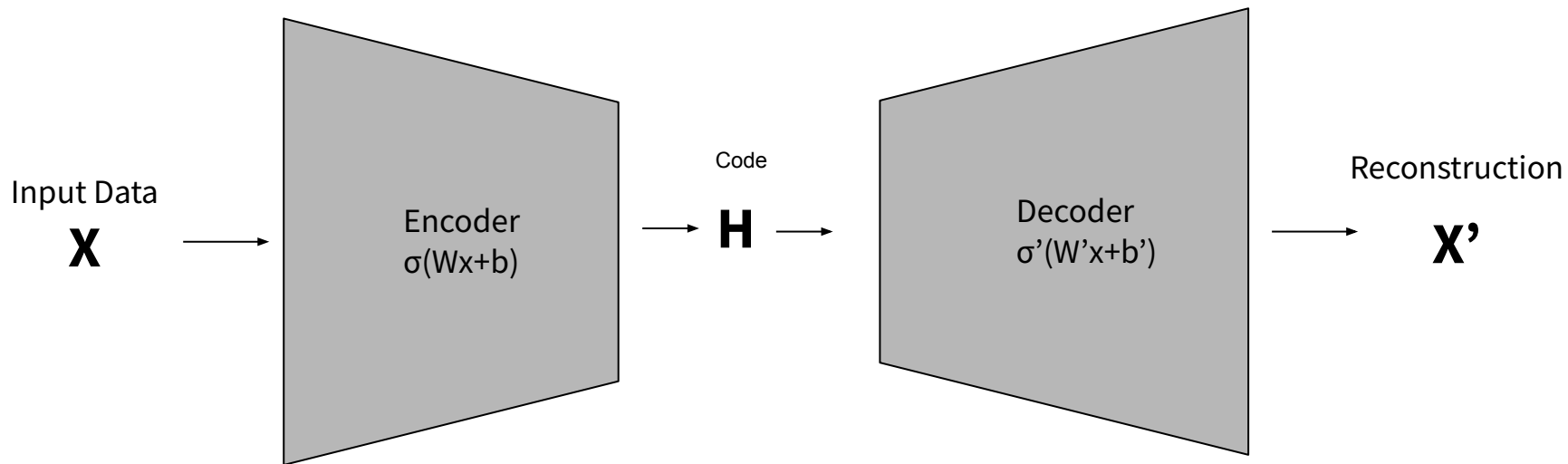
Often the encoder and decoder are mirrored architectures, but not necessarily

# Why non-linear generalization of PCA?

Linear vs nonlinear dimensionality reduction

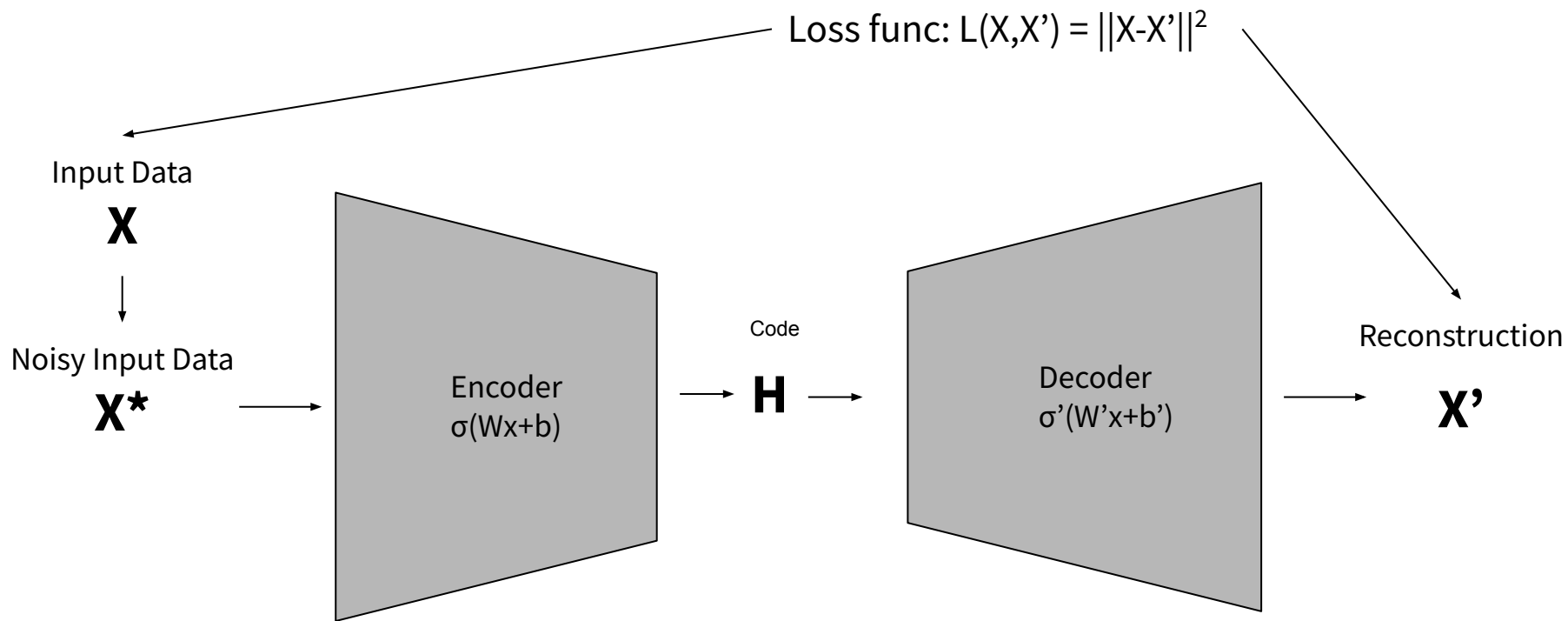


# Rank of H



$\text{rank}(\mathbf{H}) < \text{rank}(\mathbf{X})$  results in compression.  
 $\text{rank}(\mathbf{H}) > \text{rank}(\mathbf{X})$  is overcompleted.

# Denoising autoencoder





# Shortcomings of Autoencoder

Need for data

Hyperparameters, architectural choices

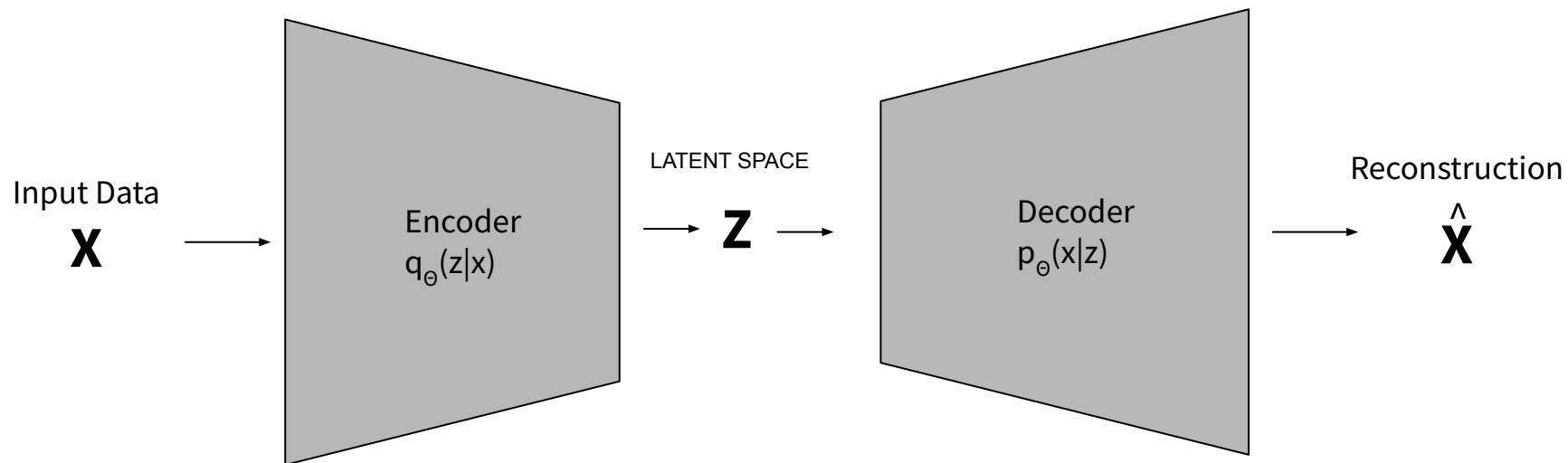
Training vs. test data

Decoding codes are typically not continuous or complete

Learnt attributes are 'static' and may not have relative relevance

# Variational autoencoder

Encoding a probability distribution for each latent attribute



# Statistical Model

The data  $x$  is generated from latent variable  $z$ . When we have a large amount of data, then we hope to estimate  $z$  in some ways.

Ideally, we would like to compute

$$p(z|x) = p(x|z)p(z) / p(x)$$

However,  $p(x)$  is intractable since  $p(x) = \int p(x|z)p(z)dz$

# Variational Inference

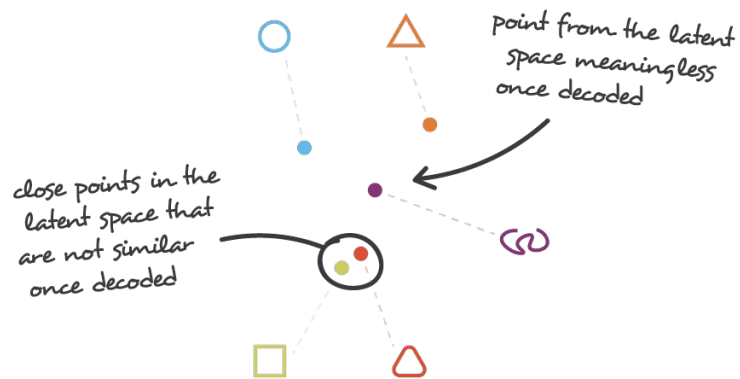
Instead of an intractable distribution  $p(z|x)$ , we introduce another tractable distribution  $q(z|x)$ .

We compare  $p(z|x)$  and  $q(z|x)$  by Kullback–Leibler divergence (also called relative entropy). And if we minimize the KL divergence, we get two distributions to be very similar.

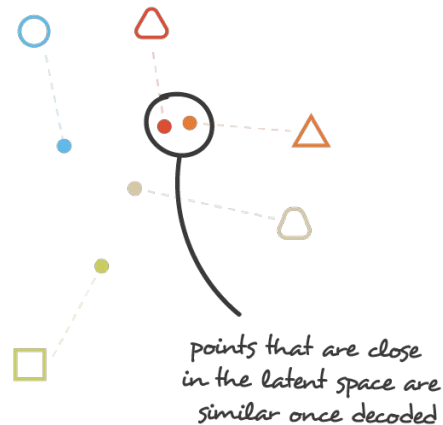
$$\min \text{KL}( q(z|x) || p(z|x) )$$

# Variational Autoencoder

- Generative model: sampling from latent space
- Desired: continuity and completeness
- Regularisation/constraint needed



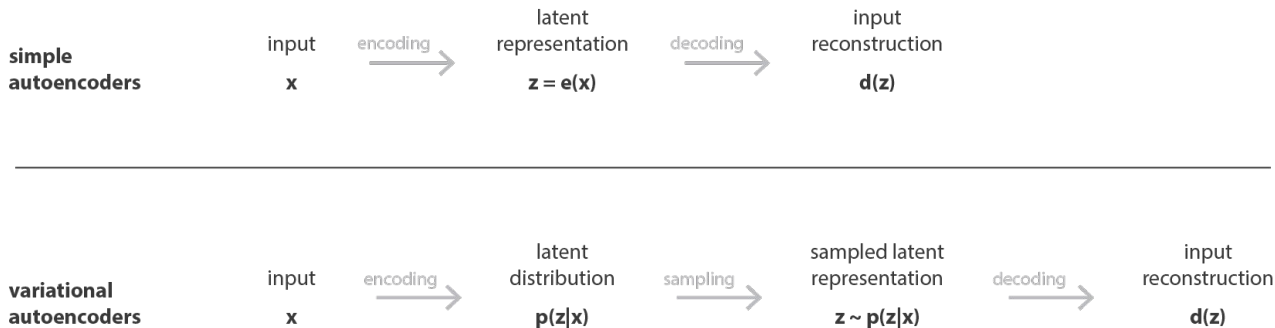
irregular latent space



regular latent space

# Variational Autoencoder

- Improvement: learn distributions instead of points
- Latent space obtained by sampling
- Force distribution to be standard normal



# VAE Loss Function

Reconstruction error + Kullback-Leibler (KL) divergence

$$\mathcal{L}(x, \hat{x}) + \sum_j KL(q_j(z|x) || p(z))$$

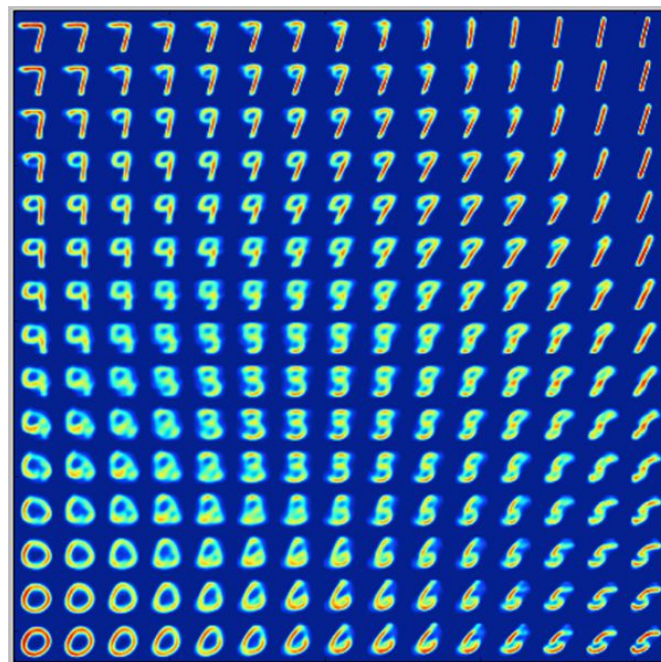
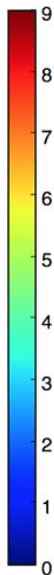
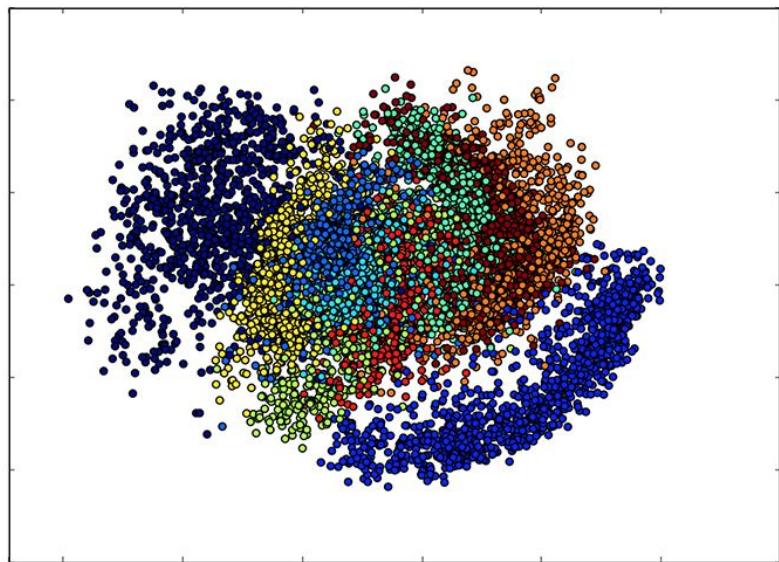
- We are minimizing this loss function, iteratively resulting in
  - Reducing the reconstruction error
  - Encouraging  $q(z|x)$  to be similar to the true distribution  $p(z)$

# VAE on MNIST

Original



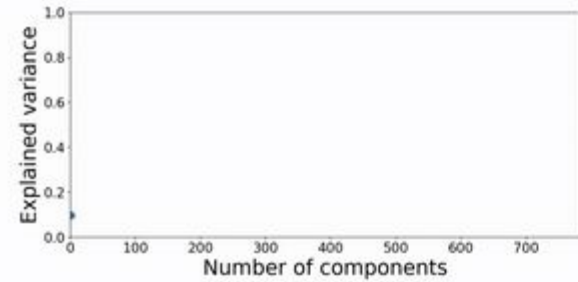
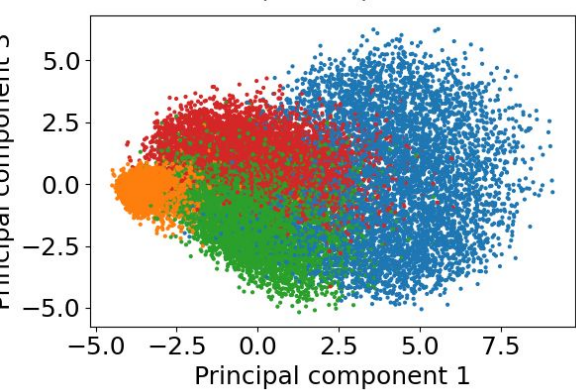
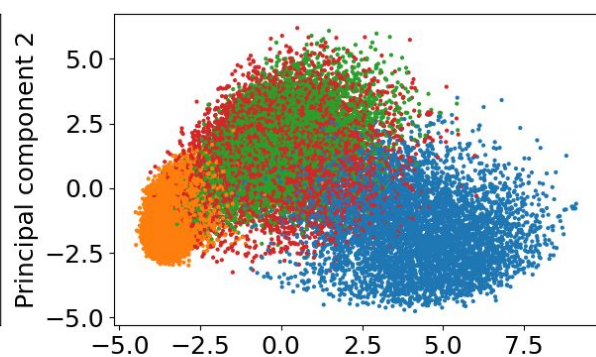
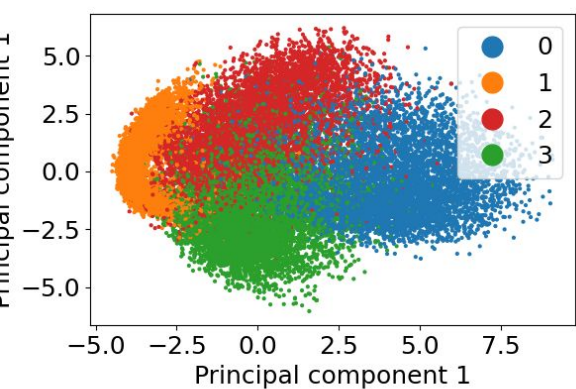
Reconstructed



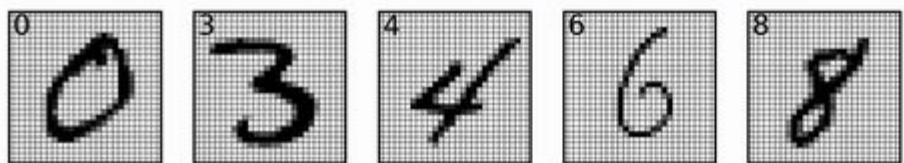


# PCA on MNIST

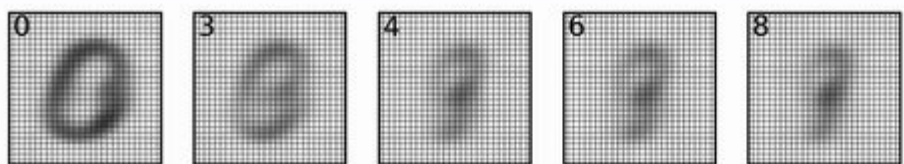
<https://gitlab.com/erikfransson/pca-mnist-testing>



Explained variance measures how much of the variation in the data can be explained by the principal components

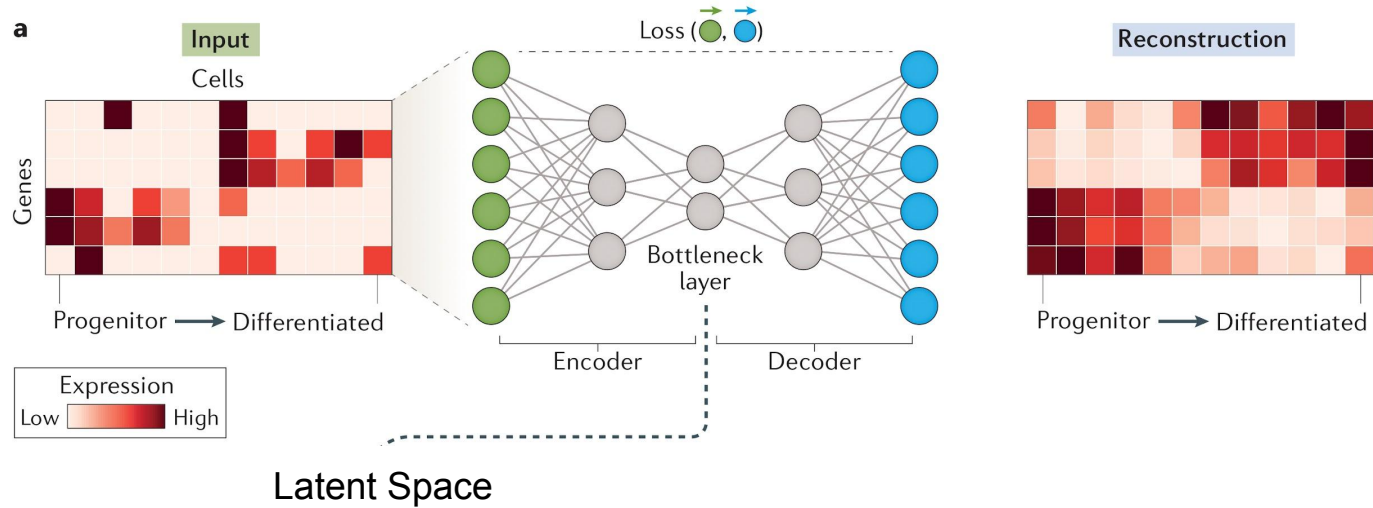


Original



Reconstructed

# On gene expression



# VAE on CelebA

Large-scale CelebFaces Attributes dataset

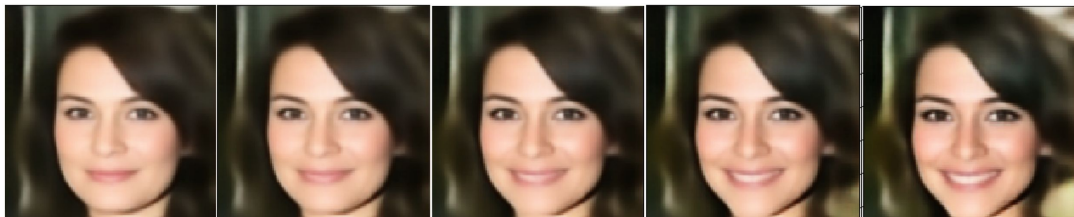


# Interpretability of unsupervised deep learning

- Concept vectors (Brocki and Chung, 2020)
- Latent space encodes high-level concepts
- Concept vectors obtained via averaging

$$\mathbf{z}_c = \text{mean}(q_\phi(\{\mathbf{x} \in \mathbf{X}_c\})) - \text{mean}(q_\phi(\{\mathbf{x} \notin \mathbf{X}_c\}))$$

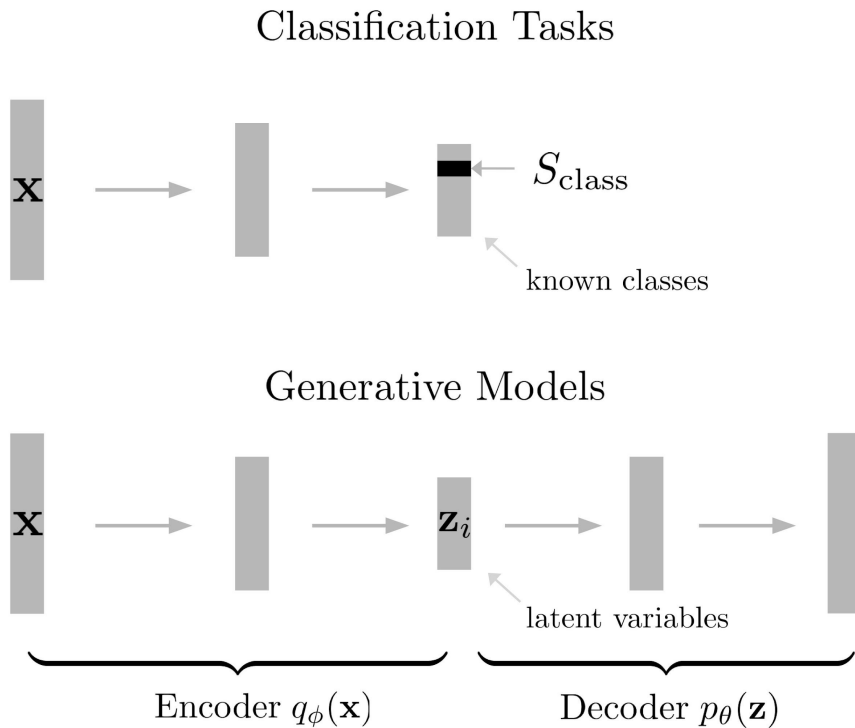
- Manipulation of attributes



$$\mathbf{z}'_i = \mathbf{z}_i + \alpha \mathbf{z}_{\text{smile}}$$

# Concept Score

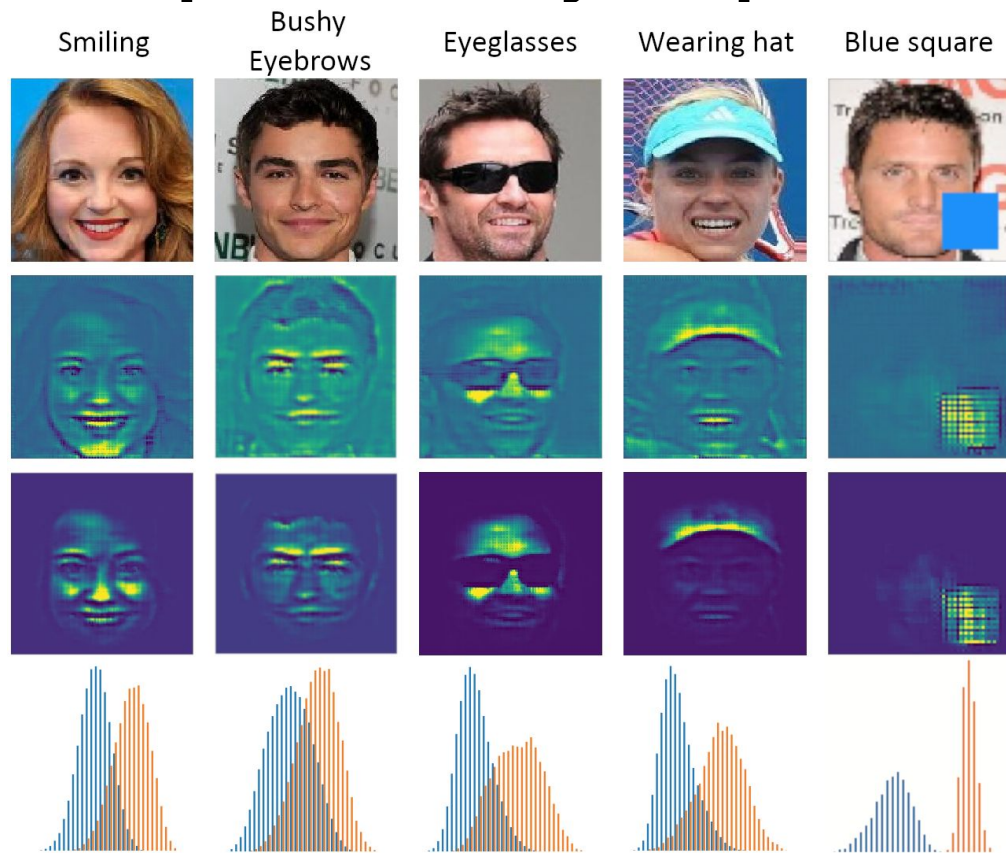
- Which input features contributes to the concept vectors?
- Calculate a dot product with the concept vectors.
- We can create saliency maps for unsupervised models
- Concepts from labels (easy supervised cases)
- Unsupervised cases using clustering, correlations, etc



$$\mathbf{z}_c = \text{mean}(q_\phi(\{\mathbf{x} \in \mathbf{X}_c\})) - \text{mean}(q_\phi(\{\mathbf{x} \notin \mathbf{X}_c\}))$$

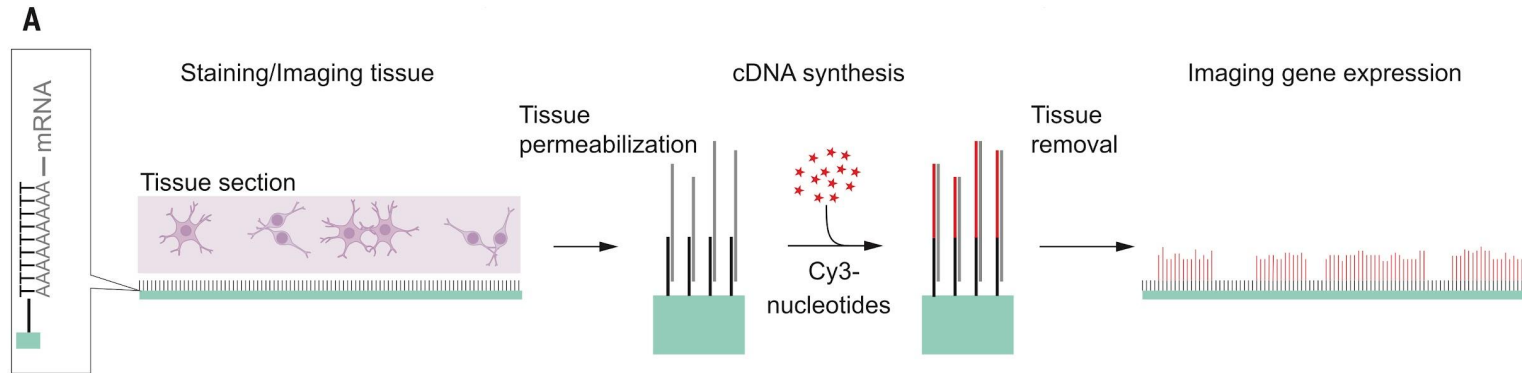
$$S_{\text{concept}} = \mathbf{z}_i \cdot \mathbf{z}_c$$

# CelebA Concept Saliency Maps



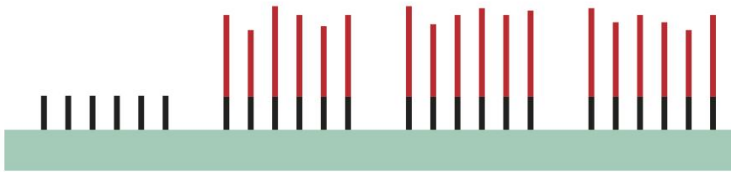
# Spatial Transcriptomics

- Tissue transcriptome usually by RNA-sequencing
- Problem: no spatial resolution, important for tissue functionality
- Stahl et al.: positional barcodes before RNA-seq



# Spatial Transcriptomics

Tissue section

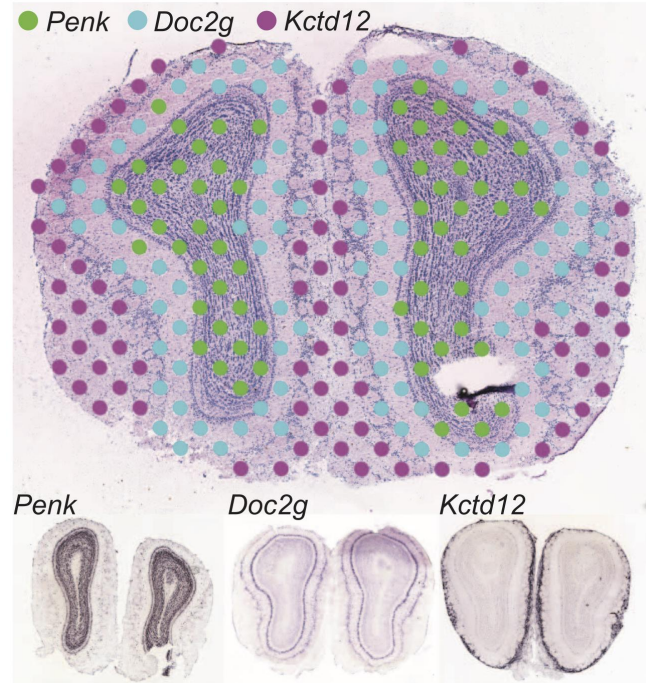


ID582

ID583

ID584

ID585



● *Penk* ● *Doc2g* ● *Kctd12*

*Penk*

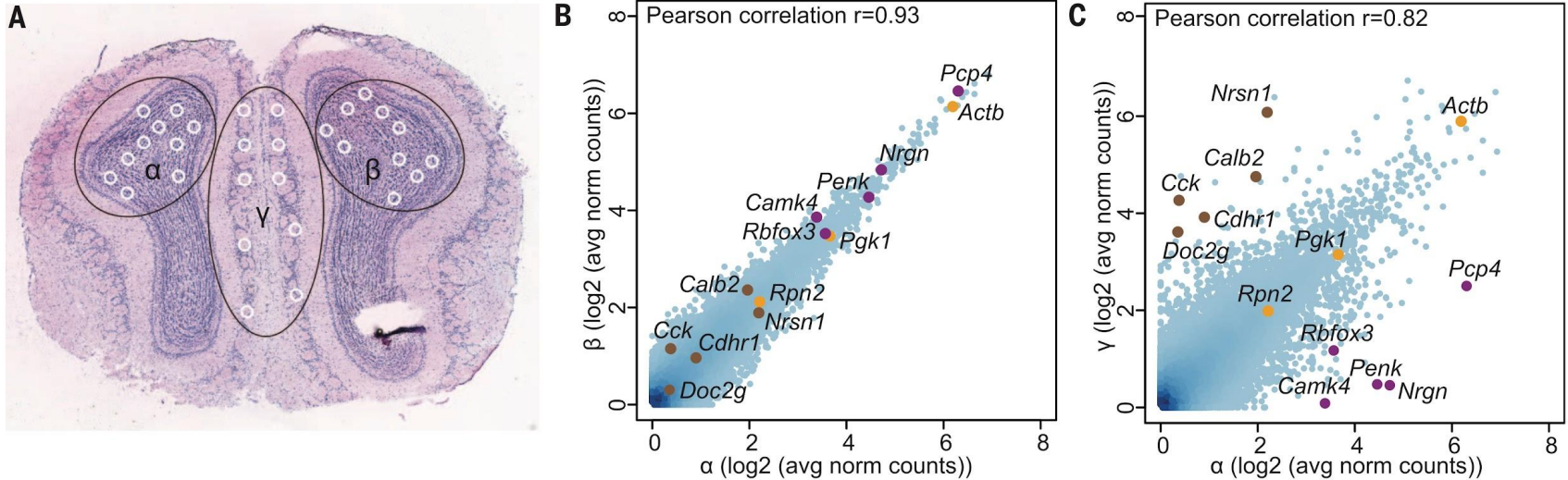
*Doc2g*

*Kctd12*



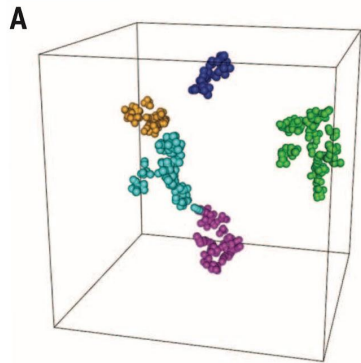
# Spatial Transcriptomics

Gene expression in different areas

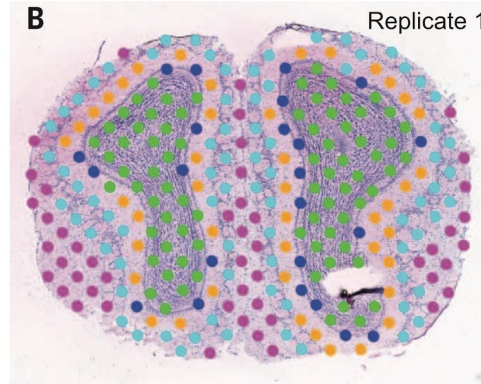


# Spatial Transcriptomics

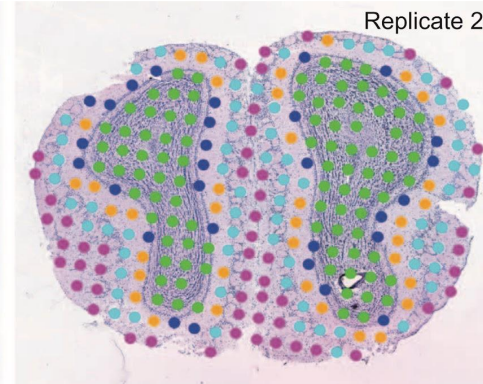
- Dimension reduction with t-sne or PCA
- Clusters map to morphological layers
- Results for t-sne:



- Cluster 1: Granular cell layer
- Cluster 2: Mitral cell layer



- Cluster 3: Outer plexiform layer
- Cluster 4: Glomerular layer



- Cluster 5: Olfactory nerve layer

# Spatial Transcriptomics

## Results for PCA

