Deep Learning in Life Sciences

(Variational) autoencoders

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Plan

DeepLearning inLifeSciences

1. Embeddings

2. Autoencoders
   - linear AE
   - sparse AE
   - denoising AE

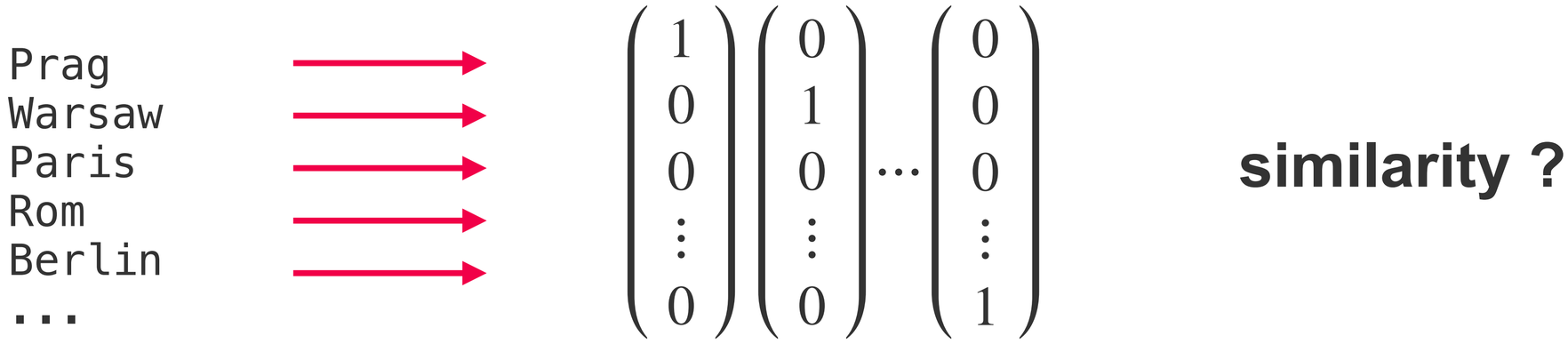
3. Variational autoencoders

DeepLearning inLifeSciences

1 - Embeddings

Embeddings

- Categorical variables are usually represented as **one-hot encoded** representations
- Limitation: there is no way to compute a similarity (or distance) between states

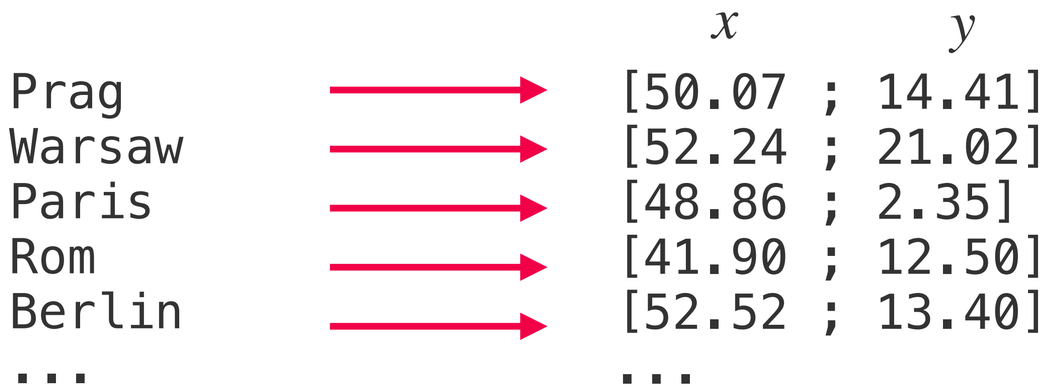


D = 195

one-hot encoded D = 195

Embeddings

- **Embeddings** are continuous representations of (categorical) variables
- Embeddings can be used as (low-dimensional) representations of high-dimensional features
- Embeddings can be used to find **similarities** between objects
- Example: capitals → 2D coordinates



D = 195

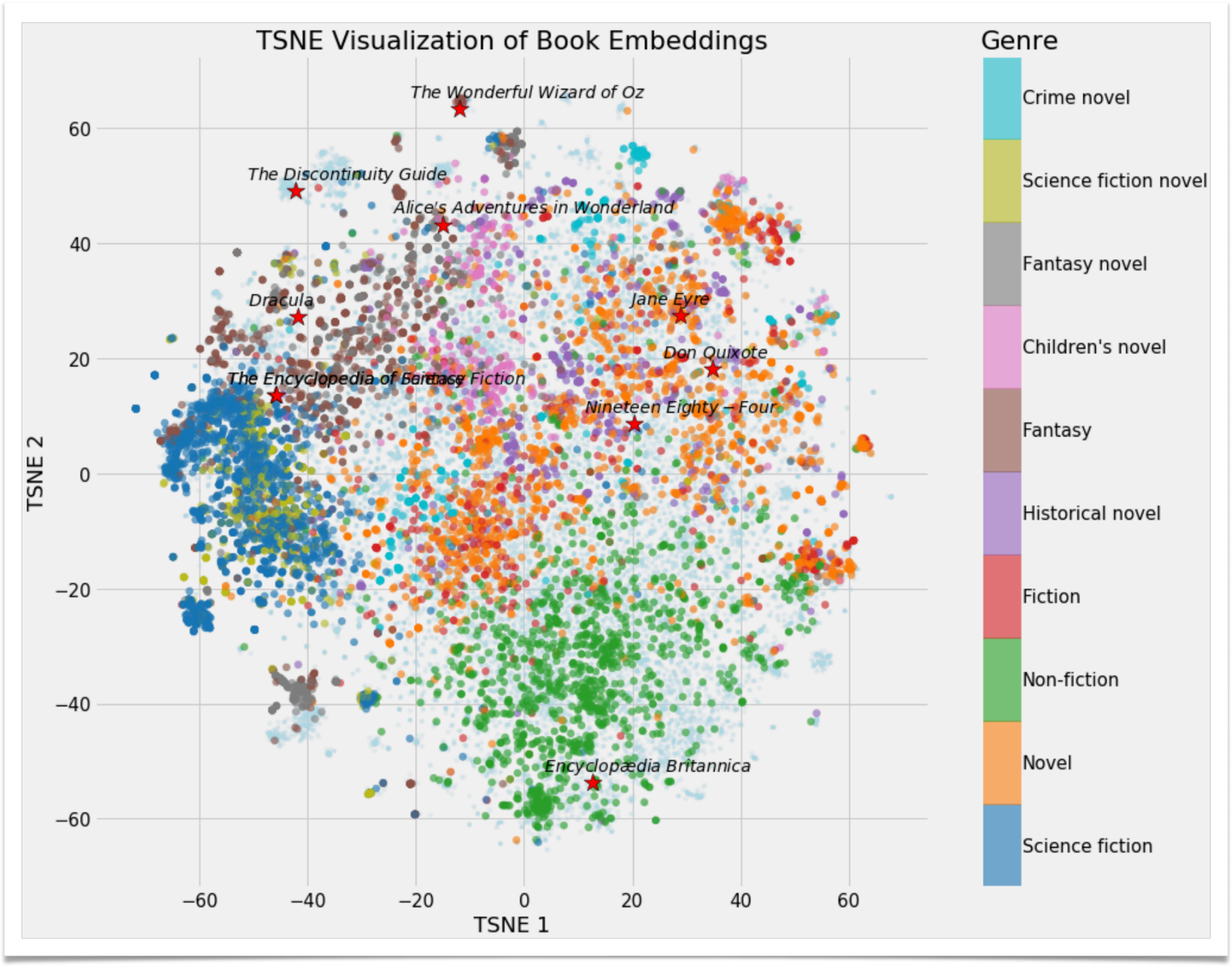
D = 2

$$d = \left(x_1 - x_2\right)^2 + \left(y_1 - y_2\right)^2$$

similarity

Embeddings

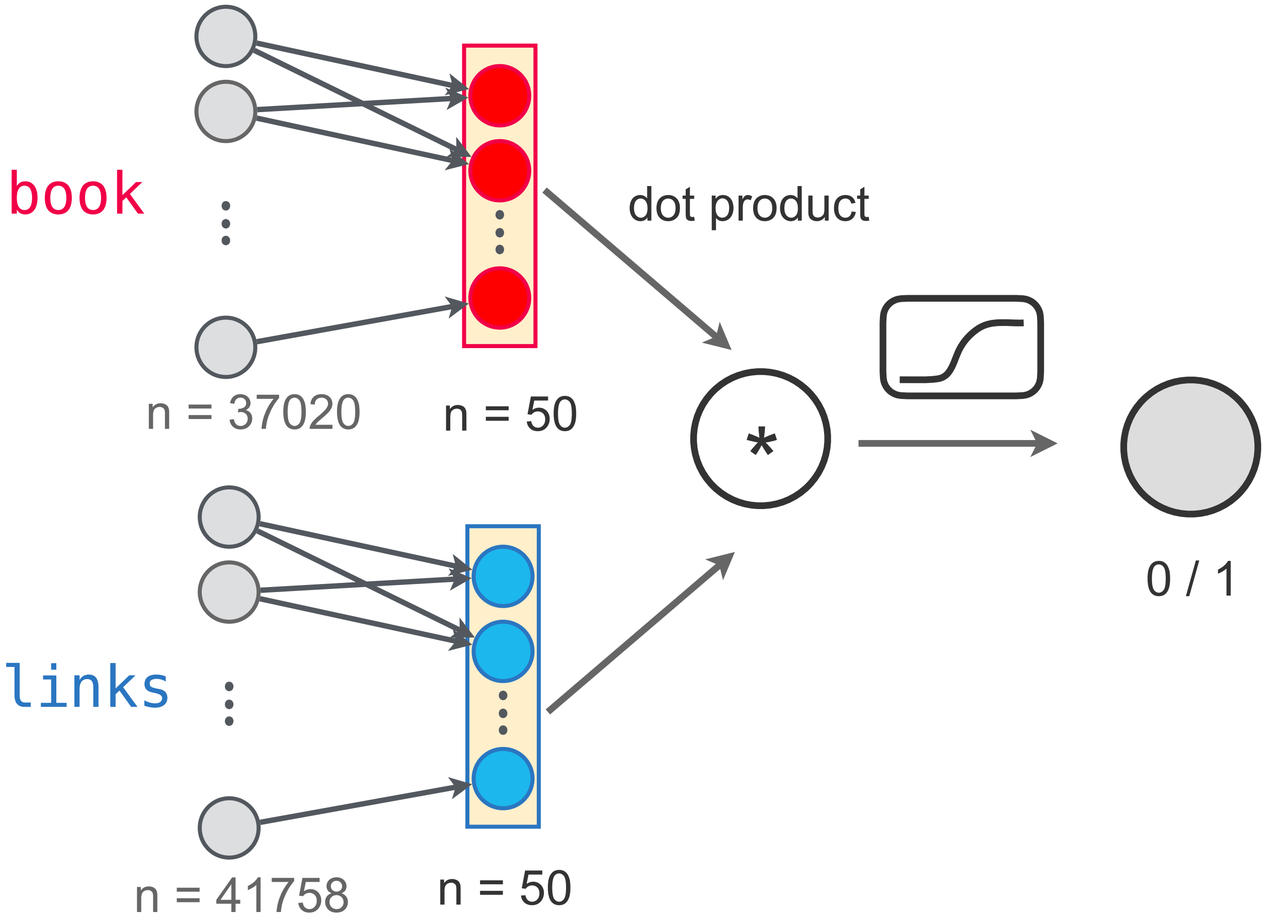
- **Embeddings** can correspond to a *natural representation* (e.g. geographical coordinates,...)
- or they can be learned through specific constraints (e.g. 2D representation of books, ...)
  → *"learned-representation"*



Example: book embedding

- **Book recommender system: books are similar if they contain similar link in their Wikipedia pages**

- Wikipedia articles about books → list of links contained in the wikipedia article `[book, link]`
- **Task: predict if a link is contained in the wikipedia page of a book**
  - `[book, link] → 1 :` article about `book` contains `link`
  - `[book, link] → 0 :` article about `book` does not contain `link`



https://github.com/WillKoehrsen/wikipedia-data-science/blob/master/notebooks/Book%20Recommendation%20System.ipynb

Example: book embedding

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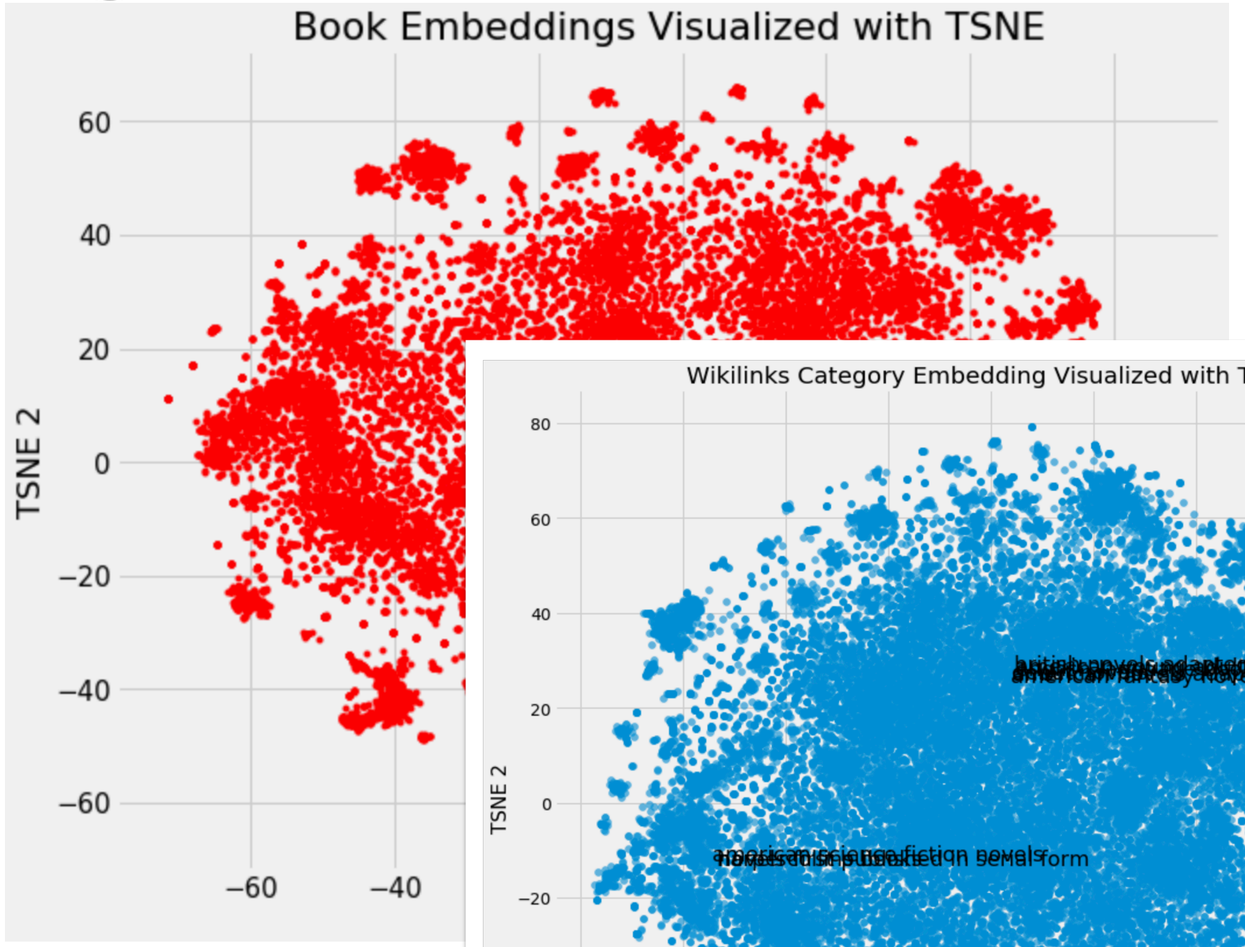
n = 37020

embedding

n = 50

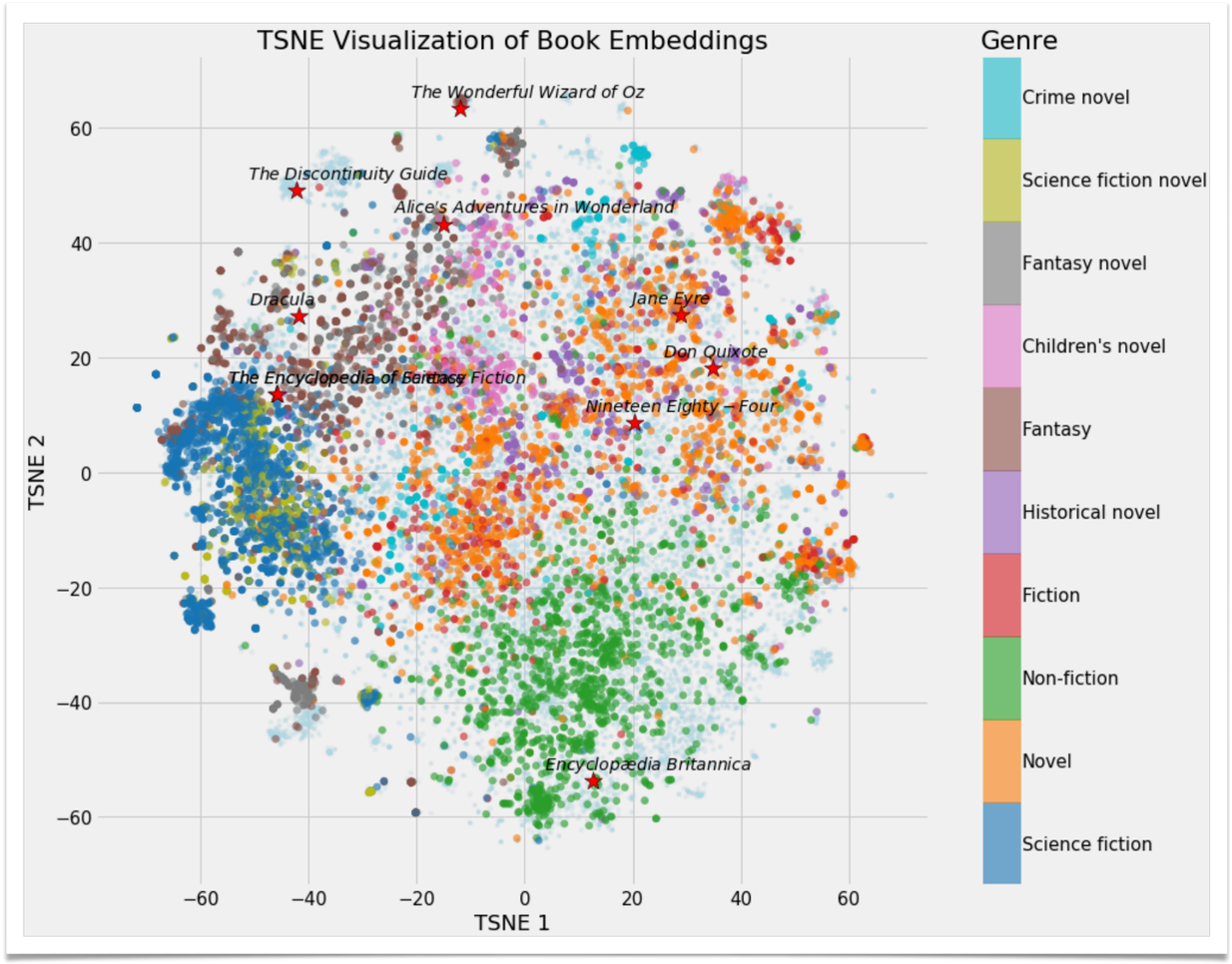
2D visualization (t-SNE)

n = 2

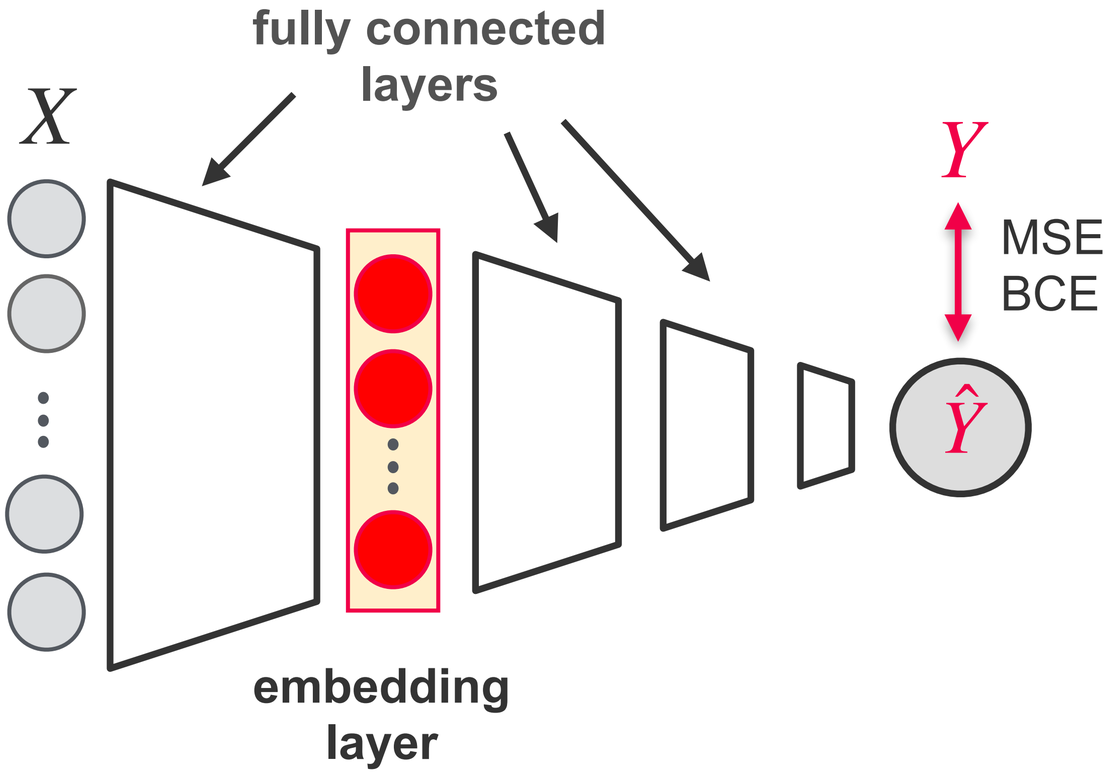


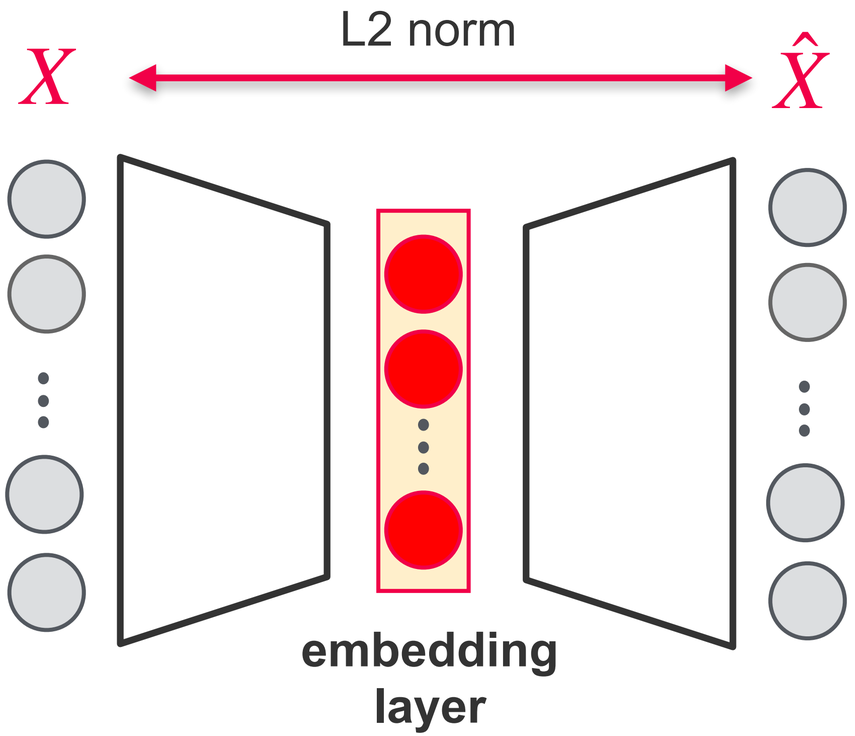
Example: book embedding

- The notion of **distance/ similarity** in the embedding space allows to compute meaningfull relationships between embedded objects
- Not possible with one-hot encoded representation!



Learning embeddings





Regression/classification DNN:
create embedding
by optimizing classification/regression
problem for labelled data

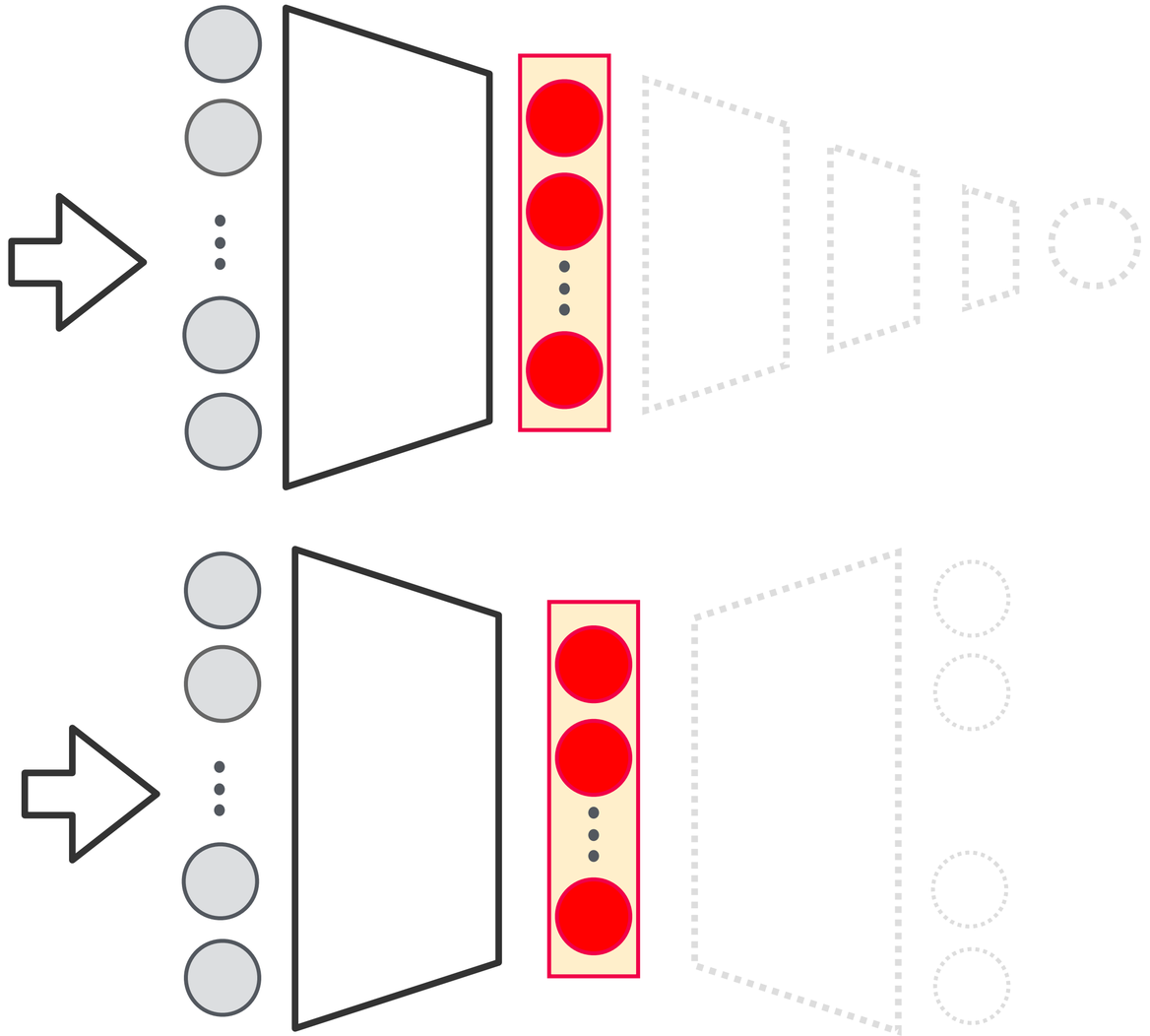
Autoencoder:
create embedding
by minimizing reconstruction error

Learning embeddings

- **Pre-trained embedding layers** can then be used to embed new samples

- Natural Language Processing
  - Skip-gram
  - Word2vec
  - ...

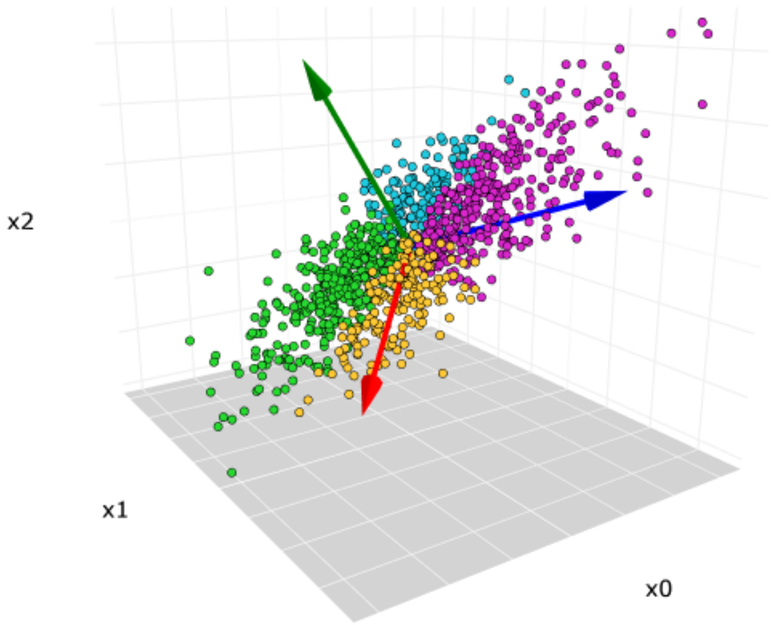
- Protein sequences
  - AlphaFold2
  - ESM2
  - RGN2
  - ...



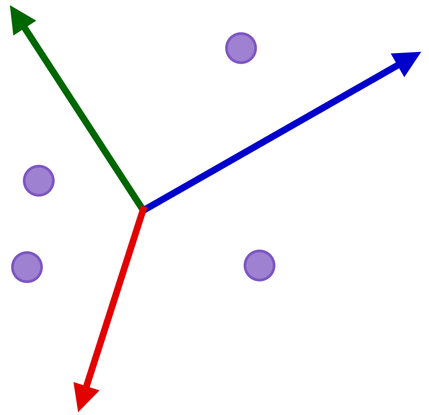
Embeddings

- **Principal component analysis (PCA)**

principal components = embedding learned from training dataset



Project data from testing set in embedding space



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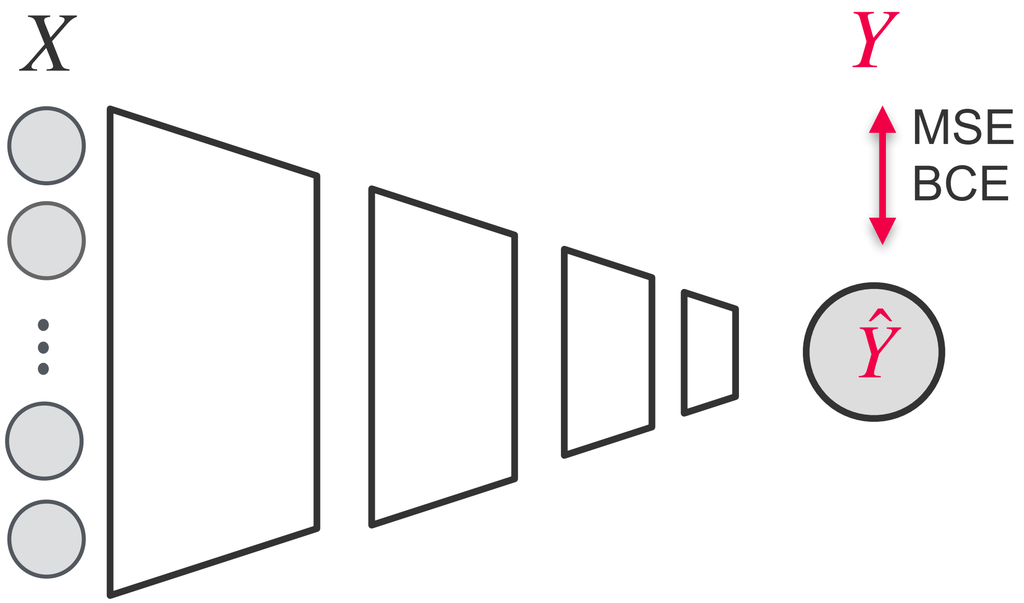
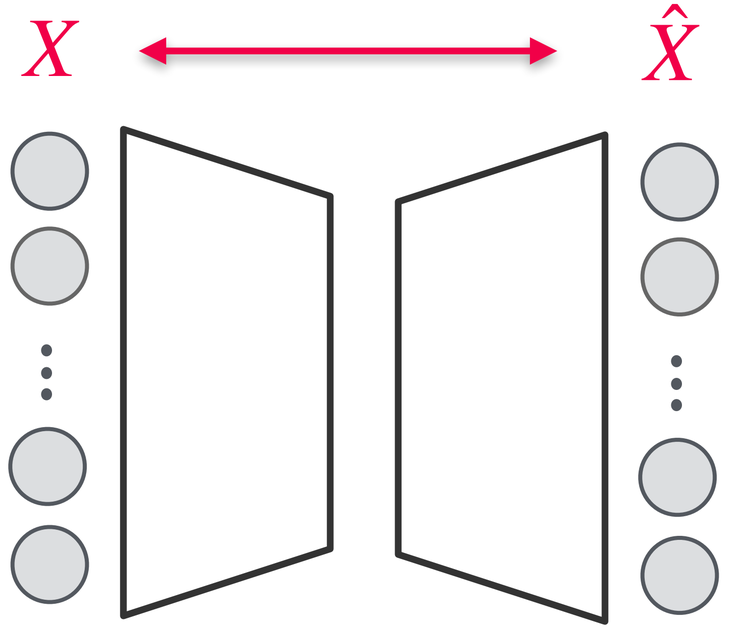
2 - Autoencoders

Supervised vs. unsupervised



Supervised approach
we have discrete (→ classification) or continuous (→ regression) labels



Unsupervised approach
we do not have/use any labels for the data X

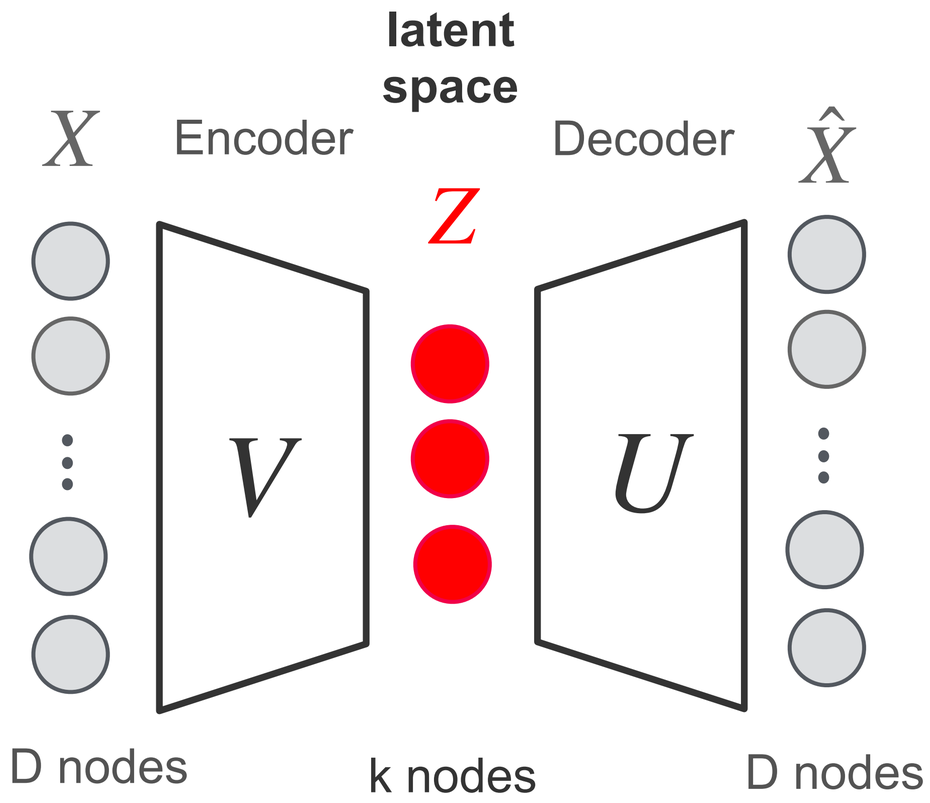
Shallow linear autoencoders

- Autoencoder = feed-forward neural net
- Input = X
- Task: reconstruct X through bottleneck layer
- Simplest example:
  - one input layer
  - latent hidden layer
  - output layer
  - **linear** activation

$$Z = VX$$
$$\hat{X} = UZ$$

- Reconstruction Loss

$$\mathscr{L} = ||X - \hat{X}||^2$$

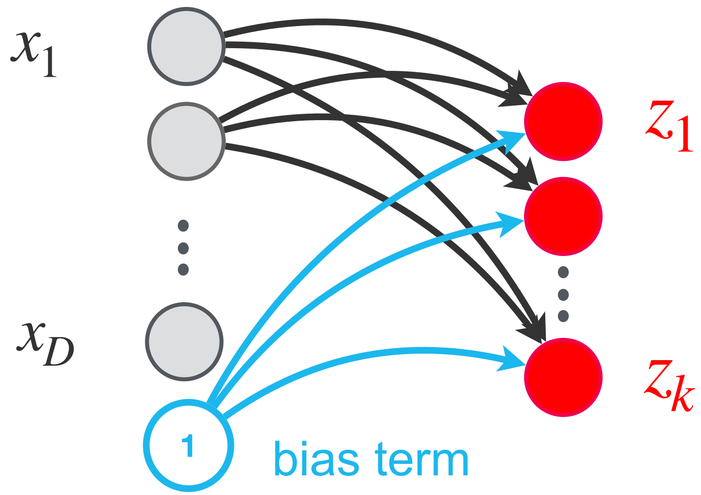


Usually: k << D

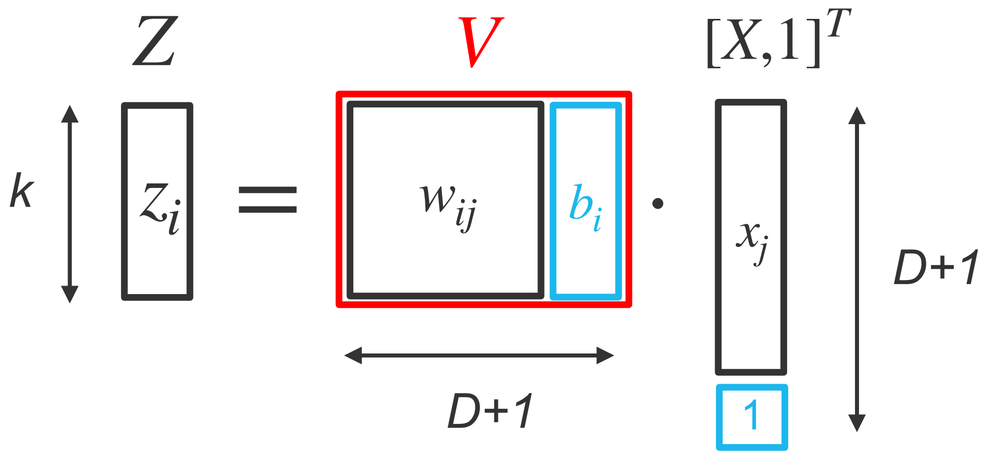
Linear layer

- Remember: fully-connected linear layer is equivalent to **matrix multiplication**

$$X = [x_1, x_2, \ldots, x_D]^T \qquad Z = [z_1, \ldots, z_k]^T$$



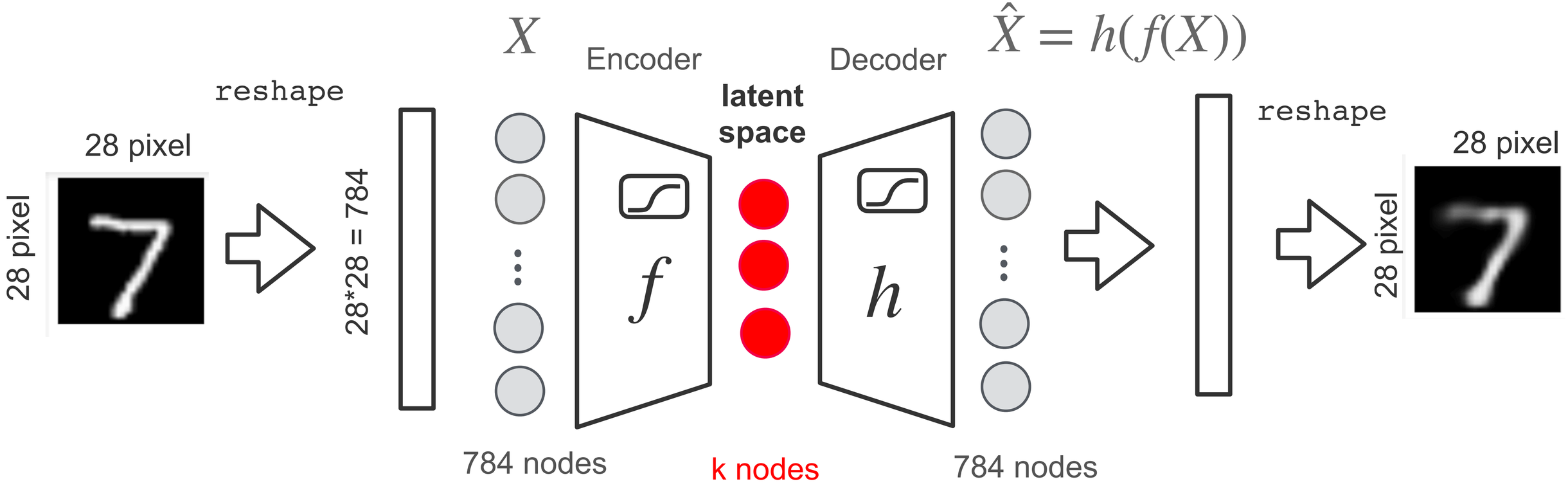
$$z_i = \sum_{j=1}^{D} w_{ij} \cdot x_j + b_i$$



For simplification of notation, we will write (in matrix notation) $Z = VX$

Example non-linear AE

- We use MNIST image data of hand-written digits
- This is a **shallow autoencoder** : just one hidden (latent) layer.
- Sigmoid activation functions (non-linear!)



Implementation

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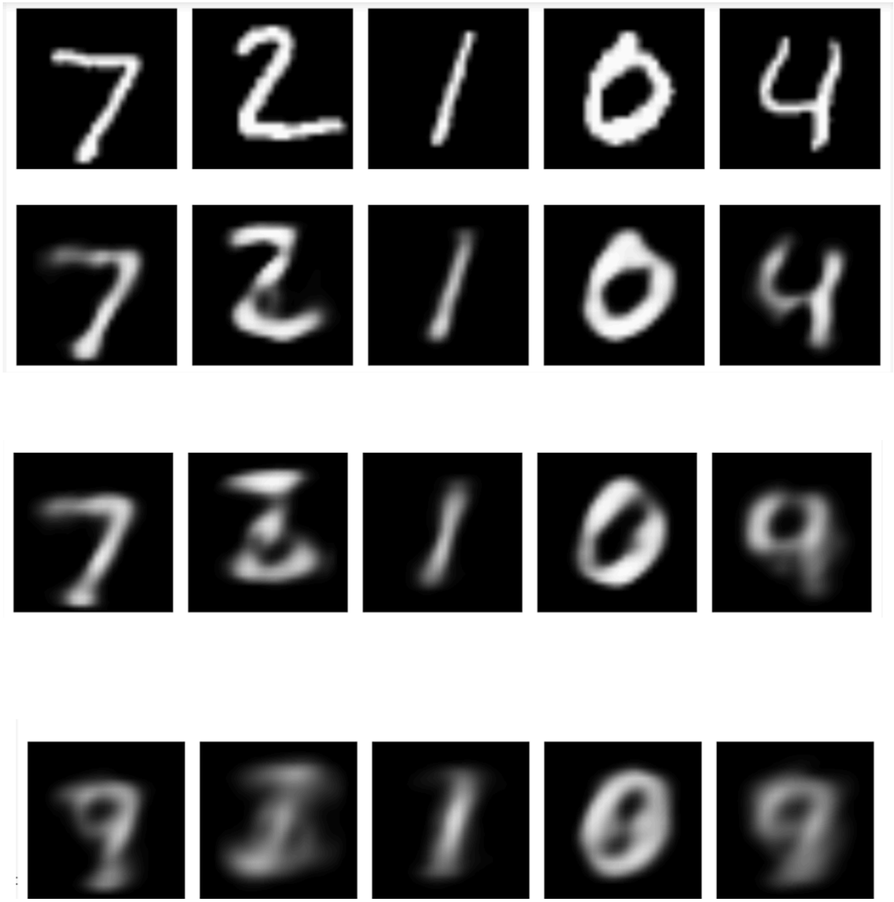
```
class AE_shallow(nn.Module):
    def __init__(self, **kwargs):
        super().__init__()
        self.encoder_hidden_layer = nn.Linear(
            in_features=kwargs["input_shape"], out_features=kwargs["z_size"]
        )
        self.decoder_output_layer = nn.Linear(
            in_features=kwargs["z_size"], out_features=kwargs["input_shape"]
        )

    def forward(self, features):
        code = self.encoder_hidden_layer(features)
        code = torch.sigmoid(code)
        activation = self.decoder_output_layer(code)
        reconstructed = torch.sigmoid(activation)
        return reconstructed
```

Example AE



Original

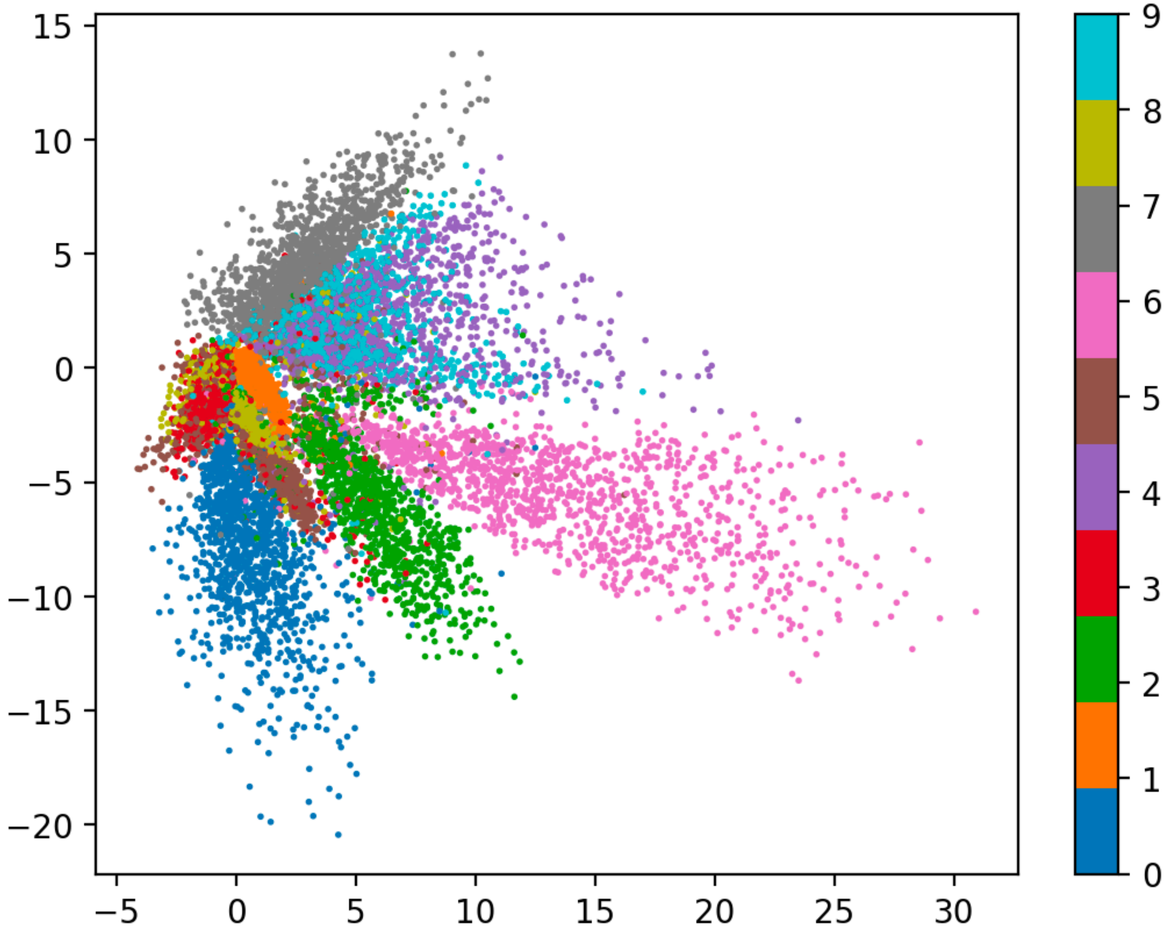
Reconstructed
k = 20

Reconstructed
k = 10

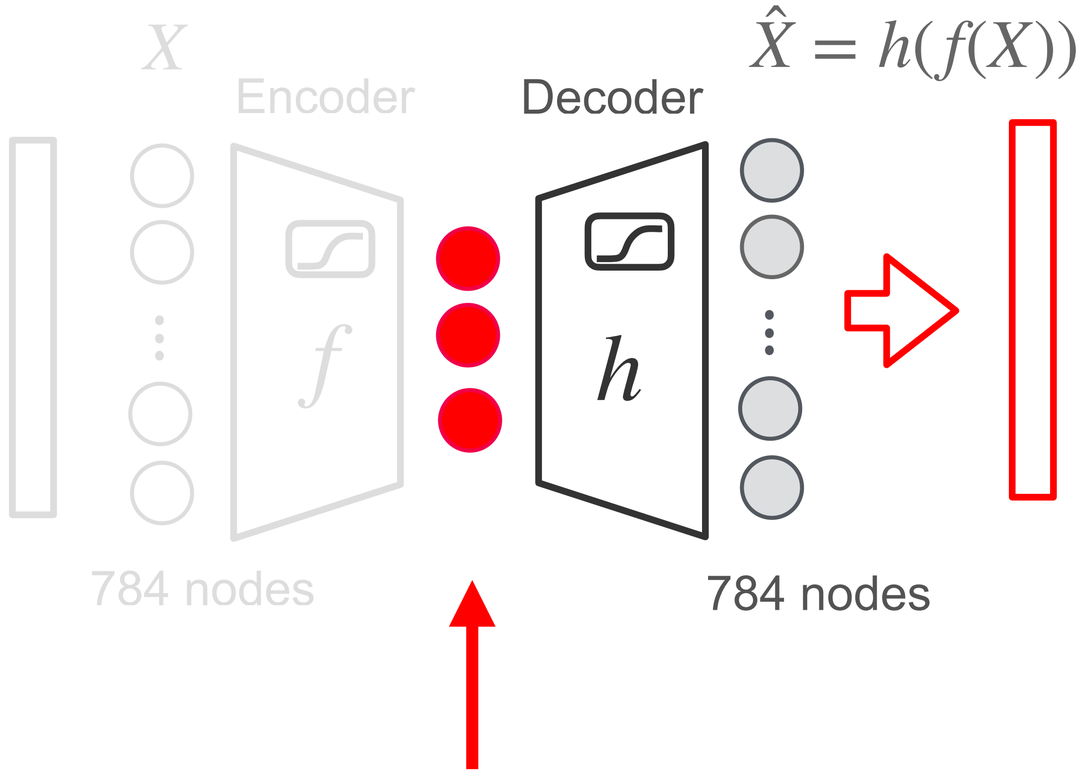
Reconstructed
k = 2

Latent space

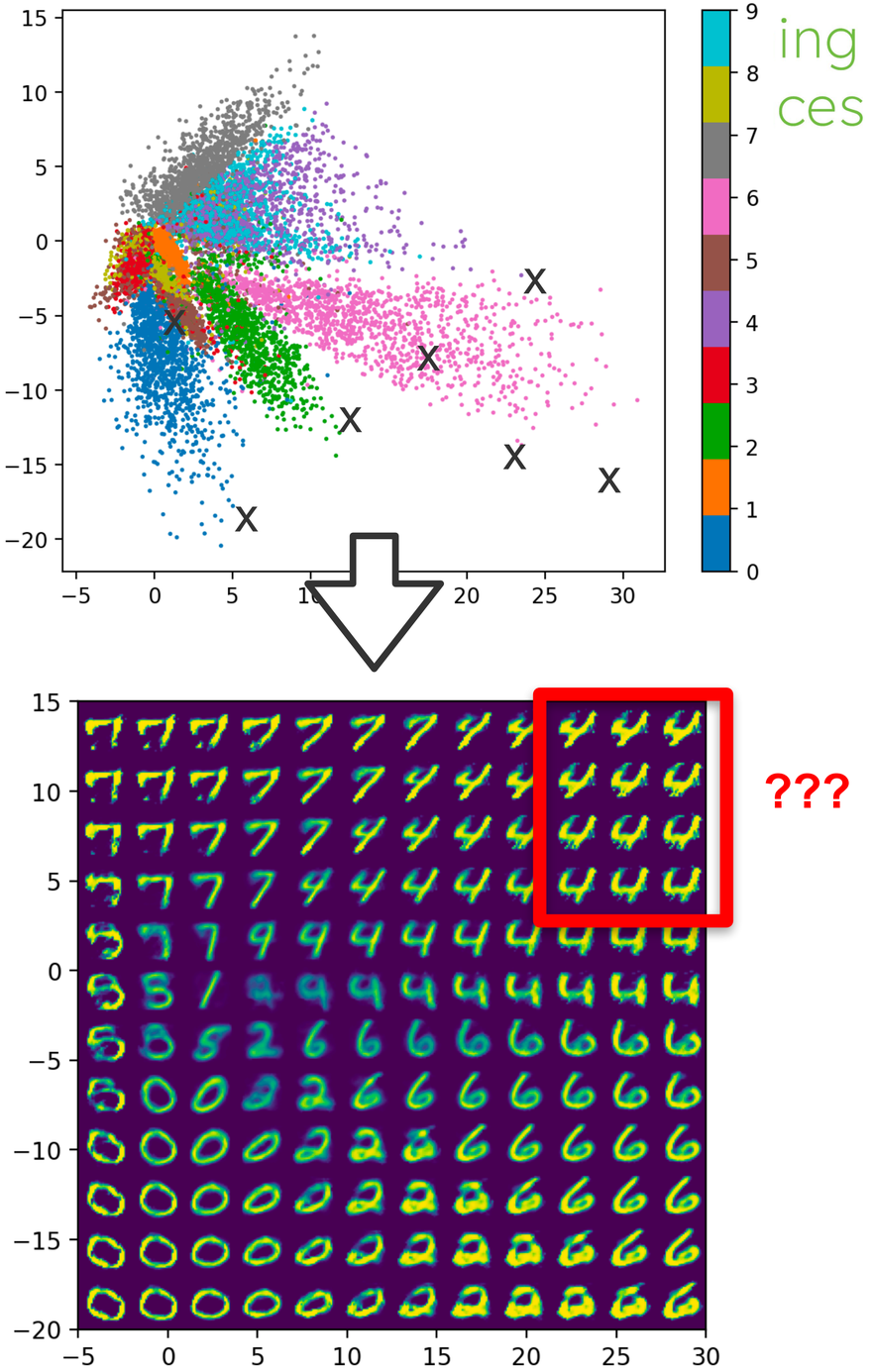
- The latent space *Z* is a lower dimensional representation of the input data *X*
- If we choose the latent dimension k=2, we can represent the input samples
- We can learn features from the latent space (bigger diversity in digit '6', digits '4' and '9' are close in latent space,...)
- even if k>2, we can project the latent space in 2d (UMAP, t-SNE,...)



Sampling from latent space

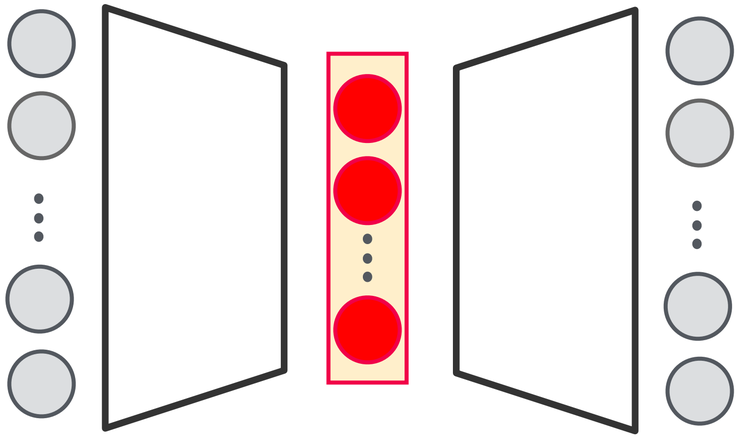


sample a random point
from the latent space

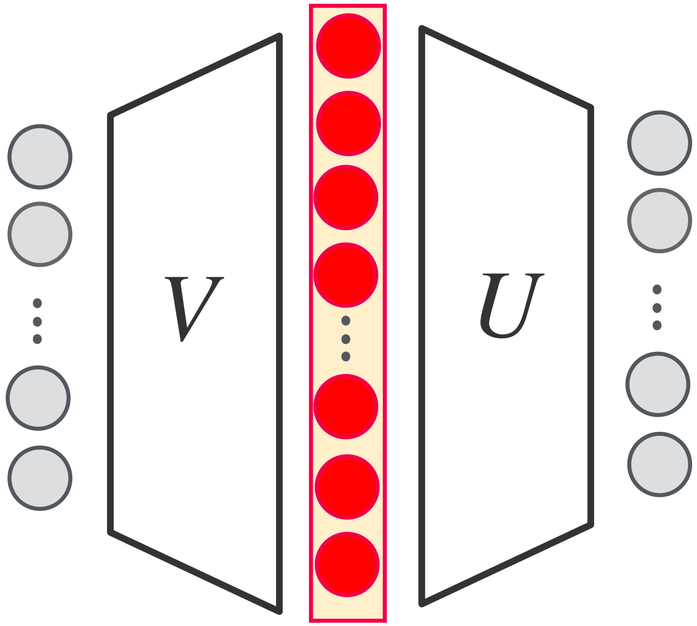


Over/Undercomplete AE

Undercomplete k < D



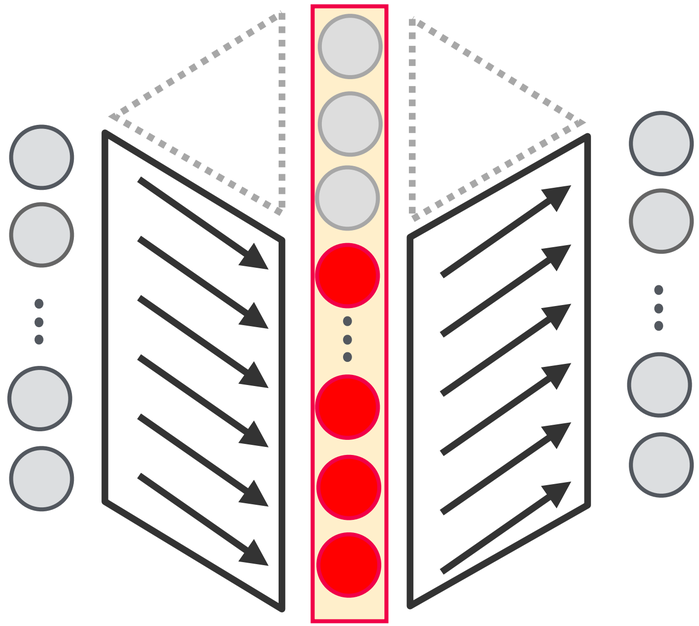
Overcomplete k > D



An overcomplete AE with linear layer could simply learn a **trivial mapping**

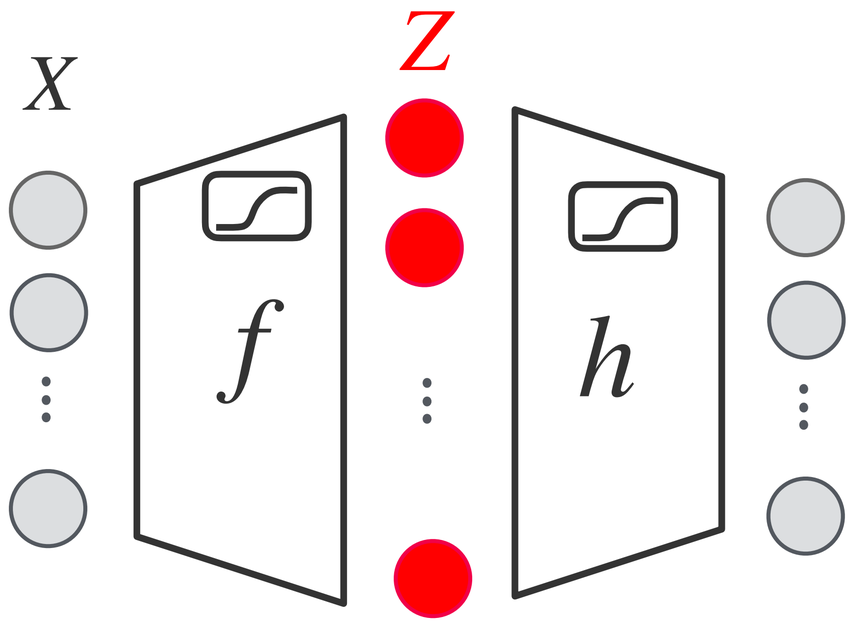
$$\hat{X} = UVX \qquad \text{with} \qquad UV = I$$

Overcomplete AE



Regularization

- To avoid learning a trivial mapping in case of overcomplete AE, we should use additional constraints
  → **regularization**
- We can apply a **sparsity** constraint
  - penalize the norm of the activation of latent nodes
  - impose a number of zero-nodes
- Adapt the **loss function**



regularization term

$$\mathscr{L} = \left\| X - h(f(X)) \right\|^2 + \lambda \cdot \Omega(Z) \qquad (\Omega \geq 0)$$

λ is a **hyperparameter**

Regularization

$$L = \|X - h(f(X))\|^2 + \lambda \cdot \Omega(Z) \qquad (\Omega \geq 0)$$

$\Omega(Z) = Z_{L1/L2}$ with  or 

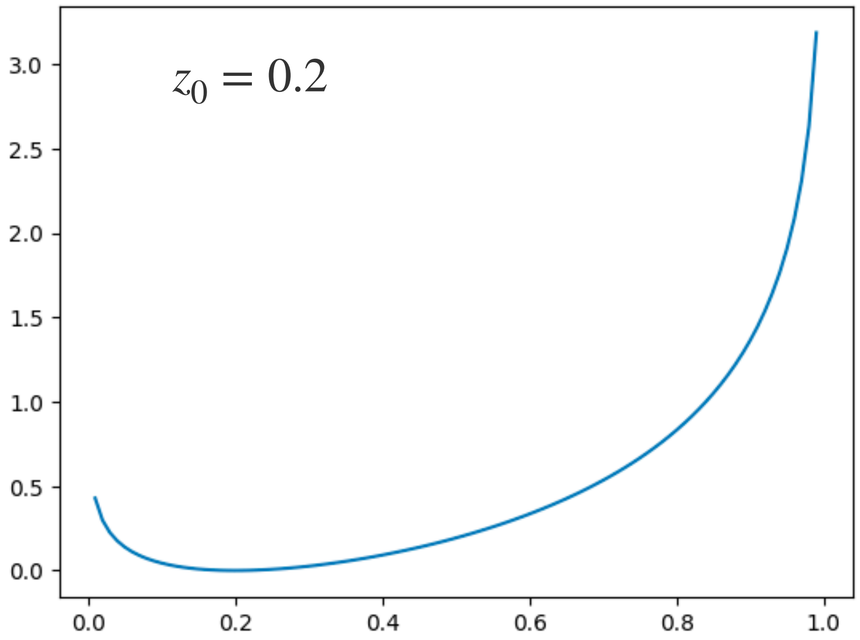
- **Sigmoid** activation function will lead to small values for the latent nodes (~ ridge regression)
- **ReLU** activation function will lead to zero latent nodes (~ LASSO regression)

Regularization

$$L = \|X - h(f(X))\|^2 + \lambda \cdot \Omega(Z) \qquad (\Omega \geq 0)$$

$$\Omega(Z) = \sum_{i=1}^{k} z_0 \log \frac{z_0}{z_i} + (1 - z_o) \log \frac{1 - z_0}{1 - z_i}$$

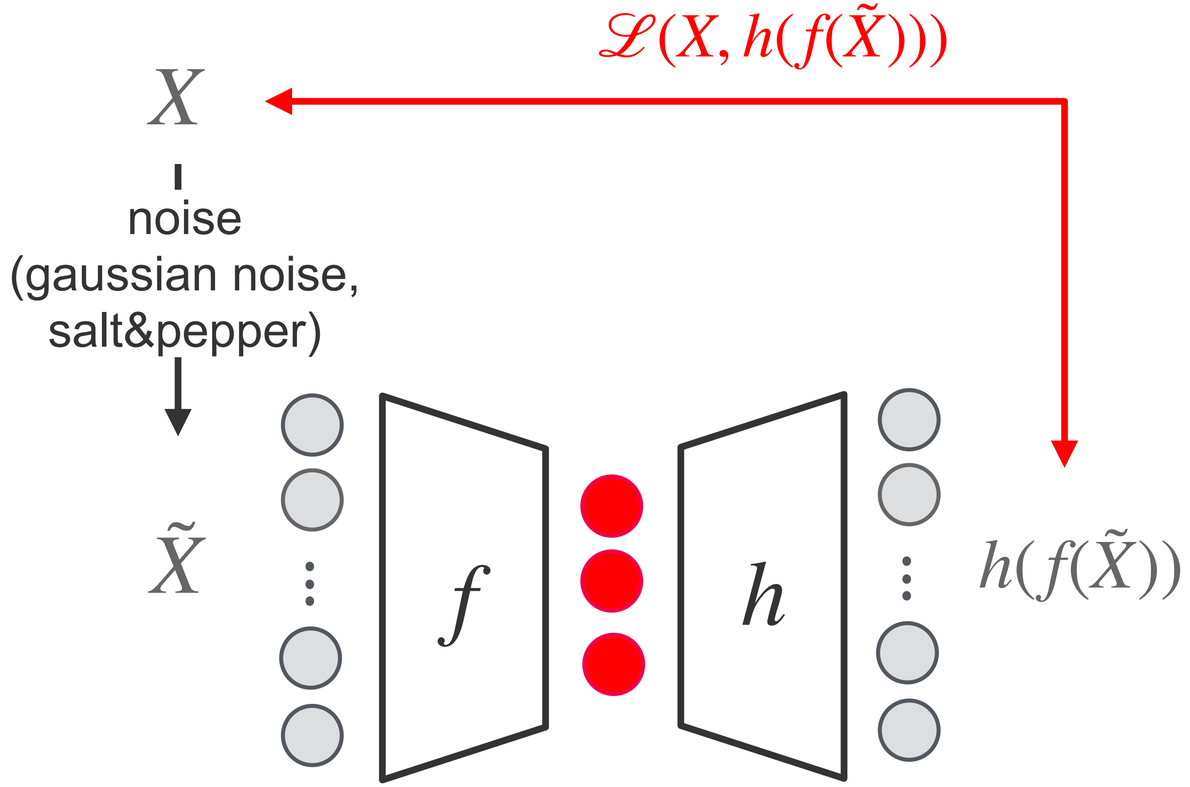
- z_0 is a small fixed value
- z_i is the average activation over training sample
- term is similar to the **Kullback-Leibler** divergence
- $\Omega(Z) = 0$ when $z_i = z_0$



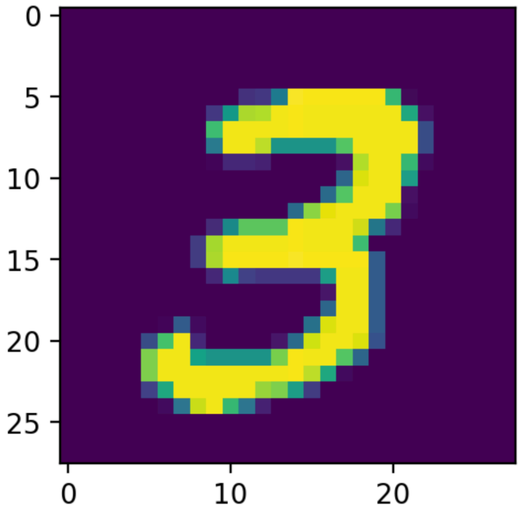
Denoising Autoencoders

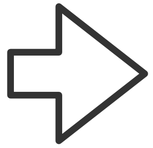
- Autoencoders are usually build to reconstruct the original input X using a loss function $\mathscr{L}(X, h(f(X)))$

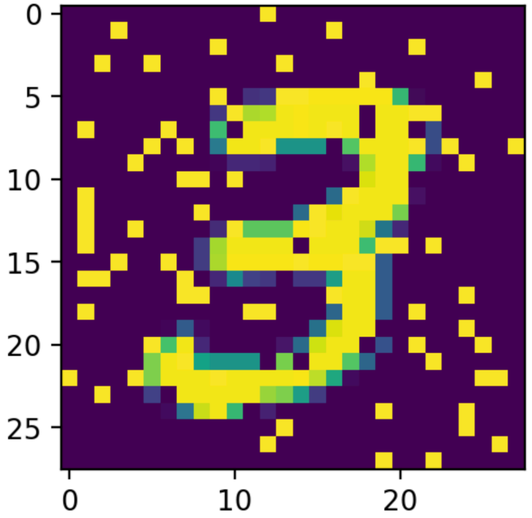
- **Denoising autoencoders** are trained to reconstruct the original image X starting from a **corrupted version** $\tilde{X}$ of the original input with a loss function $\mathscr{L}(X, h(f(\tilde{X})))$



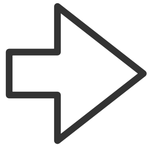
Denoising Autoencoders

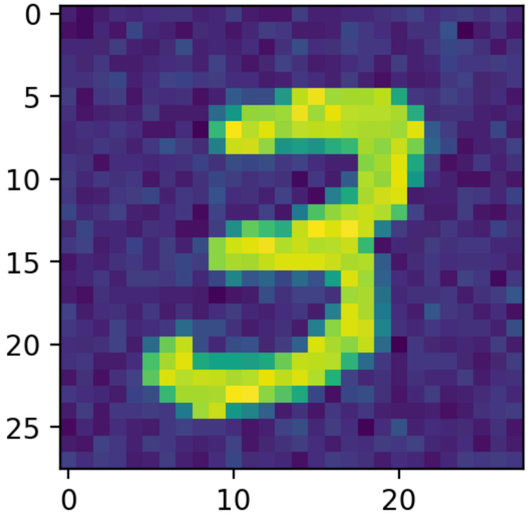






put random pixels to max value ('salt')
or min value ('pepper')





add gaussian noise to all pixels

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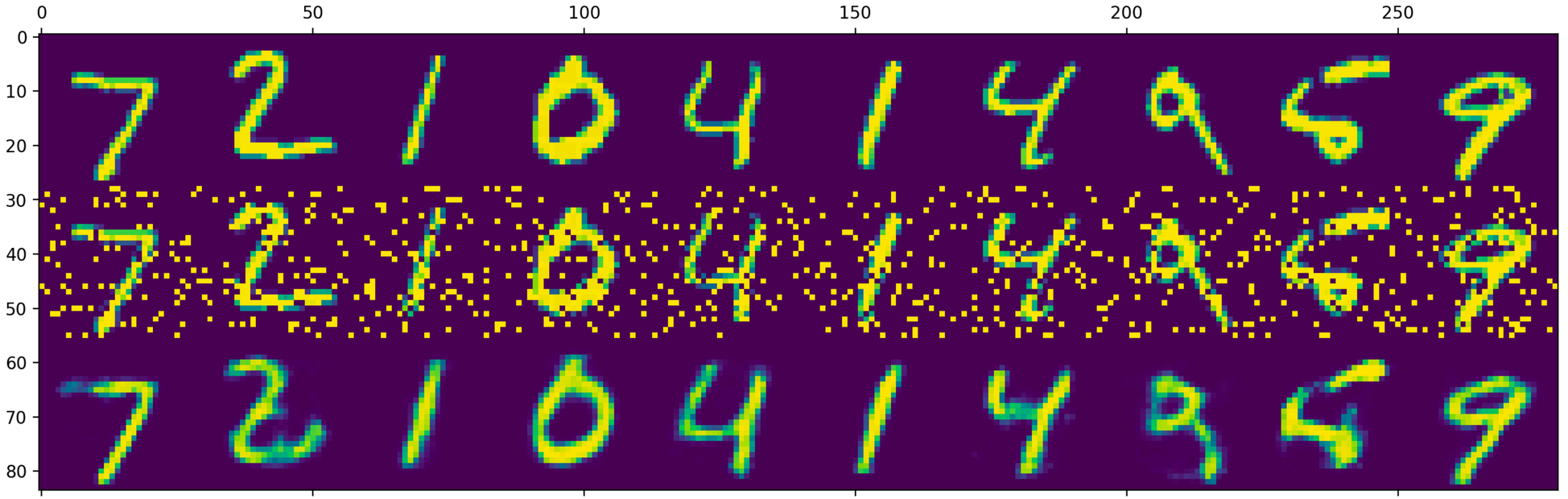


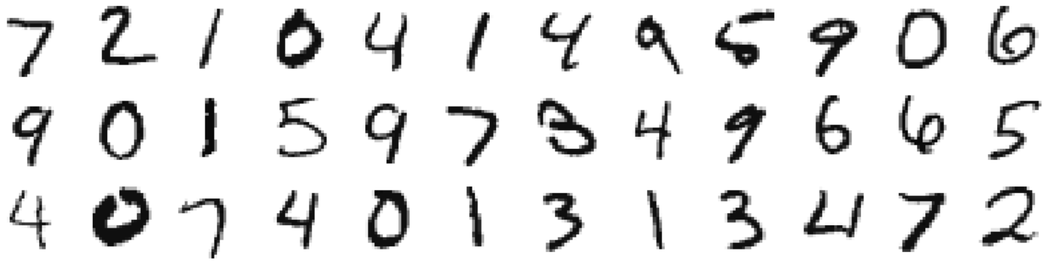
Original test set

Noisy test set
(10% salt'npepper)

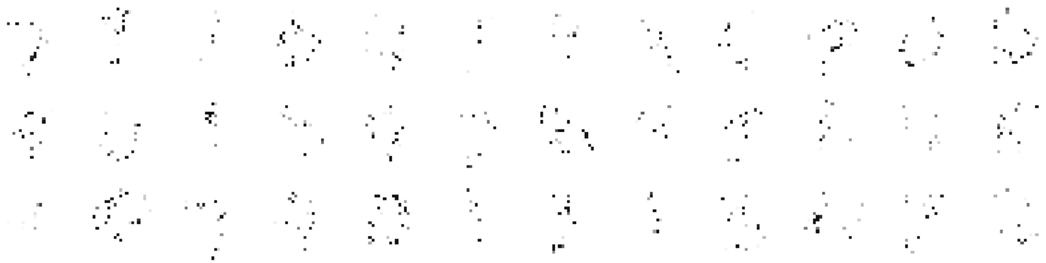
Reconstructed
test set

Example of reconstruction

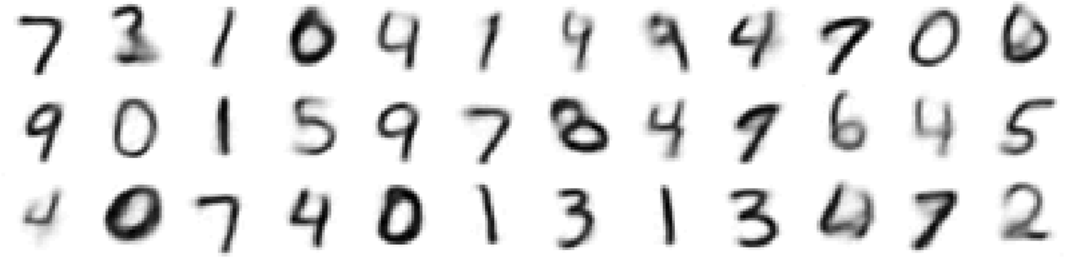
Original test set



Noisy test set
(90% pixel deletion)



Reconstructed test set



Can you spot the mistakes and understand why?

[François Fleuret]

DeepLearning
inLifeSciences

3 - Variational Autoencoders

Limitations of autoencoders

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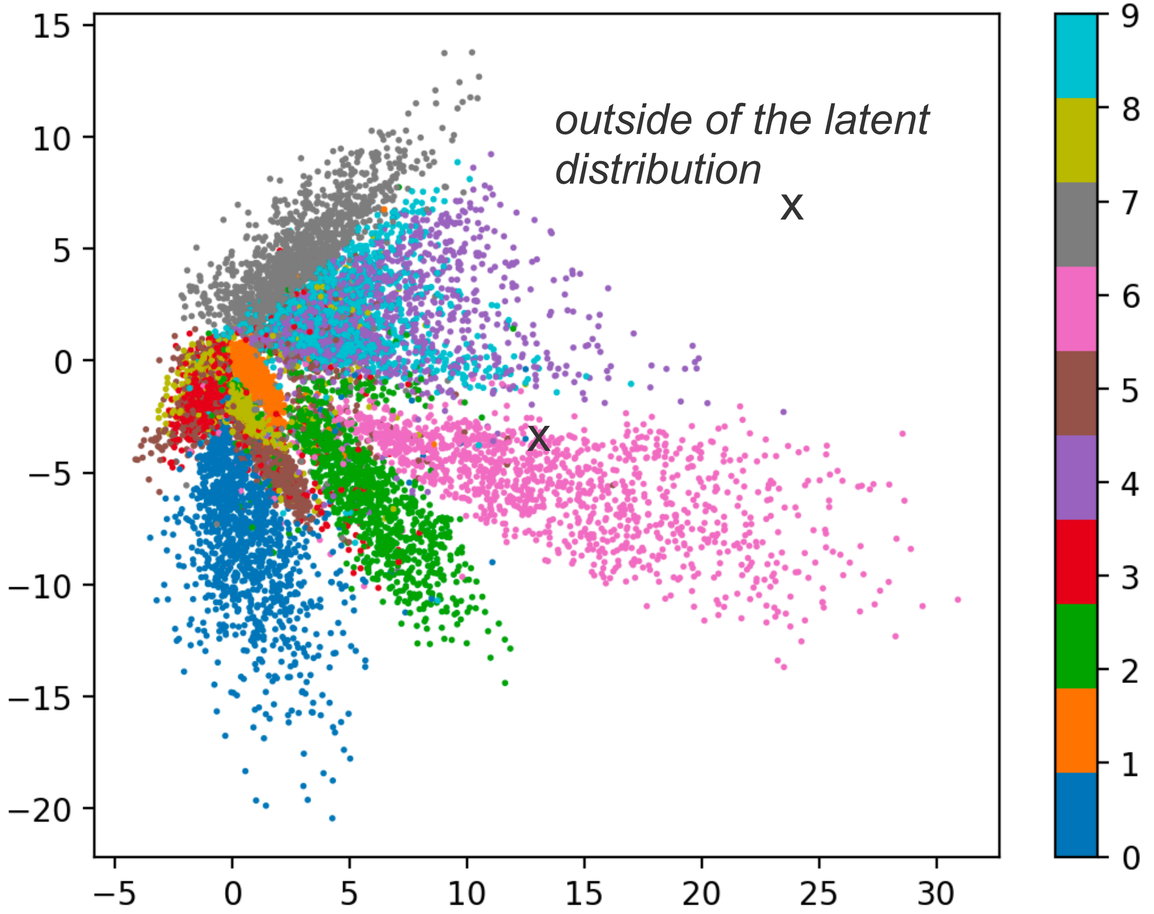
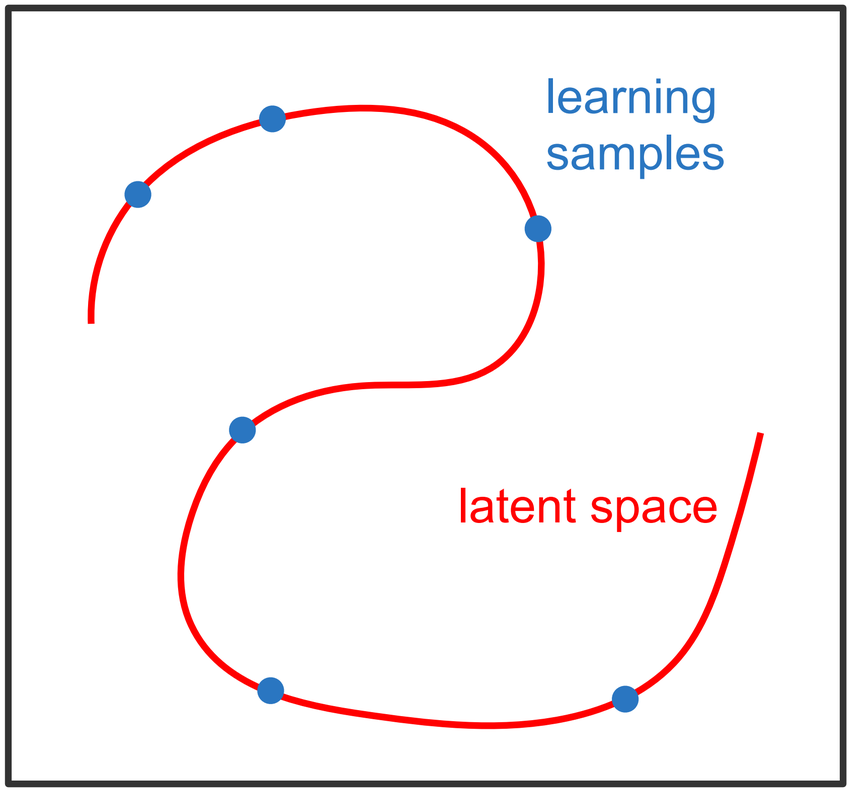
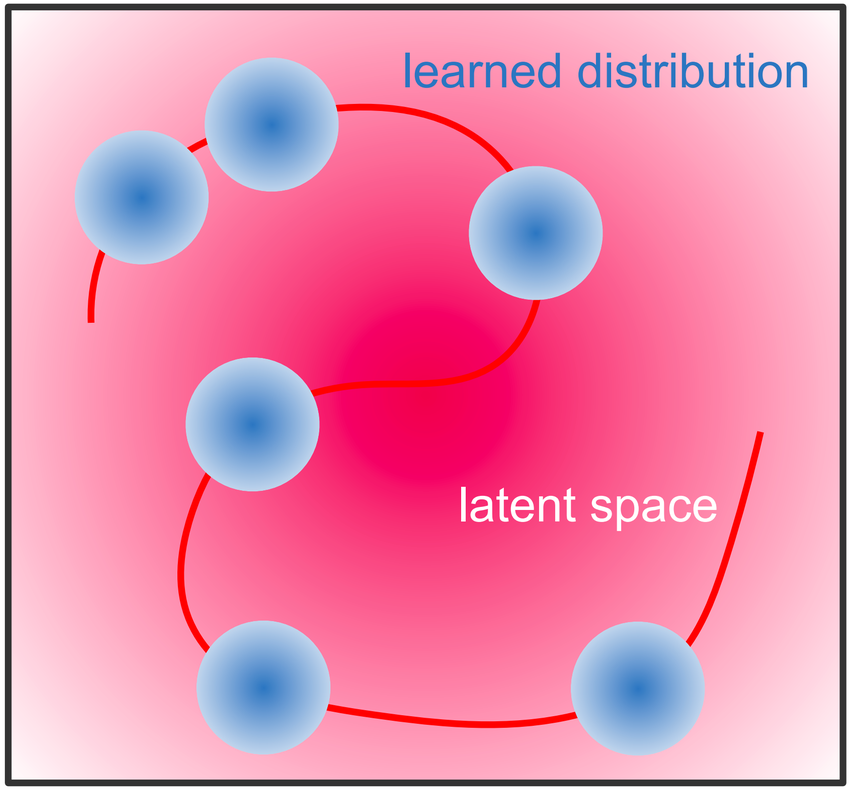
- Autoencoders define an embedding ('latent space') in a deterministic way
- The learned latent space has **zero measure** (almost all of the points in the latent space do not correspond to the data distribution)
- Hence, we **cannot sample new datapoints**, as we do not know the latent distribution
- Autoencoders are not generative models
  → **Variational autoencoders**



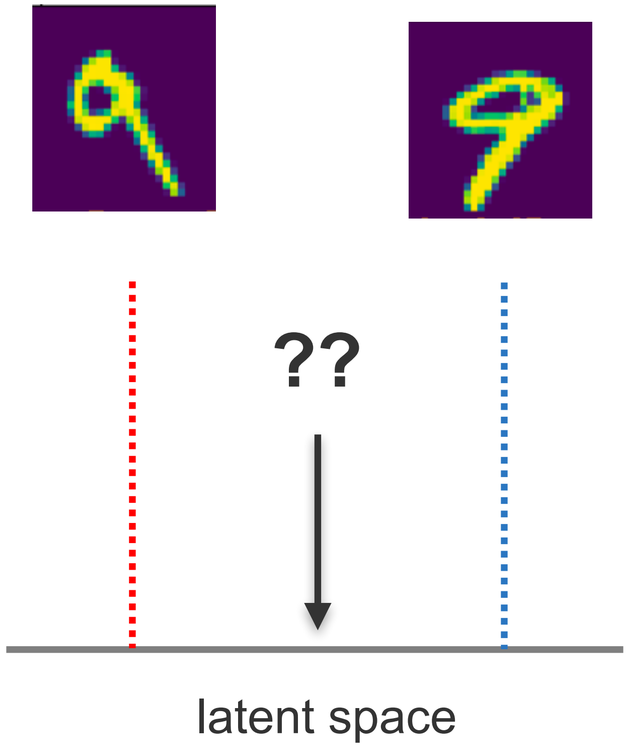
Limitations of autoencoders

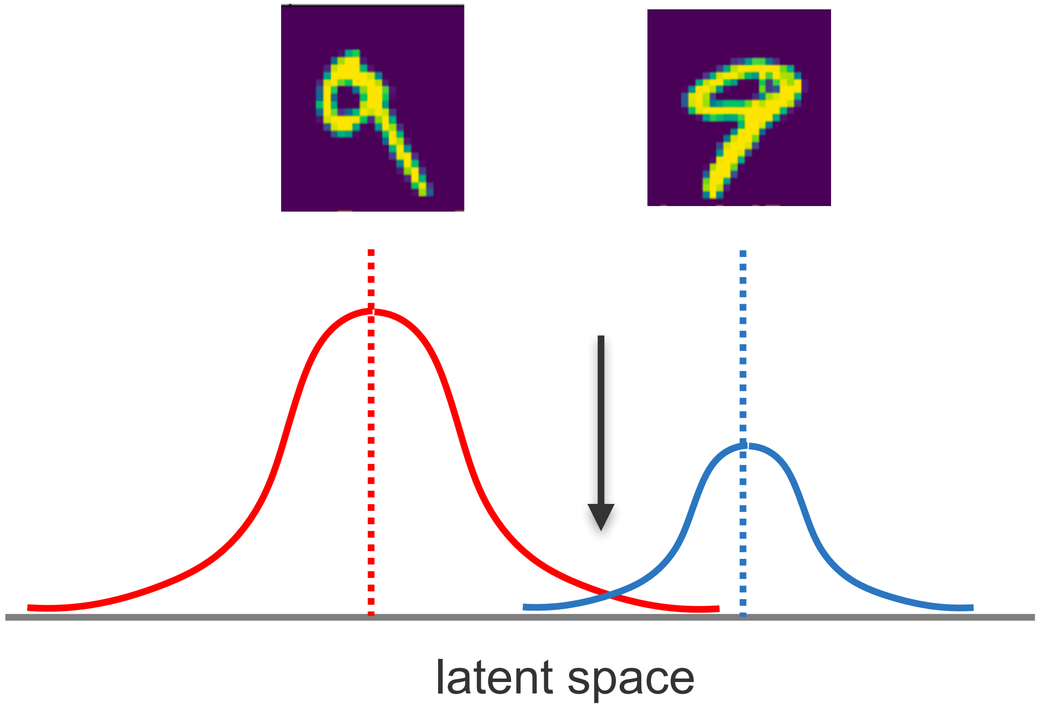


autoencoder



variational autoencoder





- Autoencoders make **point-estimates** of the training samples
- VAEs learn a **probability distribution**

Variational autoencoder

- We define a **prior probability distribution** on the latent space

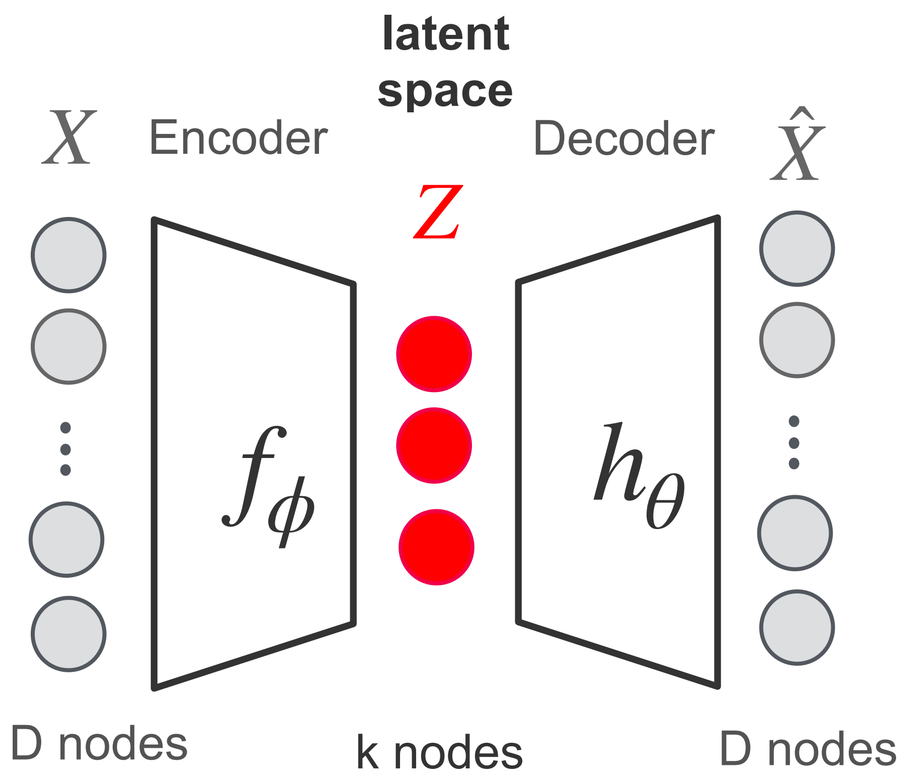
$$p(Z)$$

- The latent space is now sampled from a **posterior distribution**

$$Z \sim q_\phi(Z \mid X)$$

- New data points are then generated

$$\hat{X} \sim p_\theta(X \mid Z)$$

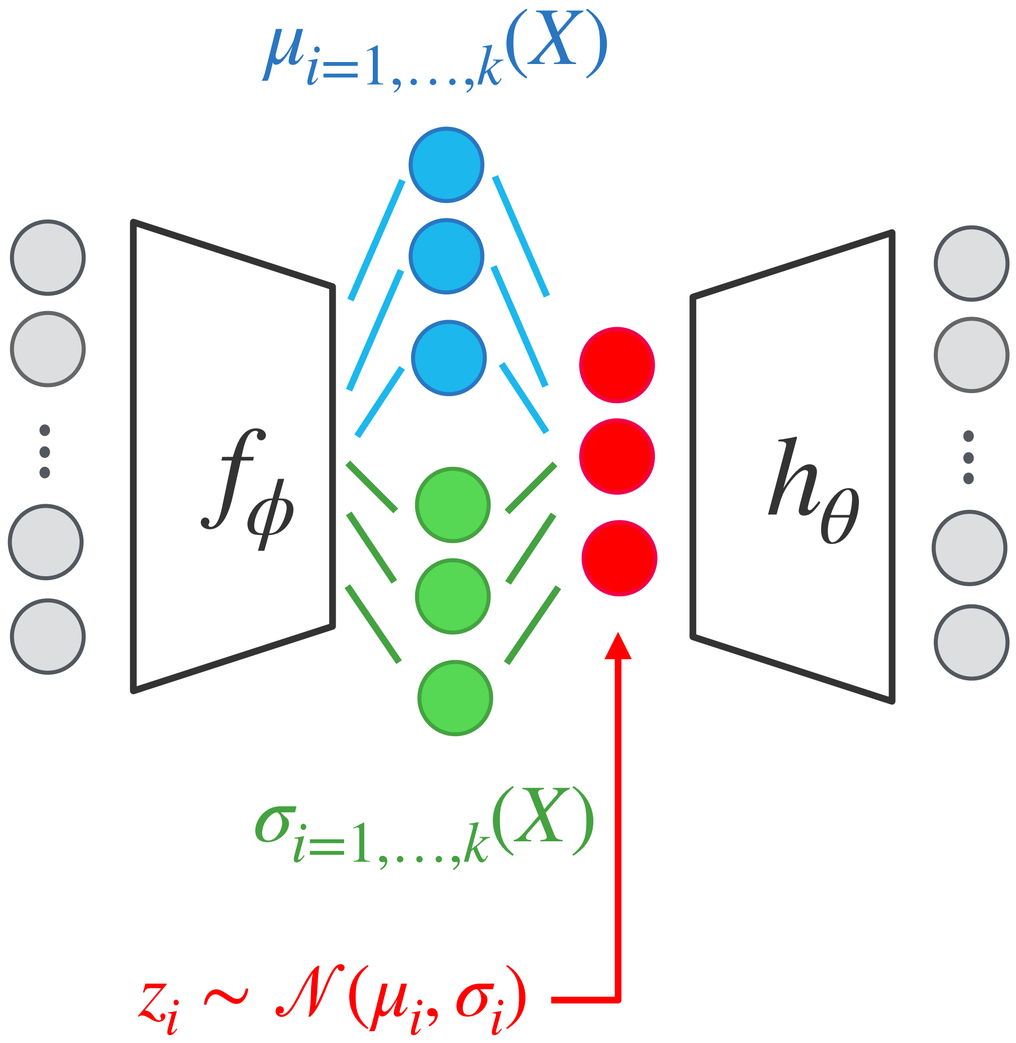


Variational autoencoder

- The model learns the parameters μ and σ of normal distributions

$$Z \ : \ z_i \sim \mathcal{N}(\mu_i, \sigma_i)$$

- New samples can be generated by sampling from the normal distribution
- VAEs belong to the class of **generative models**
- Beware that they are non-deterministic!



Loss function

DeepLearning inLifeSciences

- Let us look at the **loss function** that need to be minimized during training of a VAE

$$\mathcal{L}_{VAE} = \sum_{i=1}^{N} \left(-\mathbb{E}_{Z^i \sim q_\phi(Z^i \mid X^i)} \left(\log p_\theta(X^i \mid Z^i) \right) + KL[q_\phi(Z^i \mid X^i) \,\|\, p(Z^i)] \right)$$

- The left term is the **log-likelihood** of the data X^i given the latent variable Z^i sampled from the distribution $q_\phi(Z^i \mid X^i)$
- This term will tend to push the reconstructed X^i towards the input vector X^i
- This is equivalent to the **reconstruction error** of the loss term in the AE

Loss function

DeepLearning inLifeSciences

- Let us look at the **loss function** that need to be minimized during training of a VAE

$$\mathscr{L}_{VAE} = \sum_{i=1}^{N} \left(-\mathbb{E}_{Z^i \sim q_\phi(Z^i \mid X^i)} \left(\log p_\theta(X^i \mid Z^i) \right) + KL[q_\phi(Z^i \mid X^i) \,\|\, p(Z^i)] \right)$$

- The right term is the **Kullback-Leibler divergence**, with $p(Z^i) \sim \mathcal{N}(0,1)$ the prior distribution of the latent variables
- KL divergence is always non-negative; it is zero if both distribution are equal
- This term forces $q_\phi(Z^i \mid X^i)$ to be 'not too far' from a standard normal distribution $\mathcal{N}(0,1)$

Kullback-Leibler divergence

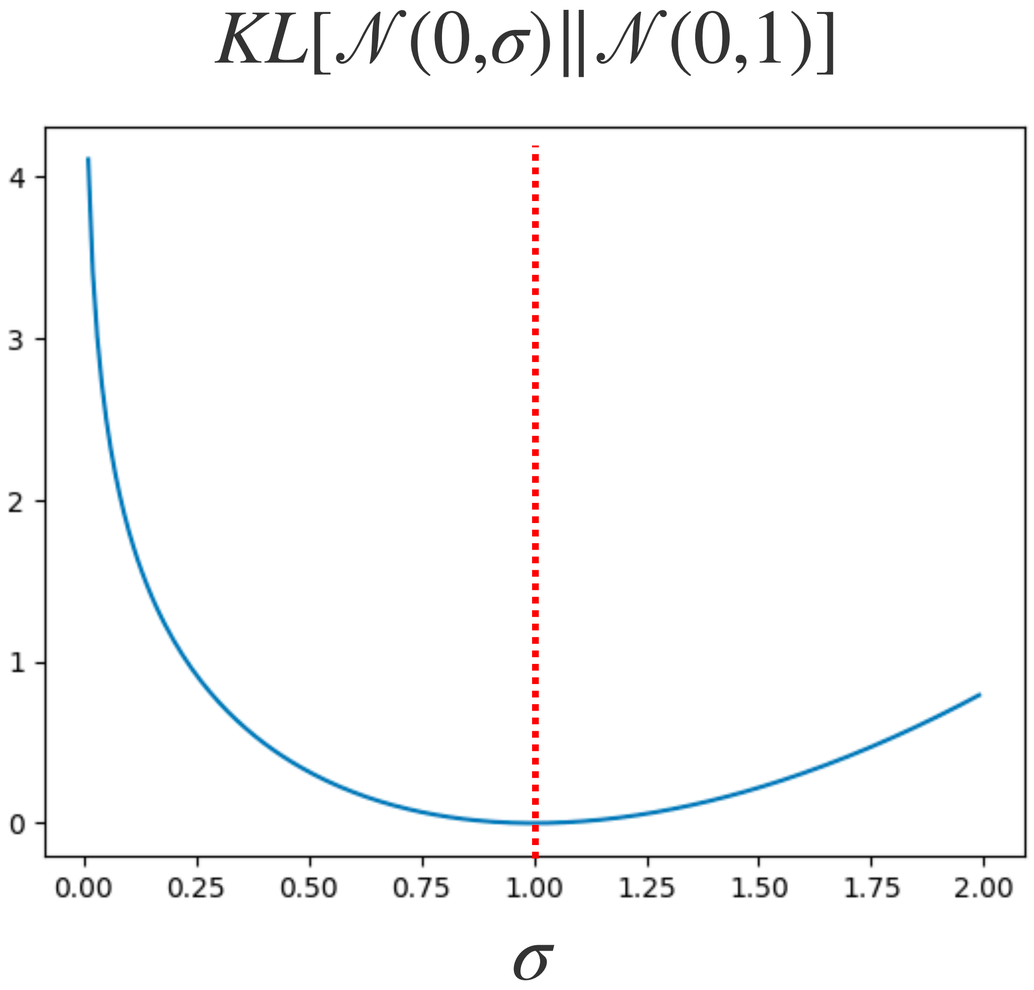
DeepLearning inLifeSciences

$$KL[p\|q] = \sum_x p(x) \log \frac{p(x)}{q(x)}$$

Note that the KL is not symmetric!

- The KL-divergence is **zero** when the 2 distributions are equal; otherwise KL > 0
- if $p \sim \mathcal{N}(\mu_0, \sigma_0)$ and $q \sim \mathcal{N}(\mu_1, \sigma_1)$, then $KL[p\|q] = \log \frac{\sigma_1}{\sigma_0} + \frac{\sigma_0^2 + (\mu_0 - \mu_1)^2}{2\sigma_1^2} - \frac{1}{2}$
- if $p \sim \mathcal{N}(\mu, \sigma)$ and $q \sim \mathcal{N}(0,1)$, then $KL[p\|q] = -\log \sigma + \frac{1}{2}\mu^2 + \frac{1}{2}\sigma^2 - \frac{1}{2}$
- Note that for $\sigma \to 0$ we have $KL \to +\infty$

Kullback-Leibler divergence



Training a VAE

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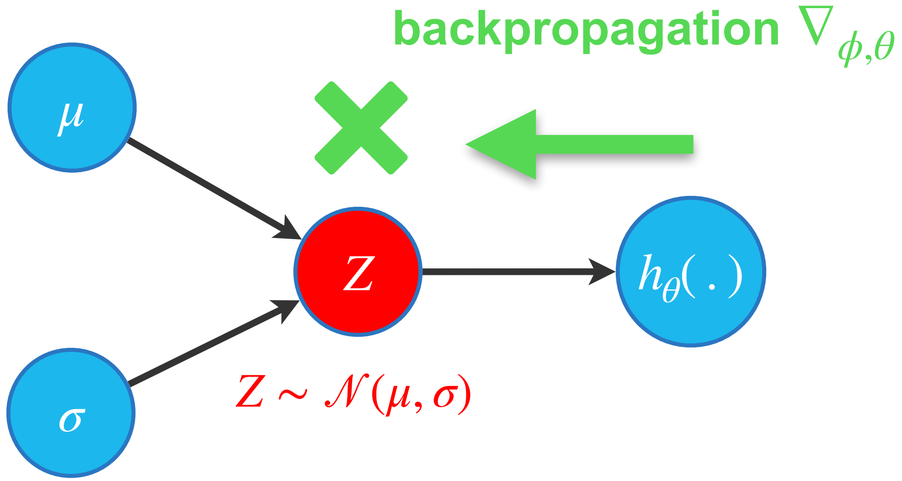
- In order to train the VAE, we need to update the parameters θ, ϕ using backpropagation
- This implies computing the gradient of the loss function $\mathscr{L}$: $\nabla_{\phi,\theta}\mathscr{L}$
- However, this is computationally challenging due to the probabilistic nature of VAEs
- Hence, we need to apply the **reparametrization trick**

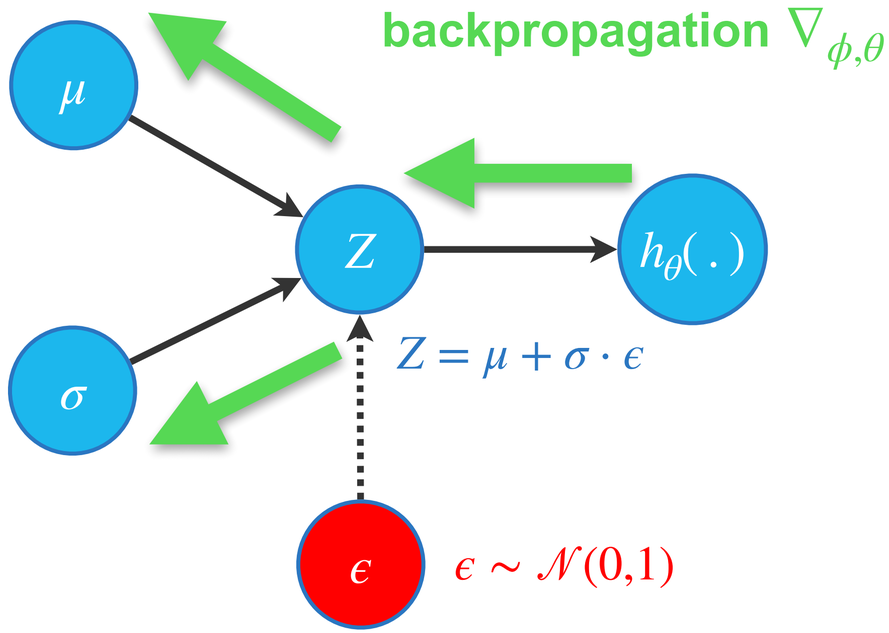
"Reparametrization trick"

DeepLearning inLifeSciences

without reparametrization



with reparametrization



= deterministic variable

= random variable

= dependent on ϕ, θ

= independent of ϕ, θ

A bit of math....

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- Remember the following formula for the **expectation**

$$\mathbb{E}_{z\sim q(z)}\left(f(z)\right) = \int_z q(z) f(z)\, dz$$

- Expectations can be evaluated using **Monte-Carlo simulation**, i.e. by averaging over training samples (mean = unbiased estimator of expectation)

$$\mathbb{E}_{z\sim q(z)}\left(f(z)\right) \approx \frac{1}{L}\sum_{i=1}^{L} q(z_i) f(z_i)$$

- Backpropagation requires to compute the **gradient** of the loss function w.r.t. the model parameters: $\nabla_{\phi,\theta}\mathscr{L}$

"Reparametrization trick" (quick version)

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- Without reparametrization:
  the gradient of the expectation term is no longer an expectation
  → cannot be estimated using Monte-Carlos simulation!

$$\nabla_{\phi,\theta}\mathbb{E}(\dots) \neq \mathbb{E}(\dots)$$

- With reparametrization trick:
  gradient of the expectation term in the loss function is an expectation itself
  → can be estimated using Monte-Carlo simulation!

$$\nabla_{\phi,\theta}\mathbb{E}(\dots) = \mathbb{E}(\dots) = \frac{1}{L}\sum_{i=1}^{L}(\dots)$$

"Reparametrization trick"

DeepLearning inLifeSciences

- Remember we need to minimize this loss function

$$\mathcal{L} = \mathcal{L}_1 + \mathcal{L}_2 = -\mathbb{E}_{Z\sim q_\phi(Z\ X)}\left(\log p_\theta(X\ \ Z)\right) - KL[q_\phi(Z\ \ X)\,\|\,p(Z)]$$

- We need to compute the gradient $\nabla_{\phi,\theta}$ of this function; let's focus on the first term

$$\nabla_{\phi,\theta}\mathcal{L}_1 = -\nabla_{\phi,\theta}\mathbb{E}_{Z\sim q_\phi(Z\ X)}(\log p_\theta(X\ \ Z)) = -\nabla_{\phi,\theta}\left(\int_Z q_\phi(Z\ \ X)\,p_\theta(X\ \ Z)\,dZ\right)$$

$$= \boxed{-\int_Z (\nabla_{\phi,\theta} q_\phi(Z\ \ X))\,p_\theta(X\ \ Z)\,dZ} \boxed{-\int_Z q_\phi(Z\ \ X))\,\nabla_{\phi,\theta} p_\theta(X\ \ Z)\,dZ}$$

this is NOT an expectation
and cannot be simply evaluated...

$$= -\mathbb{E}_{Z\sim q_\phi(Z\ X)}\left(\nabla_{\phi,\theta}\log p_\theta(X\ \ Z)\right)$$

this is an expectation and
can be computed through Monte-Carlo
(= taking the mean over training samples)

"Reparametrization trick"

DeepLearning inLifeSciences

- The trick consists in writing $Z = \mu_\phi(X) + \sigma_\phi(X) \cdot \epsilon = g_\phi(\epsilon, X)$ with $\epsilon \sim p(\epsilon) = \mathcal{N}(0,1)$
- we can now replace Z in the previous equations with $g_\phi(\epsilon, X)$

$$\nabla_{\phi,\theta}\mathcal{L}_1 = -\nabla_{\phi,\theta}\mathbb{E}_{\epsilon\sim\mathcal{N}(0,1)}(\log p_\theta(X \mid g_\phi(\epsilon, X)) = -\nabla_{\phi,\theta}\left(\int_\epsilon p(\epsilon)\, p_\theta(X \mid g_\phi(\epsilon, X))\, d\epsilon\right)$$

$$= -\int_\epsilon p(\epsilon)\, \nabla_{\phi,\theta} p_\theta(X \mid g_\phi(\epsilon, X))\, d\epsilon = -\mathbb{E}_{\epsilon\sim\mathcal{N}(0,1)}\left(\nabla_{\phi,\theta}\log p_\theta(X \mid g_\phi(\epsilon, X))\right)$$

this is an expectation and
can be computed through Monte-Carlo !

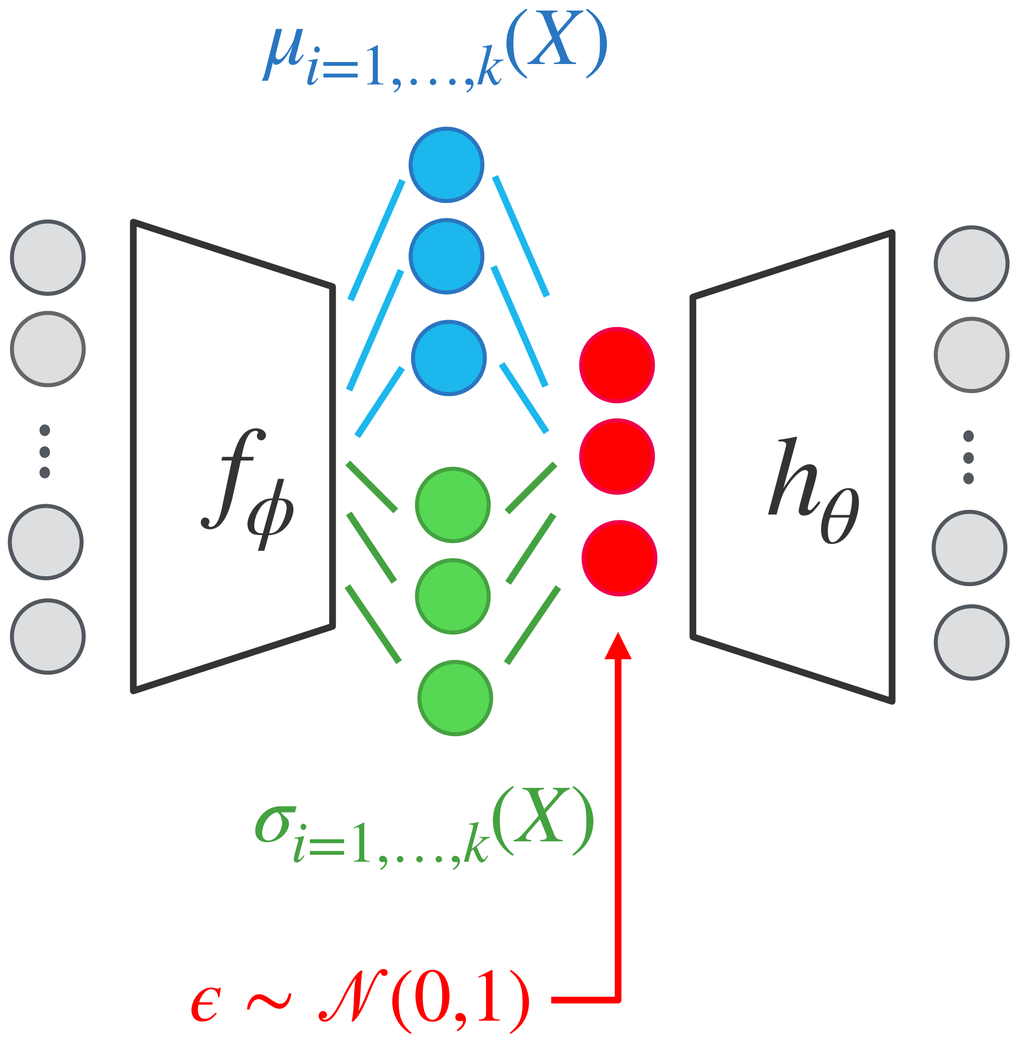
- The KL term can be computed analytically; hence the gradient of the KL term can be computed analytically without need to estimate it through Monte-Carlo

Variational autoencoder

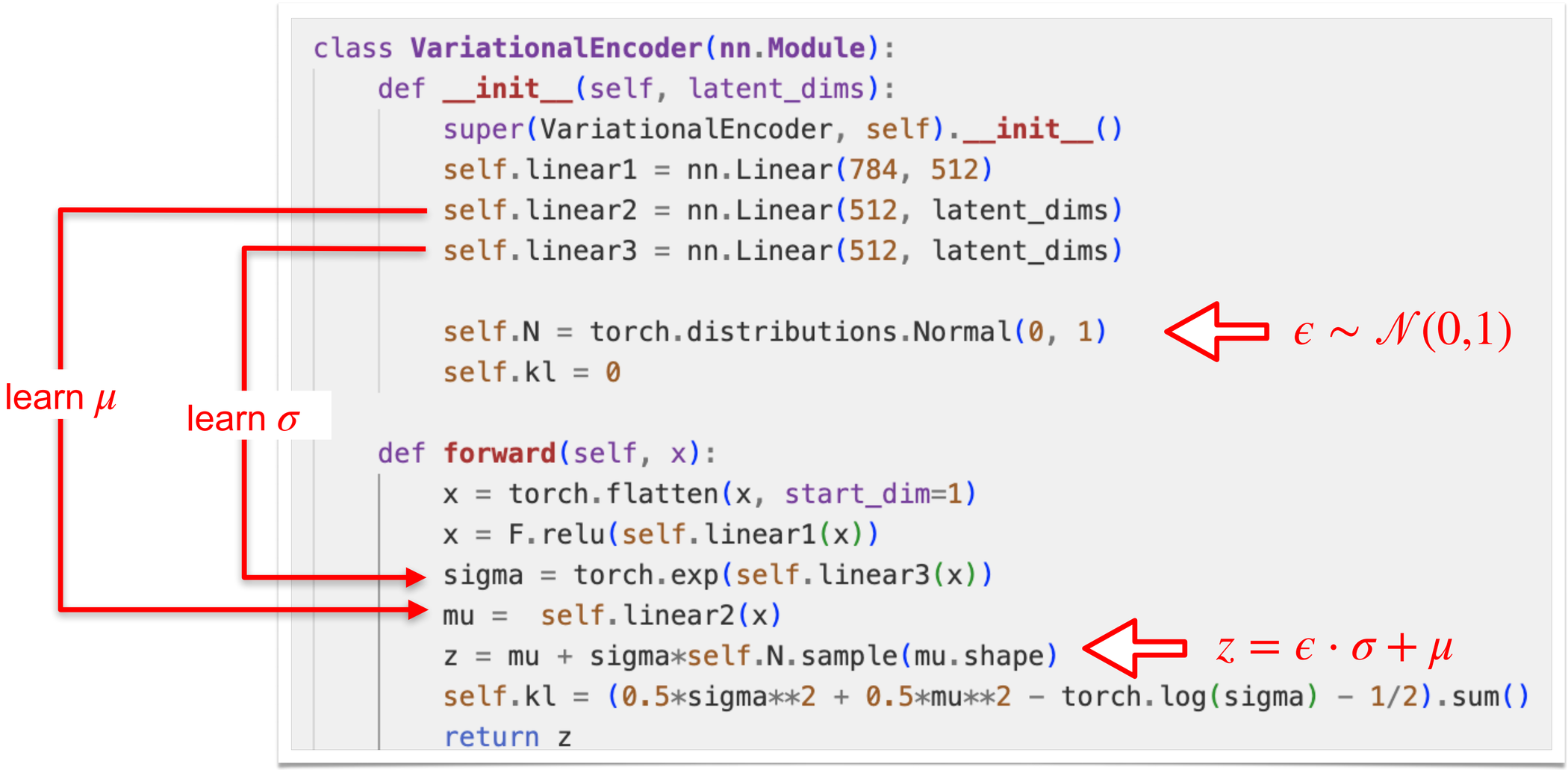
- In order to be able to perform the backpropagation (using the gradients), we need to apply the **reparametrization trick**

$$Z \ : \ z_i = \mu_i + \epsilon \cdot \sigma_i$$

- Using this trick, gradients can be computed as the random variable ϵ does not depend on the parameters ϕ, θ of the network



Implementation




```python
class VariationalEncoder(nn.Module):
    def __init__(self, latent_dims):
        super(VariationalEncoder, self).__init__()
        self.linear1 = nn.Linear(784, 512)
        self.linear2 = nn.Linear(512, latent_dims)
        self.linear3 = nn.Linear(512, latent_dims)

        self.N = torch.distributions.Normal(0, 1)
        self.kl = 0

    def forward(self, x):
        x = torch.flatten(x, start_dim=1)
        x = F.relu(self.linear1(x))
        sigma = torch.exp(self.linear3(x))
        mu =  self.linear2(x)
        z = mu + sigma*self.N.sample(mu.shape)
        self.kl = (0.5*sigma**2 + 0.5*mu**2 - torch.log(sigma) - 1/2).sum()
        return z
```

VAE latent space

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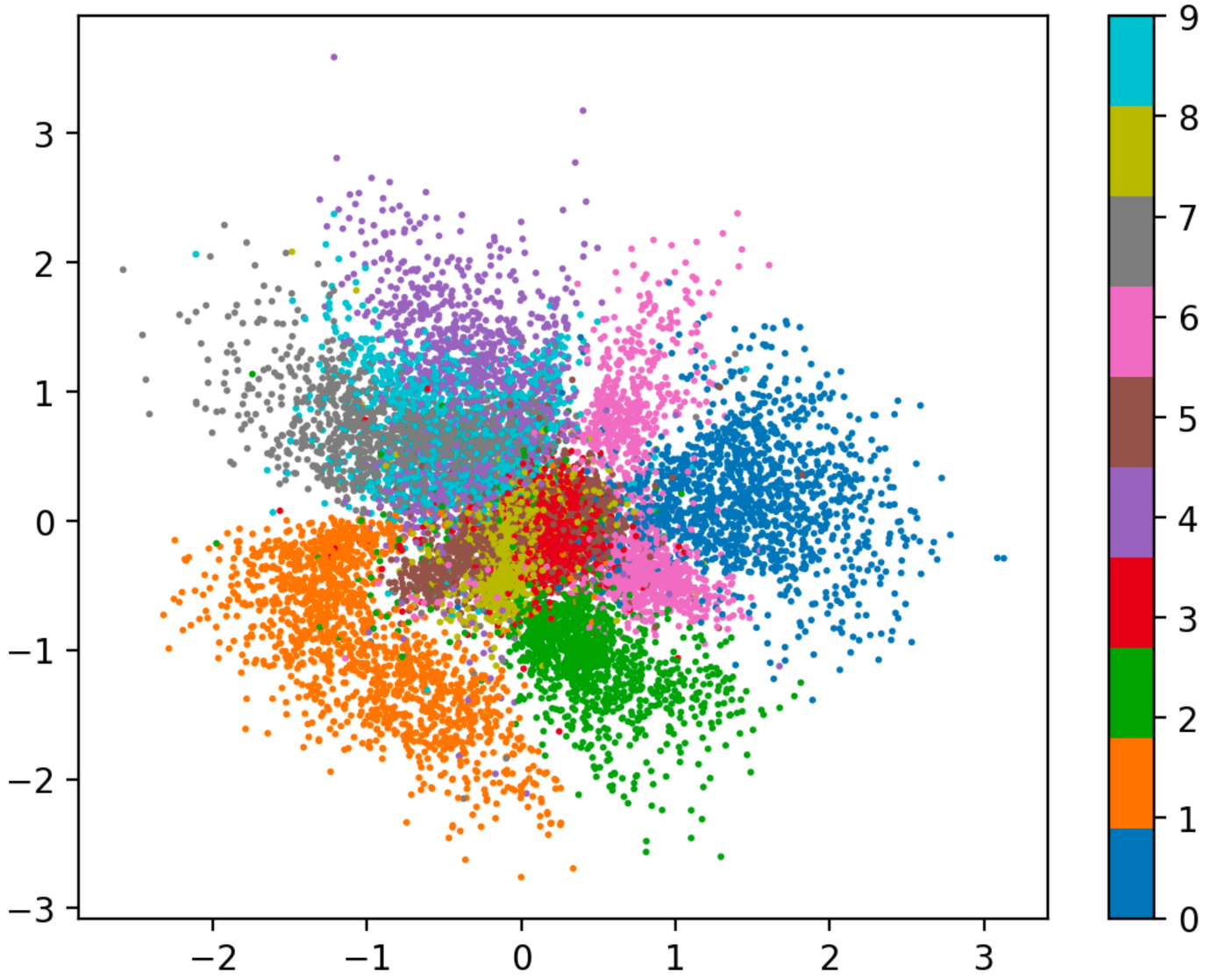

Sampling from latent space

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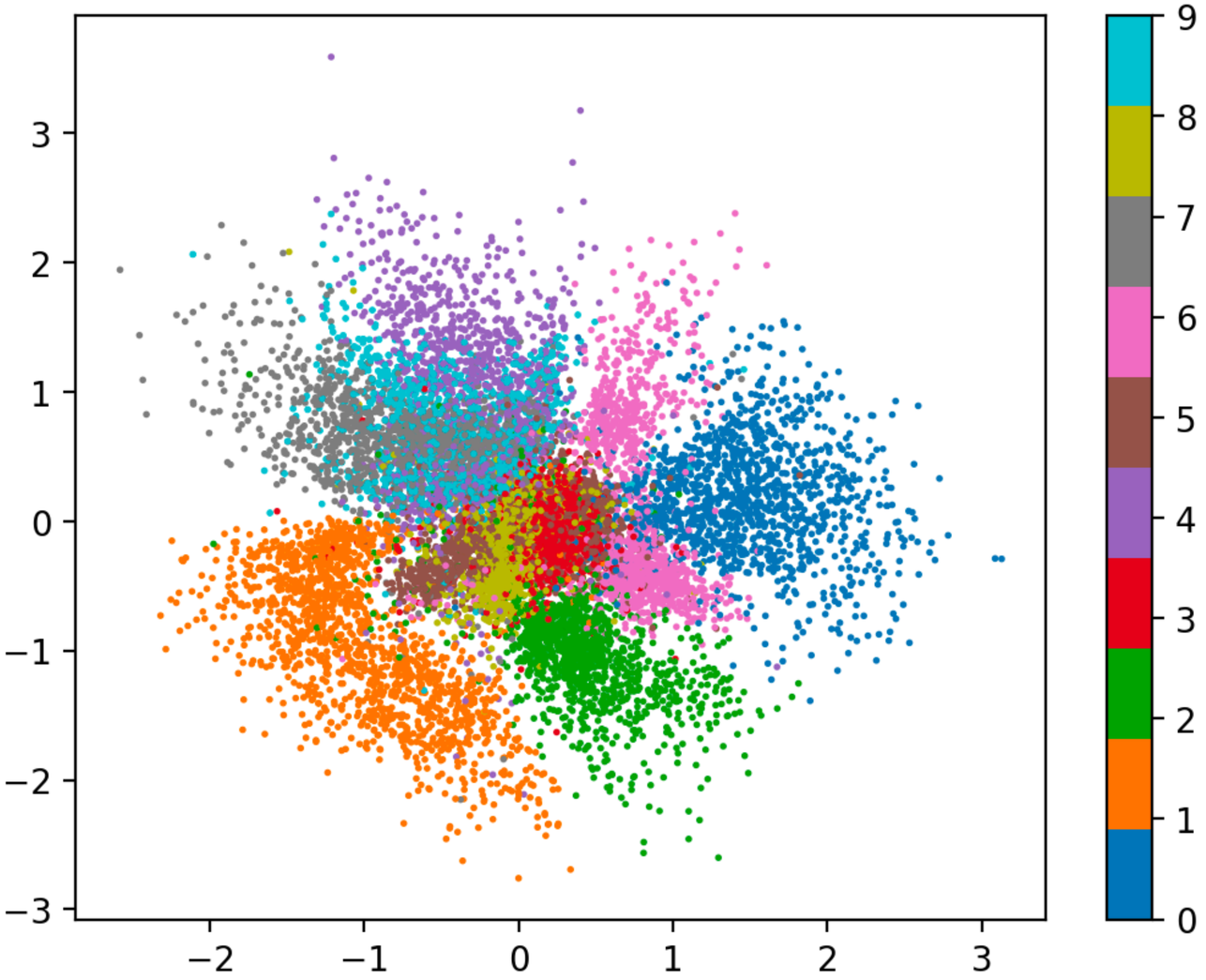

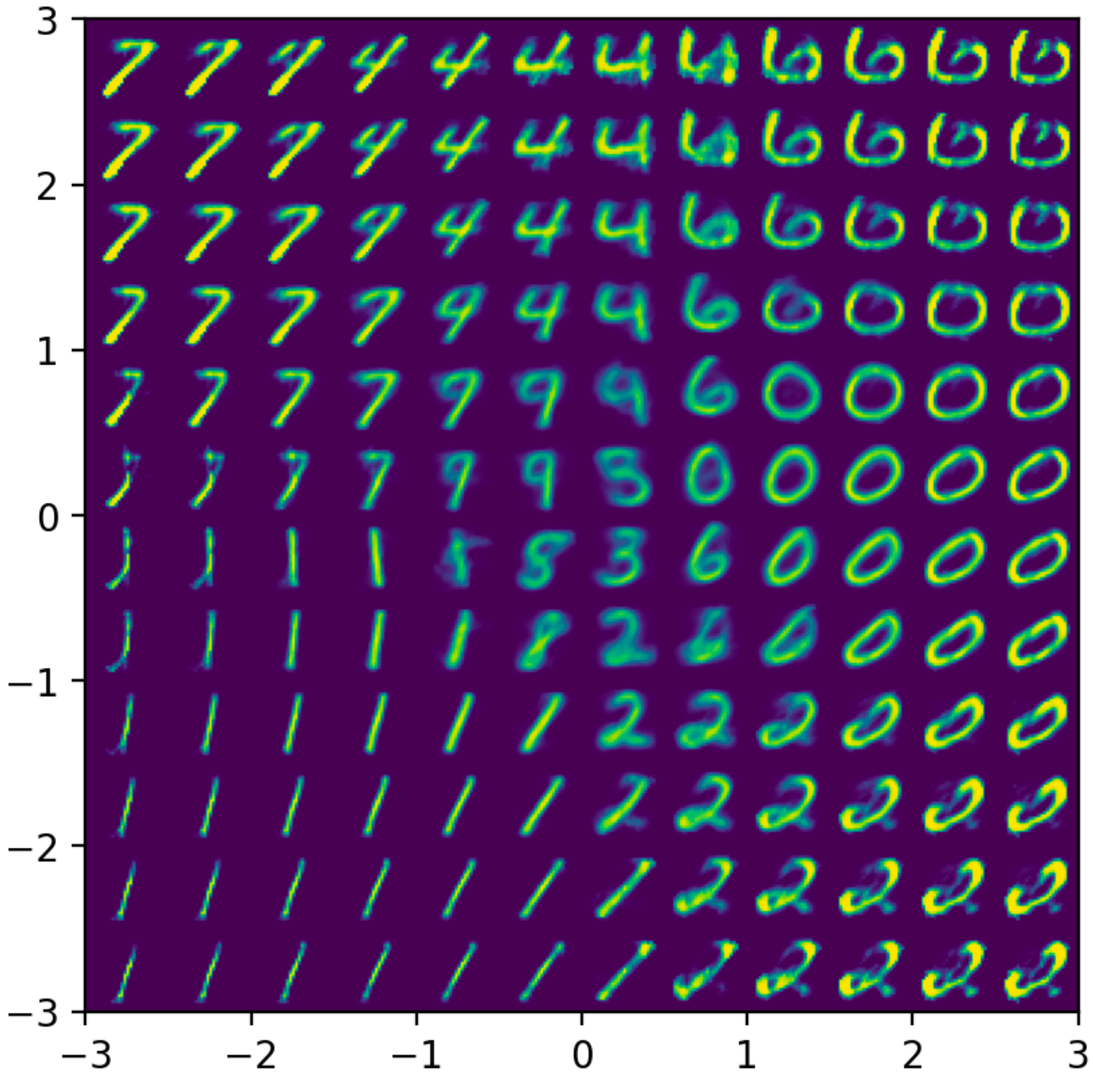

Compare to AE

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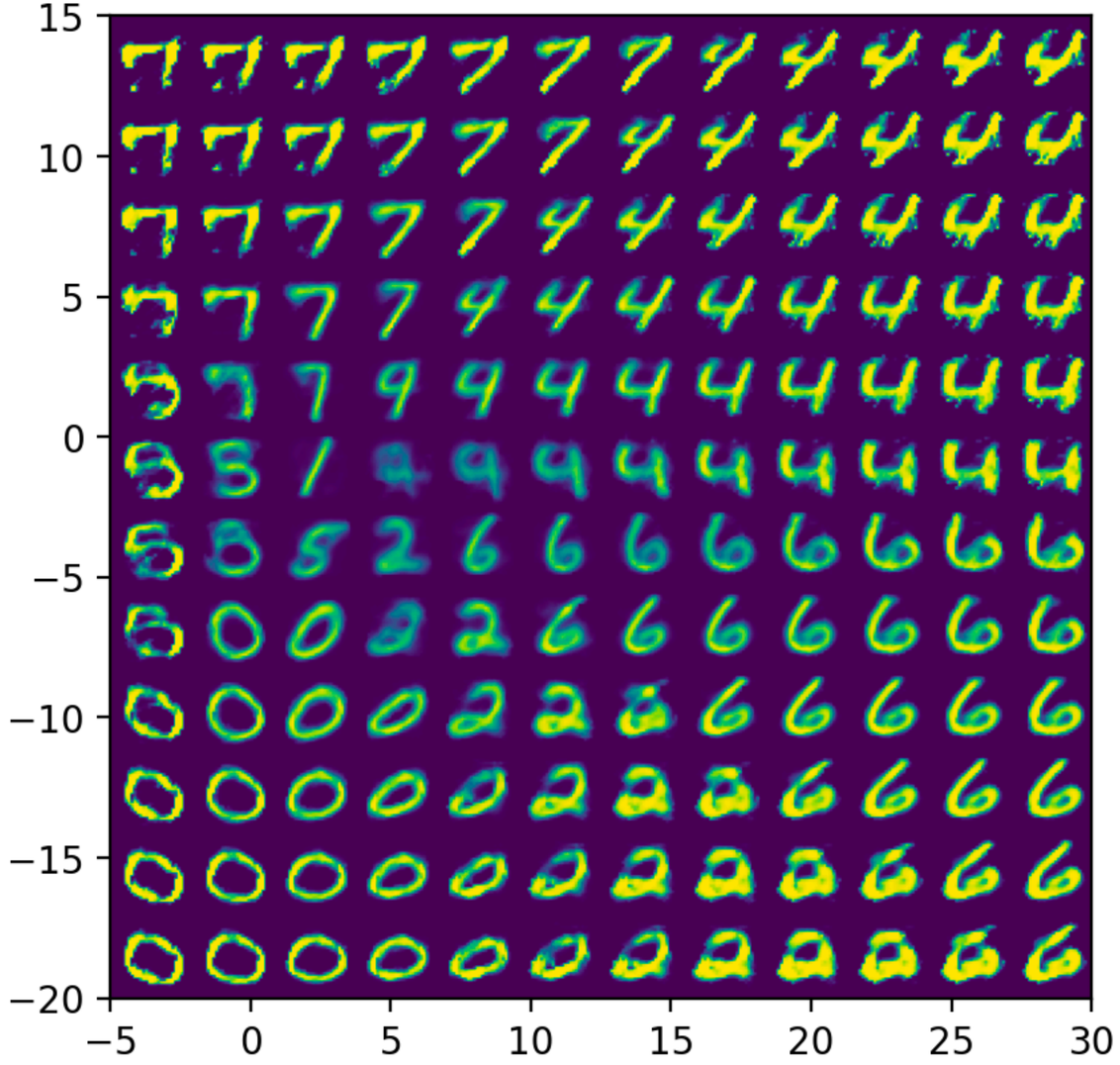
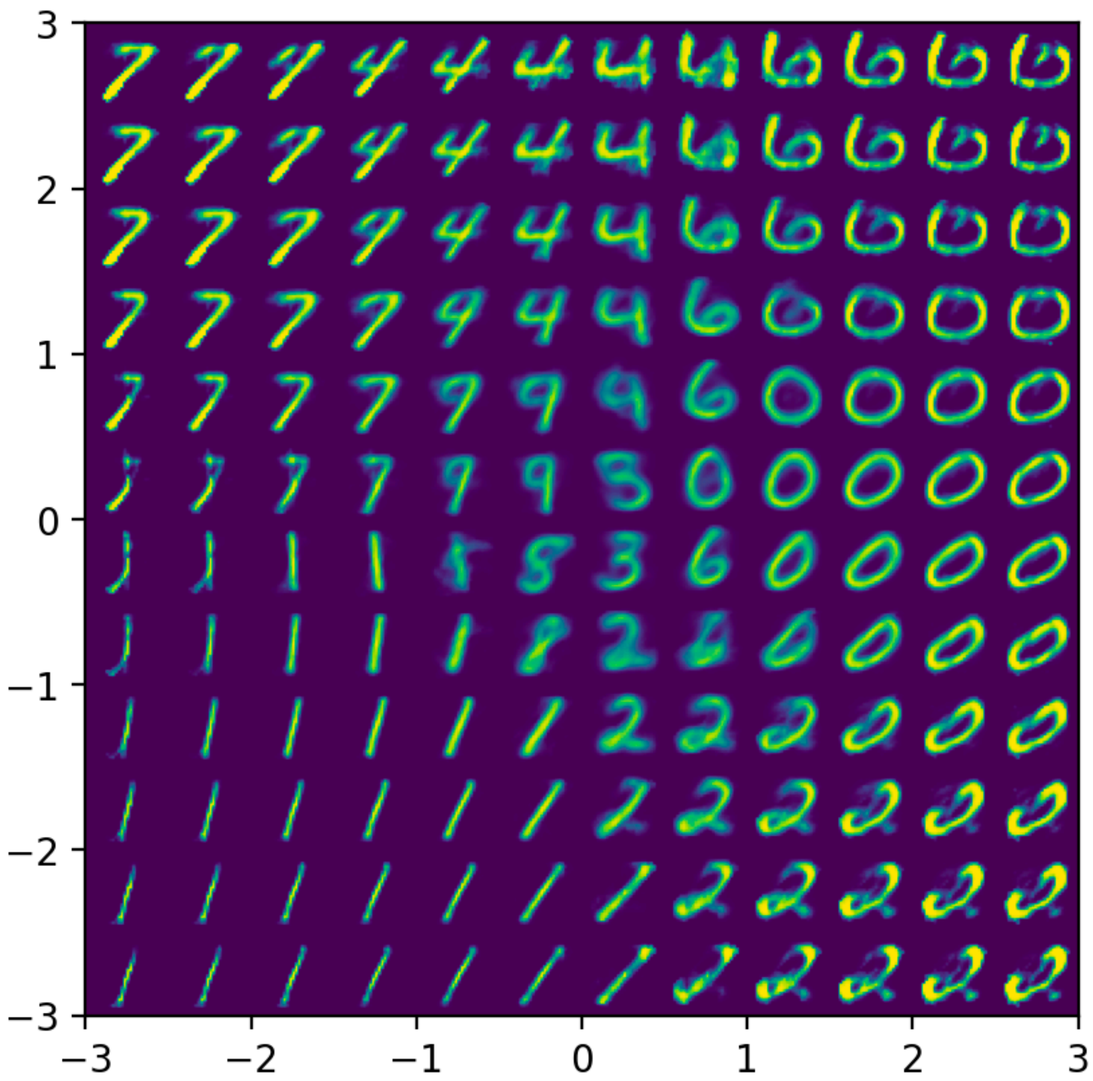
AE

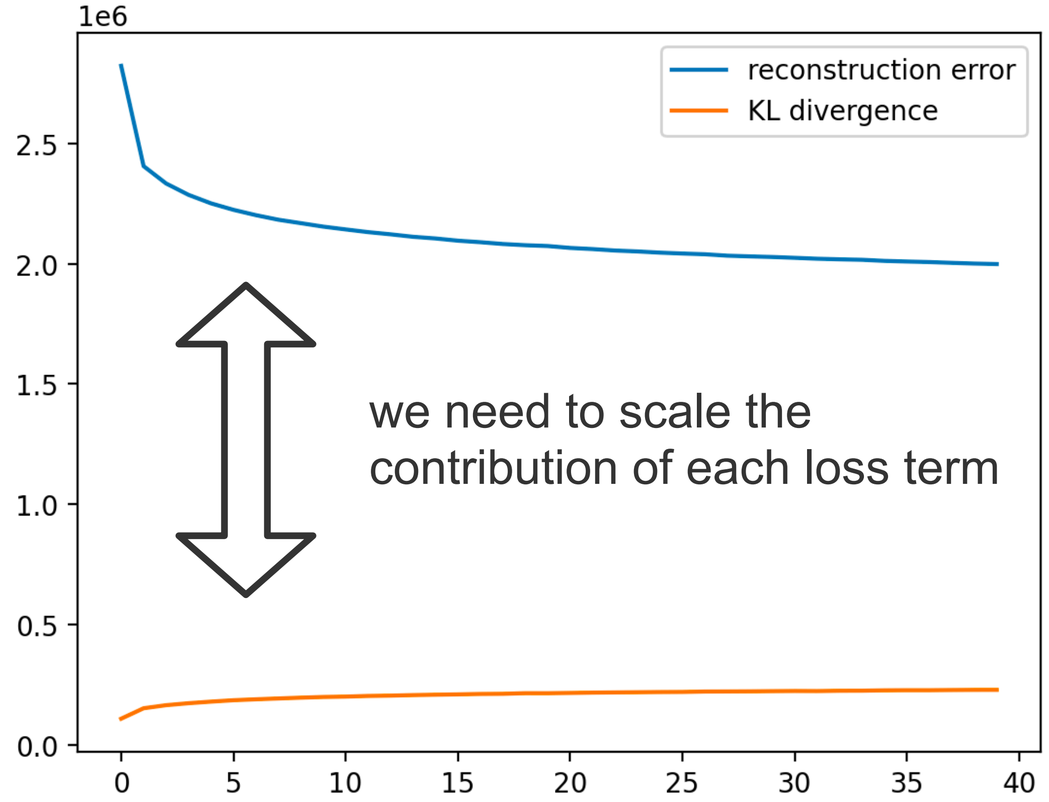


VAE



Hyperparameter

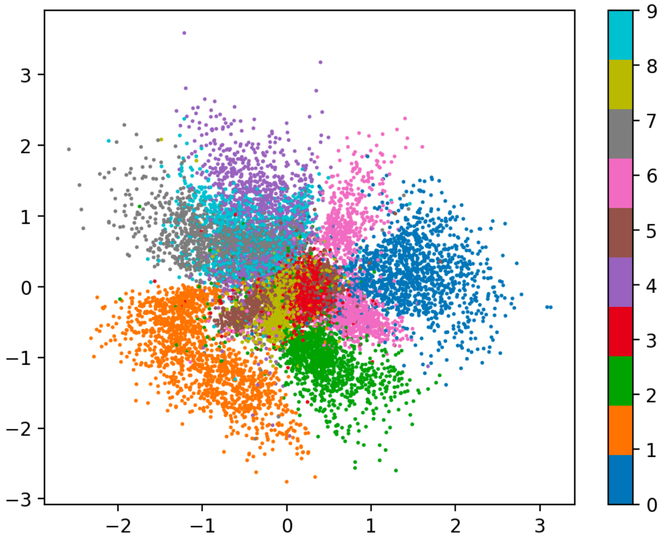
$$\mathcal{L}_{VAE} = \sum_{i=1}^{N} \left(\|X^i - \hat{X}^i\|^2 + KL[q_\phi(Z^i \mid X^i) \,\|\, p(Z^i)] \right)$$



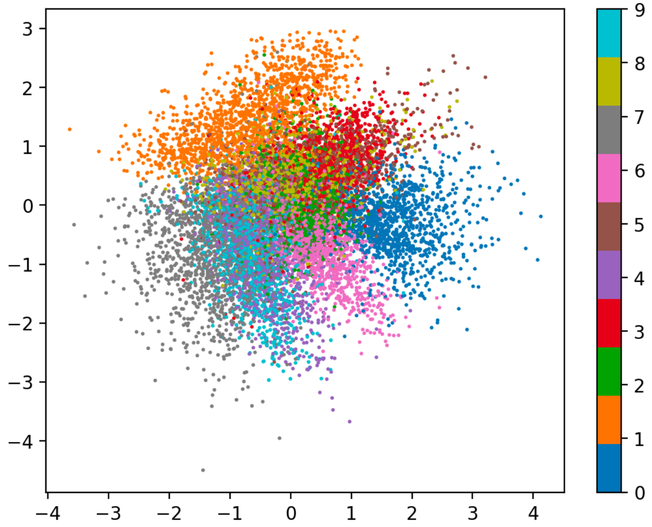
Hyperparameter

$$\mathscr{L}_{VAE} = \sum_{i=1}^{N} \left(\|X^i - \hat{X}^i\|^2 + \lambda \cdot KL[q_\phi(Z^i \mid X^i) \,\|\, p(Z^i)] \right)$$

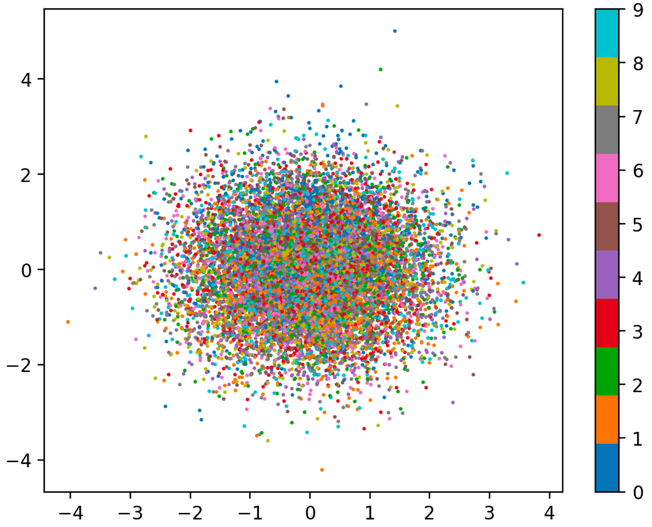
$\lambda = 1$



$\lambda = 4$



$\lambda = 10$



- As the contribution of the KL-divergence increases, the z get pushed towards $\mathcal{N}(0,1)$

Take-home messages

DeepLearning inLifeSciences

- Autoencoders are **unsupervised** models → they do not need labelled data
- **Dimensional reduction** approach: find a low-dimensional representation of the data
- **Various flavors**: undercomplete / overcomplete / sparse / denoising
- Variational autoencoders are **generative, probabilitic** models
- VAEs learn a more **continuous representation** of the data, from which we can sample new realistic data points
- **Hyperparameters** of VAEs have a strong influence on the model behavoir

References

- **VAE original paper**
  - Kingma, Welling (2013) https://arxiv.org/abs/1312.6114
- **Different views on VAEs, with mathematical details**
  - https://mbernste.github.io/posts/vae/
- **Reparametrization trick**
  - Blog: https://gregorygundersen.com/blog/2018/04/29/reparameterization/
  - Video: https://www.youtube.com/watch?v=vy8q-WnHa9A&t=447s
- **Denoising AE**
  - Slides: https://fleuret.org/dlc/materials/dlc-handout-7-3-denoising-autoencoders.pdf
  - pyTorch implementation: https://github.com/pranjaldatta/Denoising-Autoencoder-in-Pytorch/blob/master/DenoisingAutoencoder.ipynb