Computational Systems Biology
Deep Learning in the Life Sciences

6.802 6.874 20.390 20.490 HST.506

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Lecture 6

February 25, 2019

The Zen of PCA, t-SNE, and Autoencoders

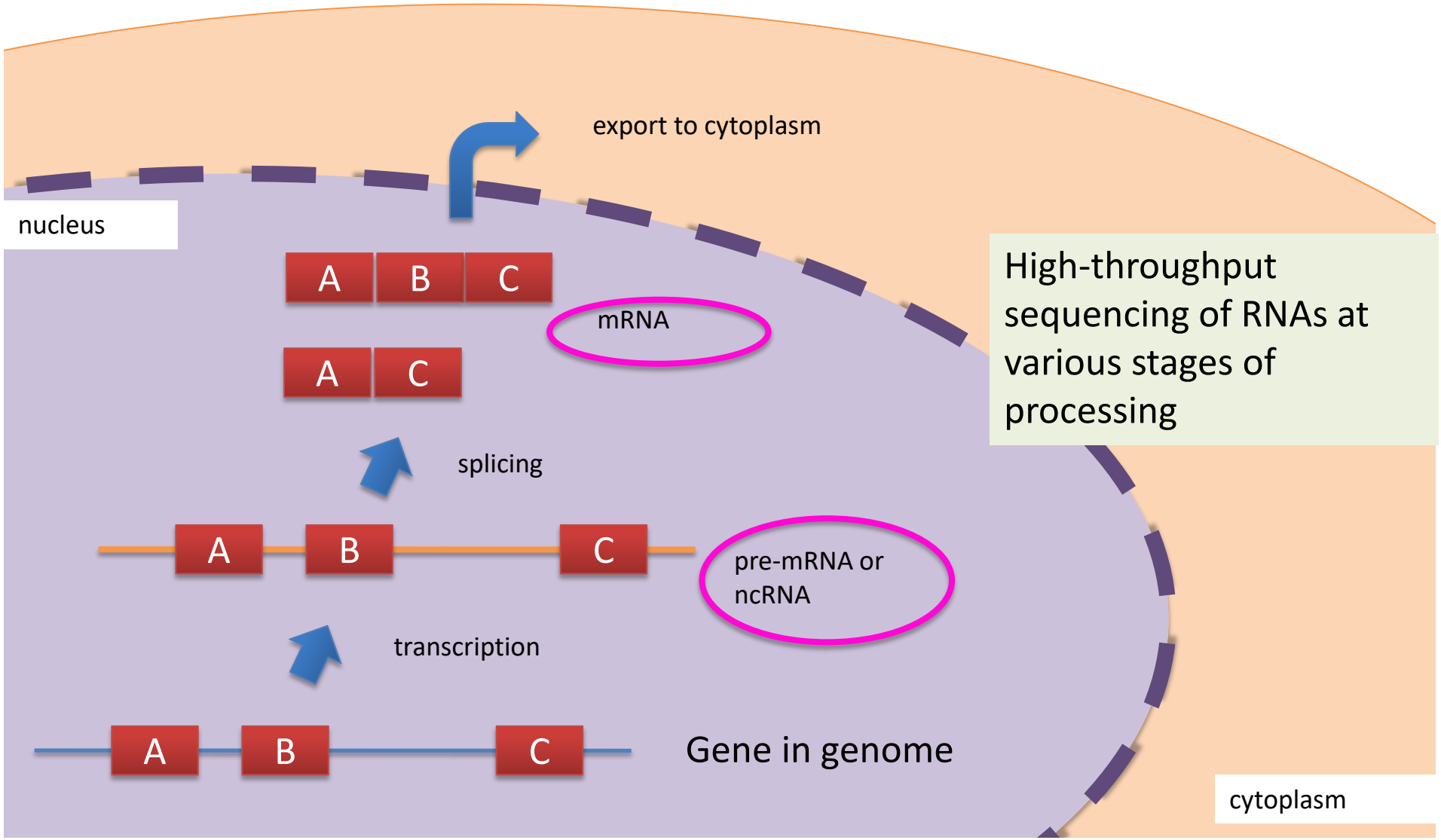
http://mit6874.github.io

Today: Gene Expression, PCA, t-SNE, autoencoders

- Gene expression analysis: The Biology of RNA-seq
- Supervised (Classification) vs. unsupervised (Clustering)
- Supervised: Differential expression analysis
- Unsupervised: Embedding into lower dimensional space
- Linear reduction of dimensionality
  - Principle Component Analysis
  - Singular Value Decomposition
- Non-linear dimensionality reduction: embeddings
  - t-distributed Stochastic Network Embedding (t-SNE)
  - Building intuition: Playing with t-SNE parameters
- Deep Learning embeddings
  - Autoencoders

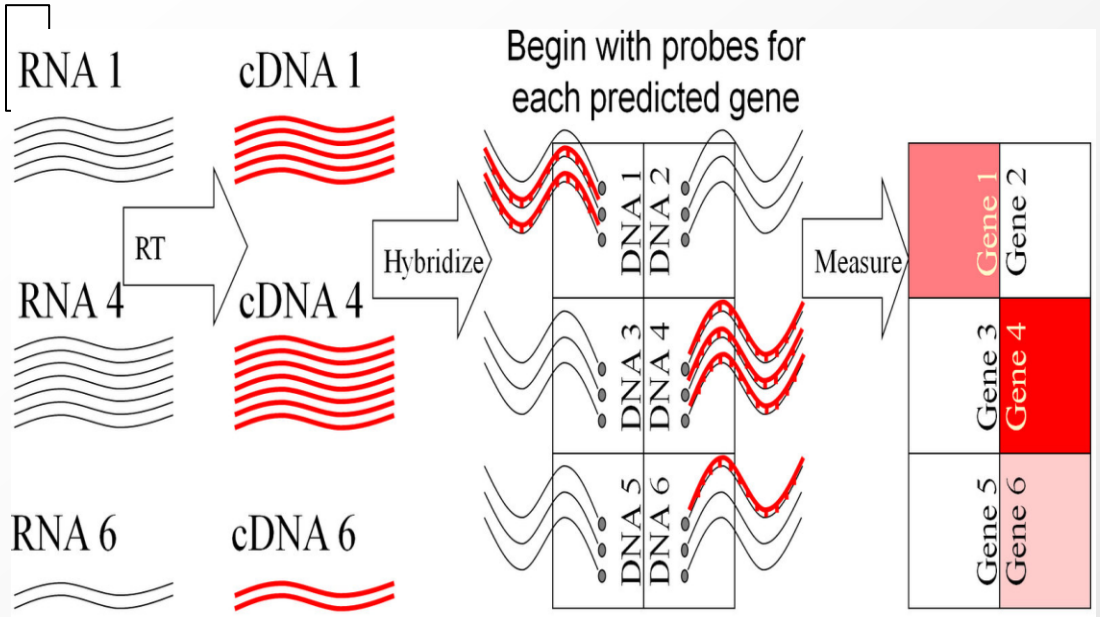
1. The biology: RNA-seq data

RNA-Seq characterizes RNA molecules

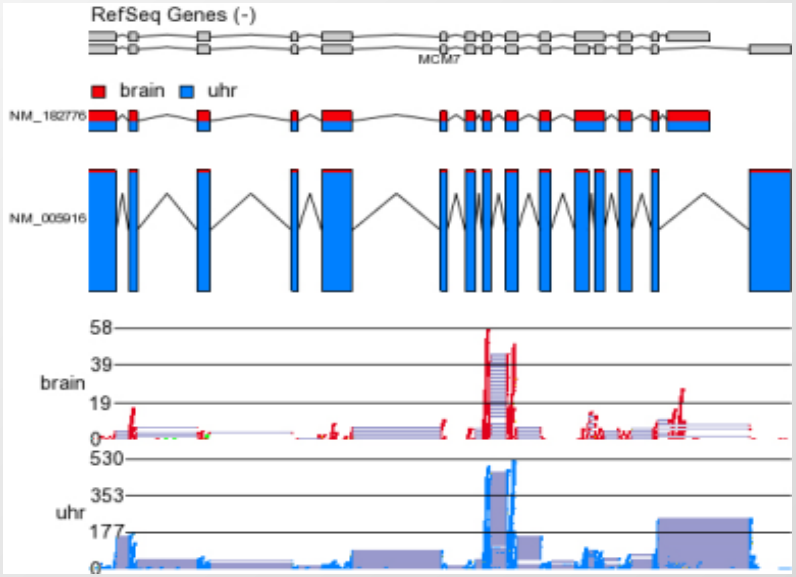


Slide courtesy Cole Trapnell

RNA-Seq: De novo tx reconstruction / quantification



Count



Microarray technology

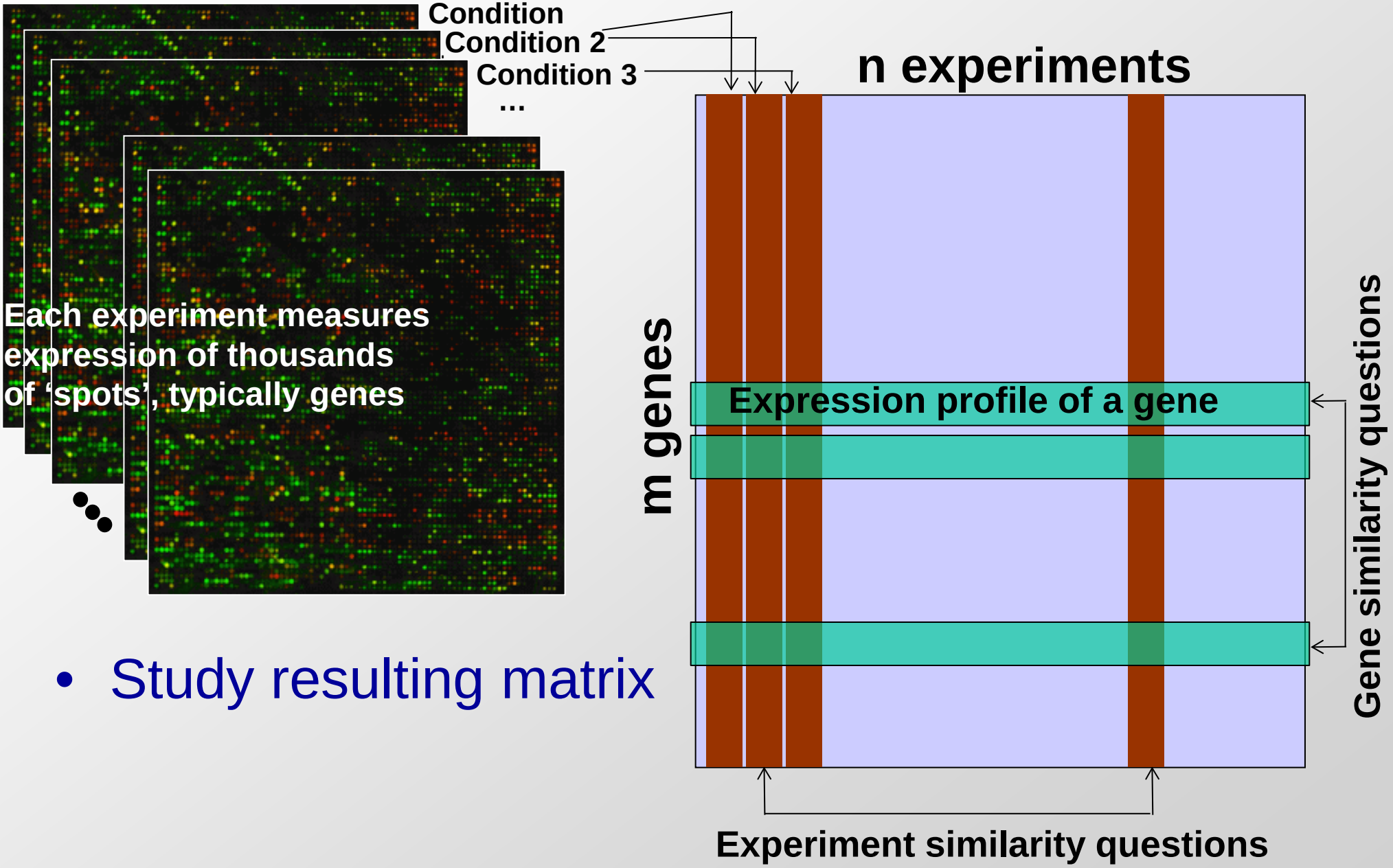
- Synthesize DNA probe array, complementary hybridization
- Variations:
  - One long probe per gene
  - Many short probes per gene
  - Tiled k-mers across genome
- Advantage:
  - Can focus on small regions, even if few molecules / cell

RNA-Seq technology:

- Sequence short reads from mRNA, map to genome
- Variations:
  - Count reads mapping to each known gene
  - Reconstruct transcriptome *de novo* in each experiment
- Advantage:
  - Digital measurements, de novo

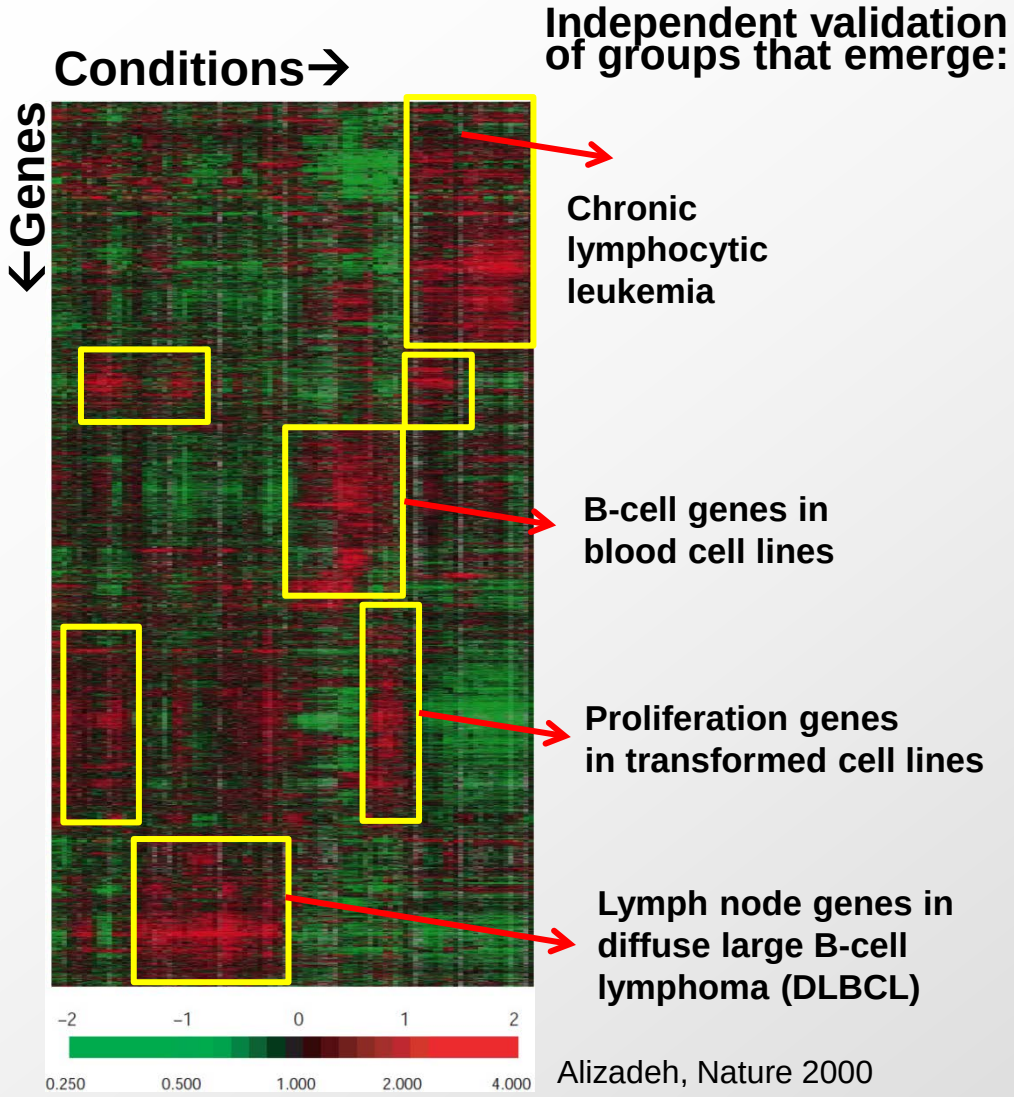
Expression Analysis Data Matrix

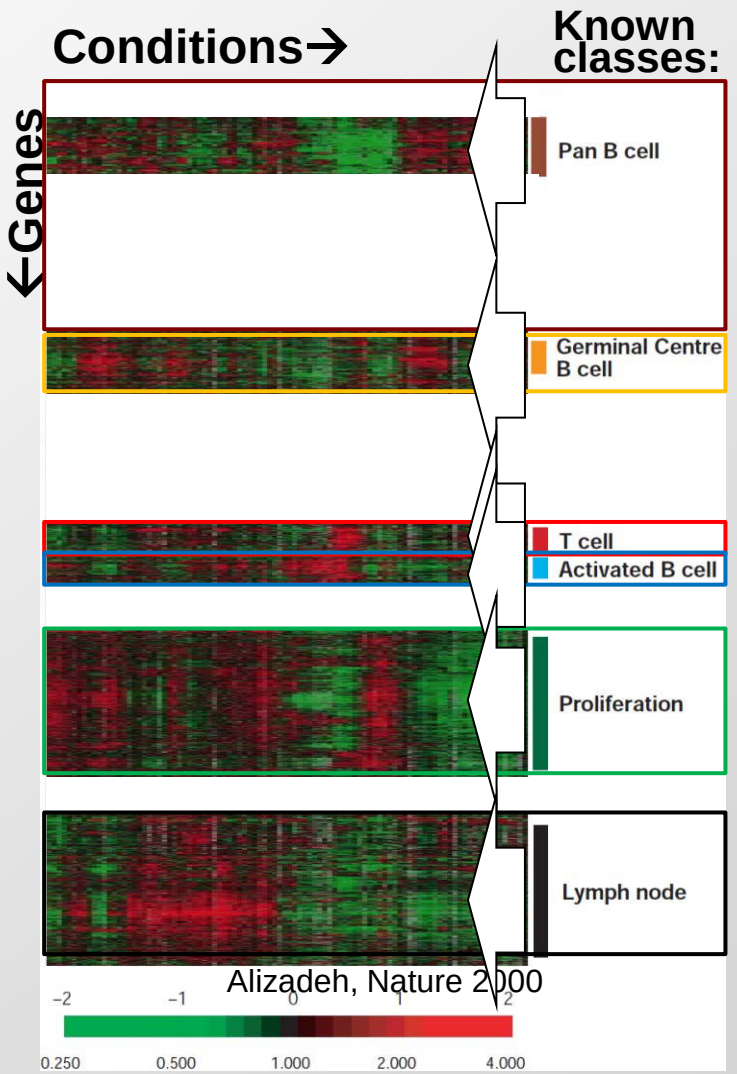
- Measure 20,000 genes in 100s of conditions



- Study resulting matrix

Clustering vs. Classification





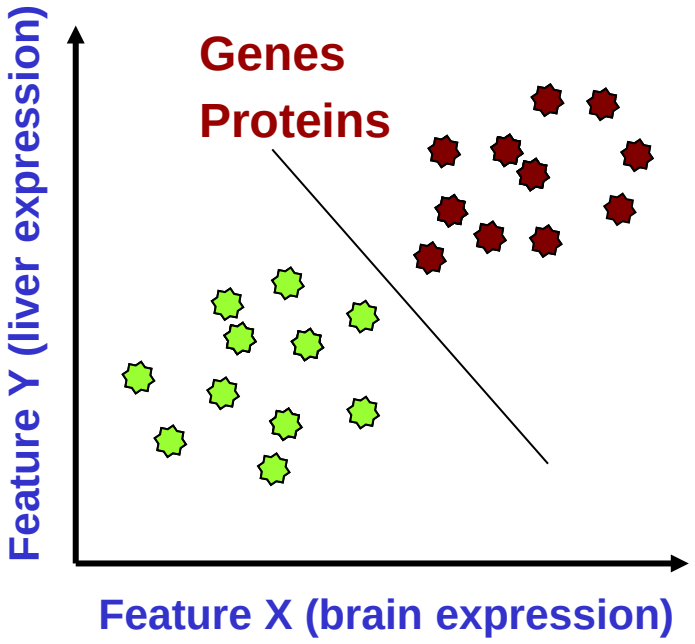
Goal of Clustering: **Group similar items** that likely come from the same category, and in doing so **reveal hidden structure**

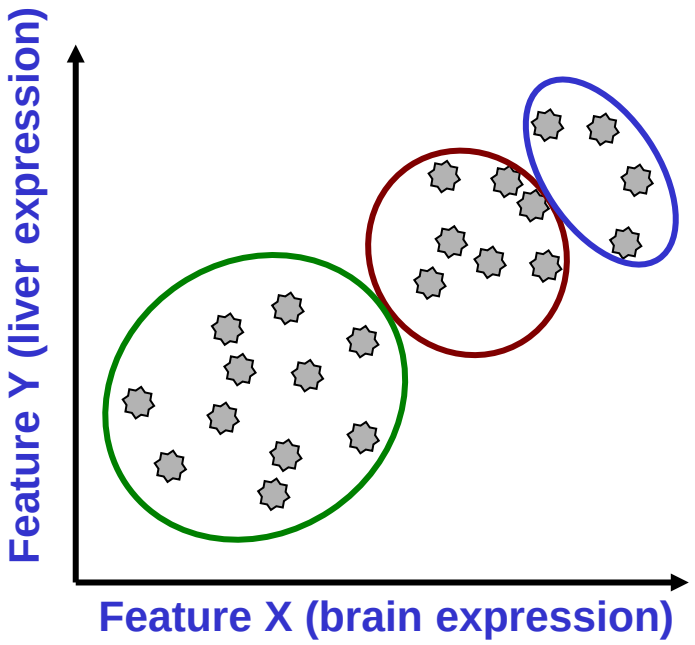
Goal of Classification: Extract features from the data that best **assign new elements** to ≥1 of **well-defined classes**

- **Unsupervised learning**
- **Supervised learning**

Clustering vs Classification

- Objects characterized by one or more features
- **Classification (supervised learning)**
  - Have labels for some points
  - Want a "rule" that will accurately assign labels to new points
  - Sub-problem: Feature selection
  - Metric: Classification accuracy
- **Clustering (unsupervised learning)**
  - No labels
  - Group points into clusters based on how "near" they are to one another
  - Identify structure in data
  - Metric: independent validation features





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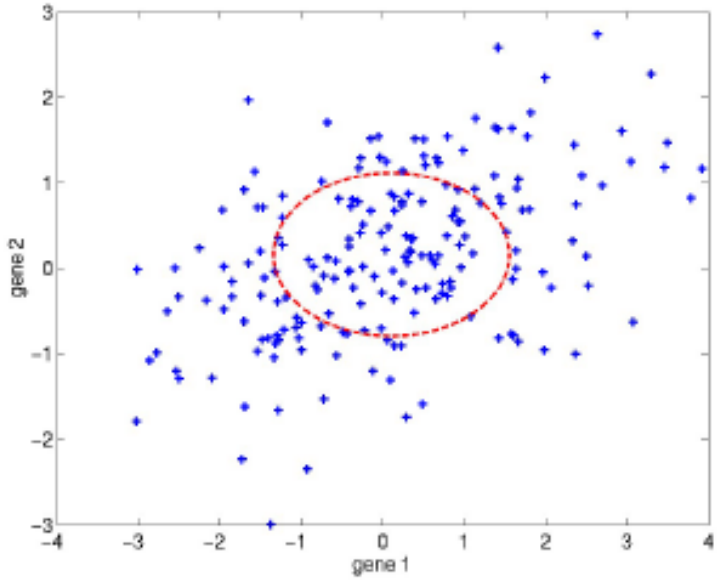
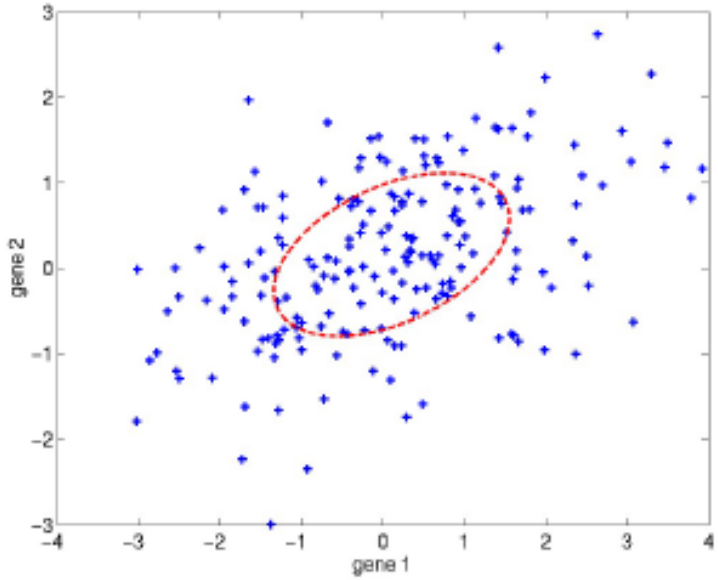
2. Supervised learning: differential gene expression

Statistical tests: example

- The alternative hypothesis H_1 is more expressive in terms of explaining the observed data



null hypothesis



alternative hypothesis

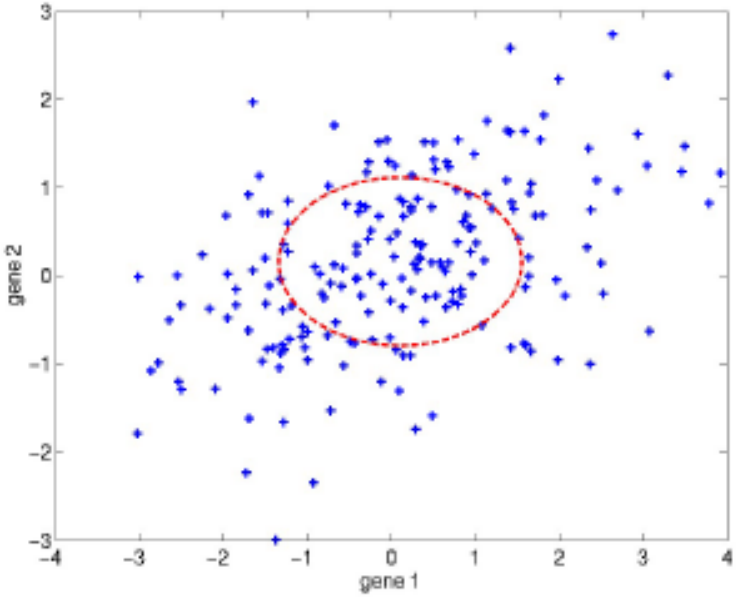
- We need to find a way of testing whether this difference is significant

Degrees of freedom

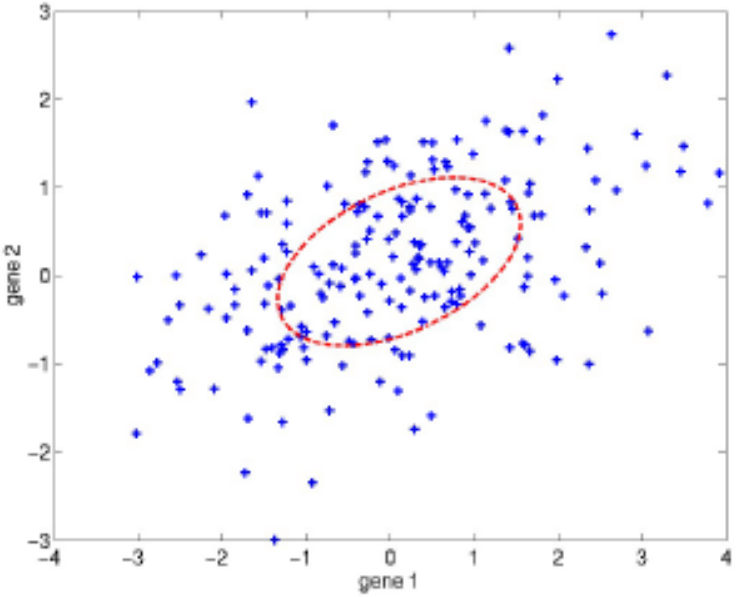
- How many degrees of freedom do we have in the two models?

$$H_0: \quad \begin{bmatrix} X_1 \\ X_2 \end{bmatrix} \sim N\left(\begin{bmatrix} \mu_1 \\ \mu_2 \end{bmatrix}, \begin{bmatrix} \sigma_1^2 & 0 \\ 0 & \sigma_2^2 \end{bmatrix}\right)$$

$$H_1: \quad \begin{bmatrix} X_1 \\ X_2 \end{bmatrix} \sim N\left(\begin{bmatrix} \mu_1 \\ \mu_2 \end{bmatrix}, \begin{bmatrix} \Sigma_{11} & \Sigma_{12} \\ \Sigma_{21} & \Sigma_{22} \end{bmatrix}\right)$$



H_0



H_1

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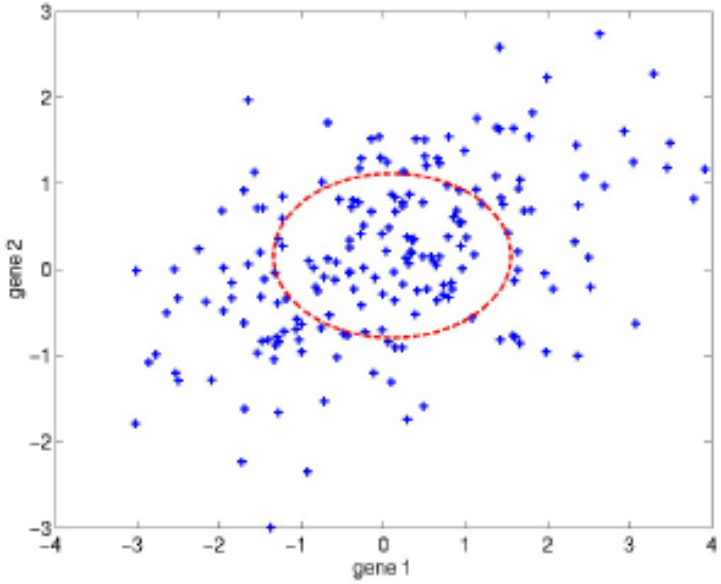
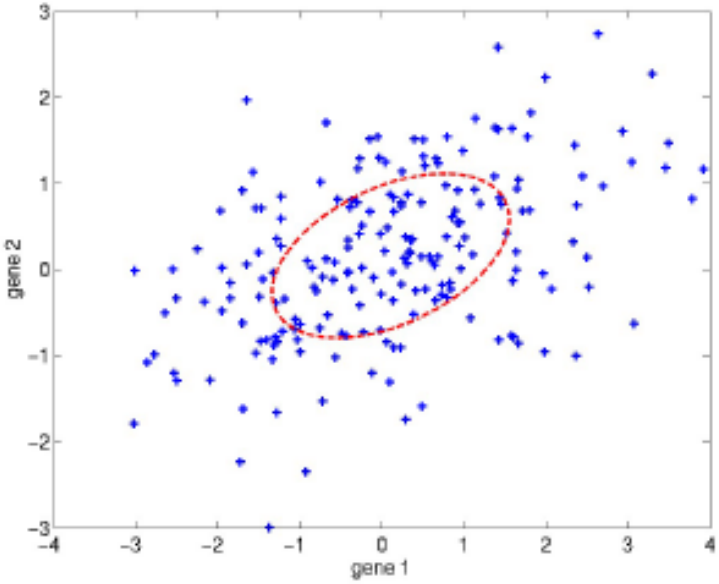


H_0



H_1

- The observed data overwhelmingly supports H_1

Test statistic

- Likelihood ratio statistic

$$T(X^{(1)}, \ldots, X^{(n)}) = 2 \log \frac{P(X^{(1)}, \ldots, X^{(n)} | \hat{H}_1)}{P(X^{(1)}, \ldots, X^{(n)} | \hat{H}_0)} \qquad (1)$$

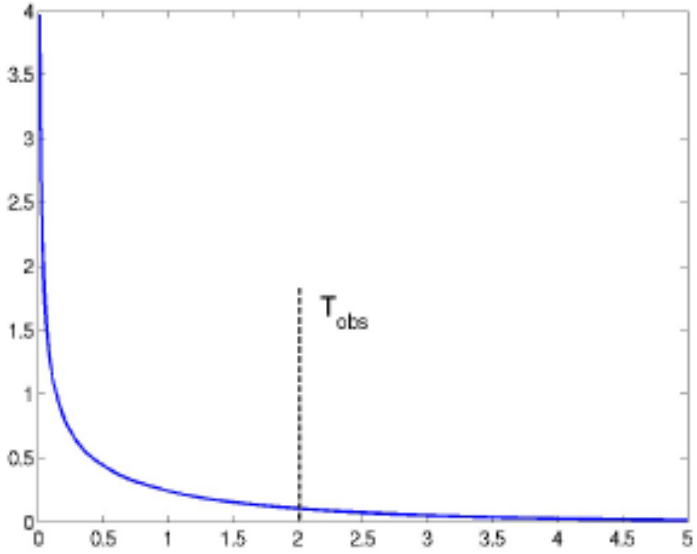
  Larger values of T imply that the model corresponding to the null hypothesis H_0 is much less able to account for the observed data

- To evaluate the P-value, we also need to know the sampling distribution for the test statistic

  In other words, we need to know how the test statistic $T(X^{(1)}, \ldots, X^{(n)})$ varies if the null hypothesis H_0 is correct

Test statistic cont'd

- For the likelihood ratio statistic, the sampling distribution is χ^2 with degrees of freedom equal to the difference in the number of free parameters in the two hypotheses



- Once we know the sampling distribution, we can compute the P-value

$$p = Prob(\, T(X^{(1)}, \ldots, X^{(n)}) \geq T_{obs} \,|\, H_0 \,) \tag{2}$$

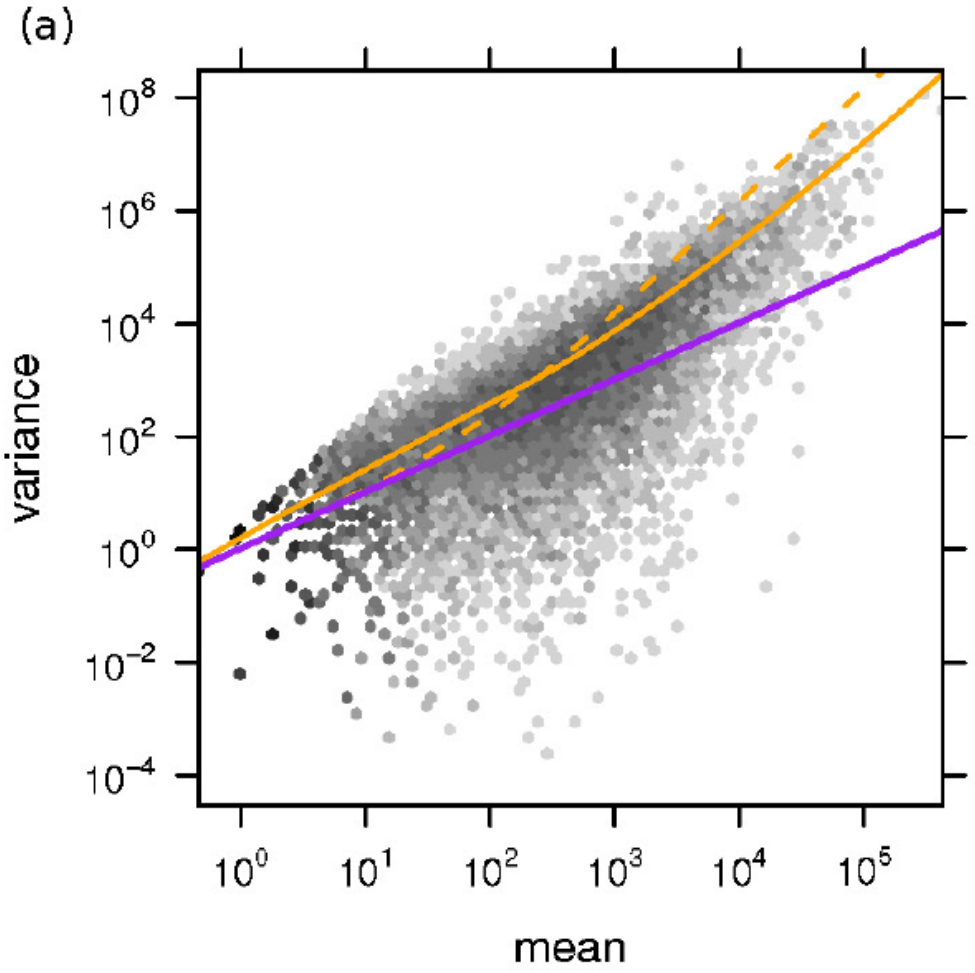
What is the right distribution for modeling read counts?

$$\lambda = \frac{\sum_{i=1}^{n} x_i}{n}$$

$$f(x; \lambda) = \frac{\lambda^x e^{-\lambda}}{x!}$$

Poission?

Read count data is overdispersed for a Poission
Use a Negative Binomial instead



Orange Line – DESeq
Dashed Orange – edgeR
Purple - Poission

$$\sigma_{ij}^2 = \mu_{ij} + s_j^2 v_p\left(q_{ip(j)}\right)$$

Anders and Huber *Genome Biology* 2010, **11**:R106
http://genomebiology.com/2010/11/10/R106

A Negative Binomial distribution is better (DESeq)

- i gene or isoform p condition
- j sample (experiment) p(j) condition of sample j
- m number of samples
- K_{ij} number of counts for isoform i in experiment j
- q_{ip} Average scaled expression for gene i condition p

$$q_{ip} = \frac{1}{\#\text{ of replicates}} \sum_{\text{j in replicates}} \frac{K_{ij}}{s_j}$$

$$\mu_{ij} = q_{ip(j)} s_j \qquad \sigma_{ij}^2 = \mu_{ij} + s_j^2 v_p\left(q_{ip(j)}\right)$$

$$K_{ij} \sim NB\left(\mu_{ij}, \sigma_{ij}^2\right)$$

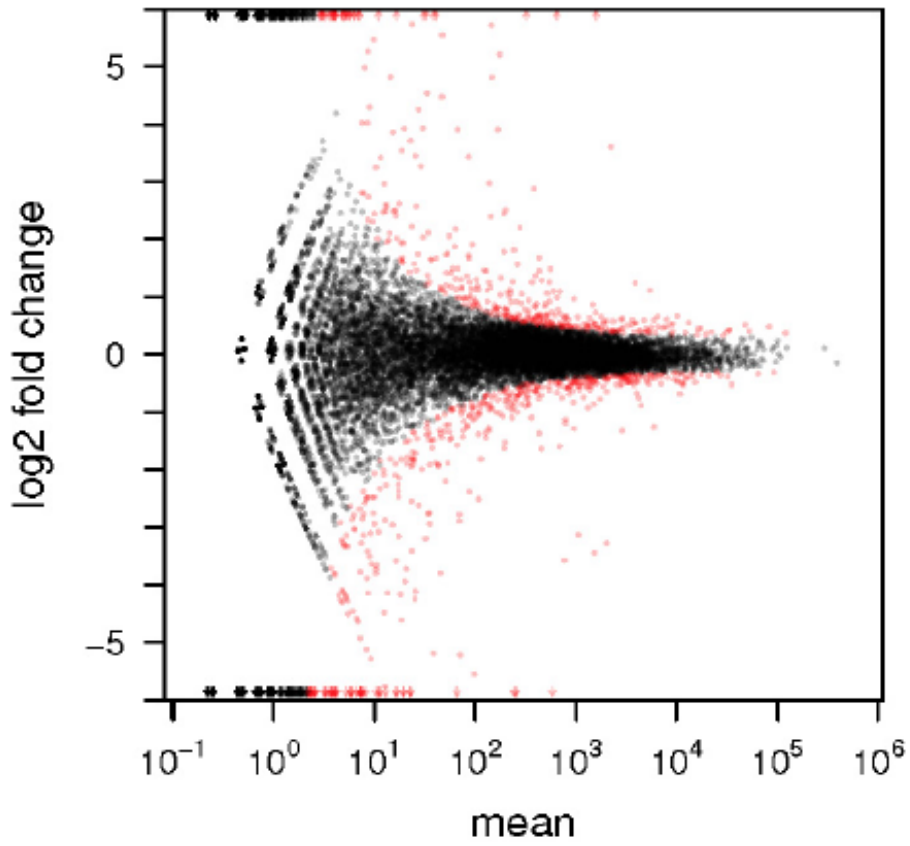


Figure 3 Testing for differential expression between conditions *A* and *B*: Scatter plot of $\log_2$ ratio (fold change) versus mean. The red colour marks genes detected as differentially expressed at 10% false discovery rate when Benjamini-Hochberg multiple testing adjustment is used. The symbols at the upper and lower plot border indicate genes with very large or infinite log fold change. The corresponding volcano plot is shown in Supplementary Figure S8 in Additional file 2.

Hypergeometric test for gene set overlap significance

N – total # of genes 1000

n1 - # of genes in set A 20

n2 - # of genes in set B 30

k - # of genes in both A and B

3

$$P(k) = \frac{\binom{n1}{k}\binom{N-n1}{n2-k}}{\binom{N}{n2}}$$

0.017

$$P(x \geq k) = \sum_{i=k}^{\min(n1,n2)} P(i)$$

0.020

Bonferroni correction

- Total number of rejections of null hypothesis over all N tests denoted by R.

$$Pr(R>0) \tilde{=} N\alpha$$

- Need to set α' = Pr(R>0) to required significance level **over all tests**. Referred to as the **experimentwise error rate**.
- With 100 tests, to achieve overall experimentwise significance level of α'=0.05:

$$0.05 = 100\alpha$$

$$\rightarrow \alpha = 0.0005$$

- **Pointwise** significance level of 0.05%.

Example - Genome wide association screens

- Risch & Merikangas (1996).
- 100,000 genes.
- Observe 10 SNPs in each gene.
- 1 million tests of null hypothesis of no association.
- To achieve experimentwise significance level of 5%, require pointwise p-value less than 5×10^{-8}

Bonferroni correction - problems

- Assumes each test of the null hypothesis to be **independent**.
- If not true, Bonferroni correction to significance level is **conservative**.
- Loss of power to reject null hypothesis.
- Example: genome-wide association screen across linked SNPs – correlation between tests due to LD between loci.

Benjamini Hochberg

- Select False Discovery Rate α
- Number of tests is *m*
- Sort p-values $P_{(k)}$ in ascending order (most significant first)
- Assumes tests are uncorrelated or positively correlated

1. For a given α, find the largest k such that $P_{(k)} \leq \frac{k}{m}\alpha$.
2. Reject the null hypothesis (i.e., declare discoveries) for all $H_{(i)}$ for $i = 1, \ldots, k$.

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3. **Unsupervised learning:**
dimensionality reduction

Dimensionality reduction has multiple applications

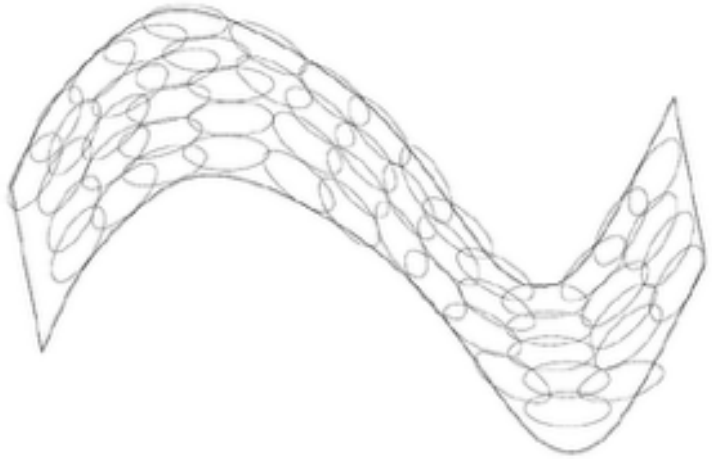
- Uses:
  - Data Visualization
  - Data Reduction
  - Data Classification
  - Trend Analysis
  - Factor Analysis
  - Noise Reduction

- Examples:
  - How many unique “sub-sets” are in the sample?
  - How are they similar / different?
  - What are the underlying factors that influence the samples?
  - Which time / temporal trends are (anti)correlated?
  - Which measurements are needed to differentiate?
  - How to best present what is “interesting”?
  - Which “sub-set” does this new sample rightfully belong?

A manifold is a topological space that locally resembles Euclidean space near each point

A manifold embedding is a structure preserving mapping of a high dimensional space into a manifold

Manifold learning learns a lower dimensional space that enables a manifold embedding



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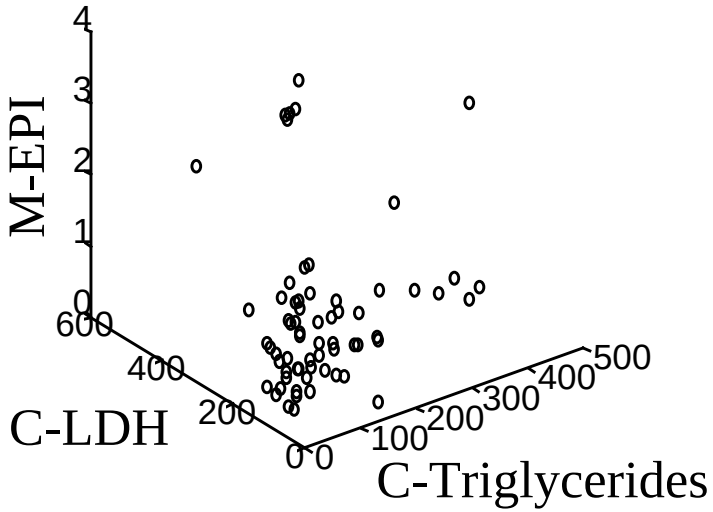
4. Principal Component Analysis

Example data

- Example: 53 Blood and urine measurements (wet chemistry) from 65 people (33 alcoholics, 32 non-alcoholics)

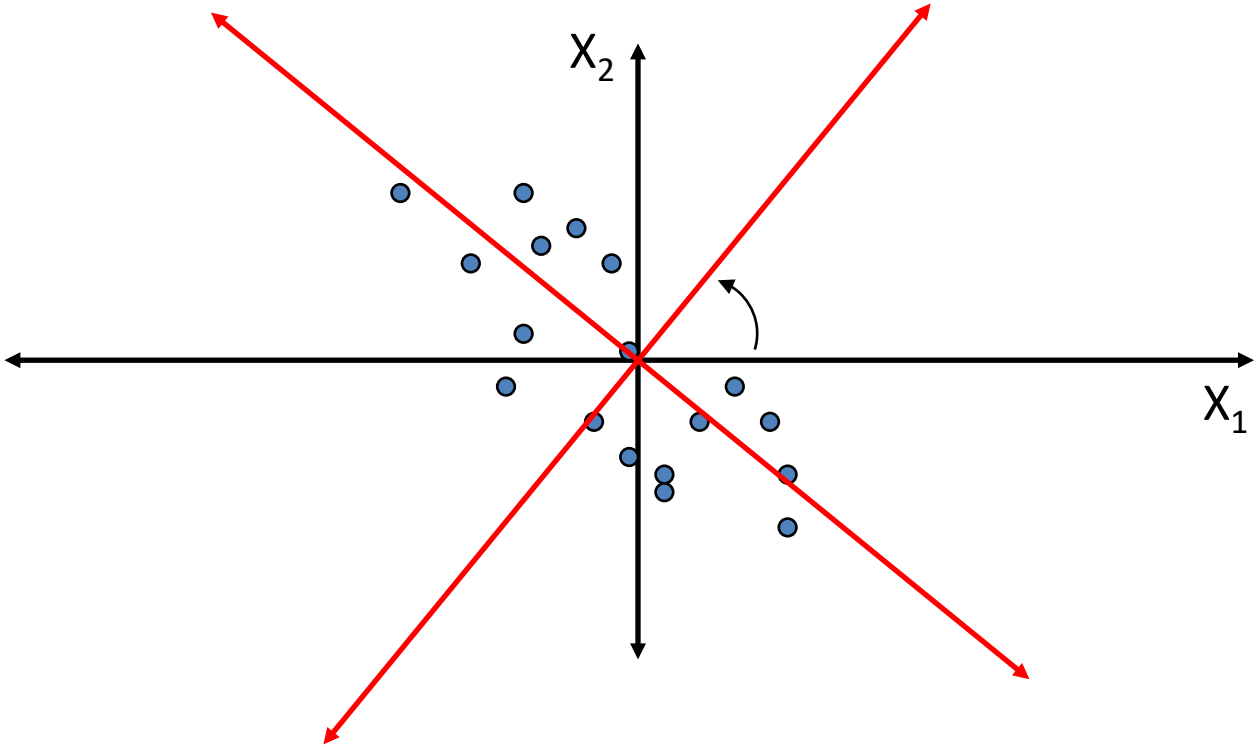
- Trivariate plot



	H-WBC	H-RBC	H-Hgb	H-Hct	H-MCV	H-MCH	H-MCHC
A1	8.0000	4.8200	14.1000	41.0000	85.0000	29.0000	34.0000
A2	7.3000	5.0200	14.7000	43.0000	86.0000	29.0000	34.0000
A3	4.3000	4.4800	14.1000	41.0000	91.0000	32.0000	35.0000
A4	7.5000	4.4700	14.9000	45.0000	101.0000	33.0000	33.0000
A5	7.3000	5.5200	15.4000	46.0000	84.0000	28.0000	33.0000
A6	6.9000	4.8600	16.0000	47.0000	97.0000	33.0000	34.0000
A7	7.8000	4.6800	14.7000	43.0000	92.0000	31.0000	34.0000
A8	8.6000	4.8200	15.8000	42.0000	88.0000	33.0000	37.0000
A9	5.1000	4.7100	14.0000	43.0000	92.0000	30.0000	32.0000

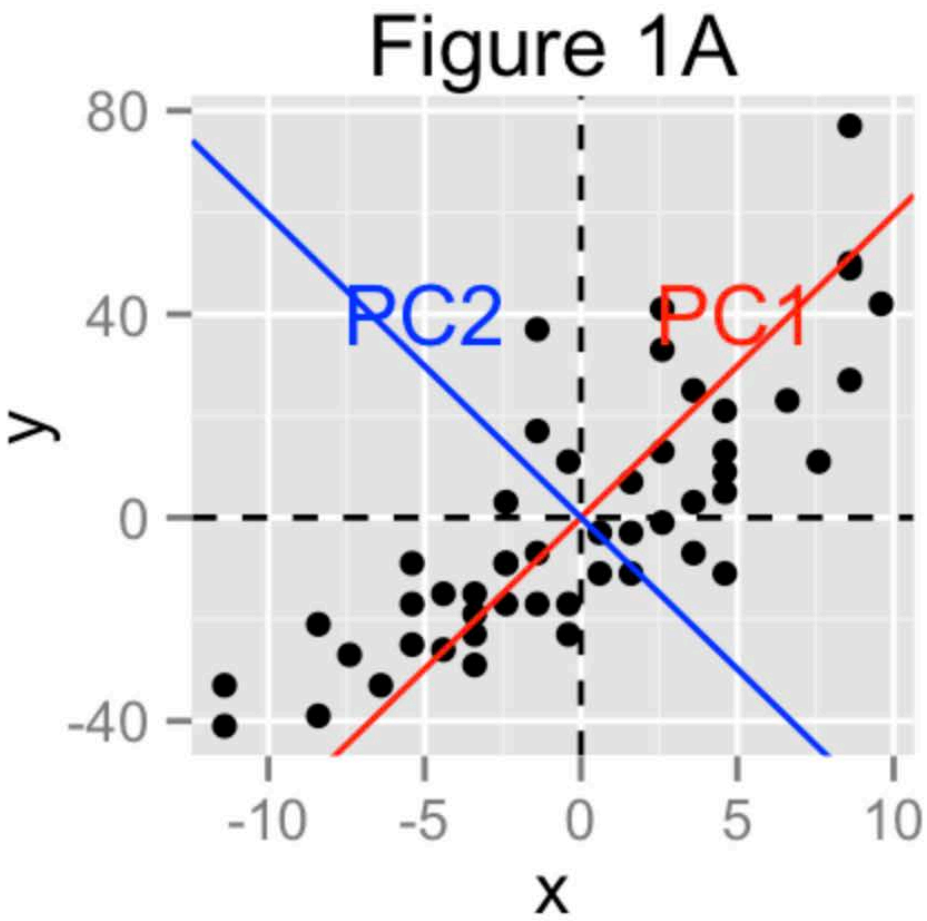
Principal Component = axis of greatest variability

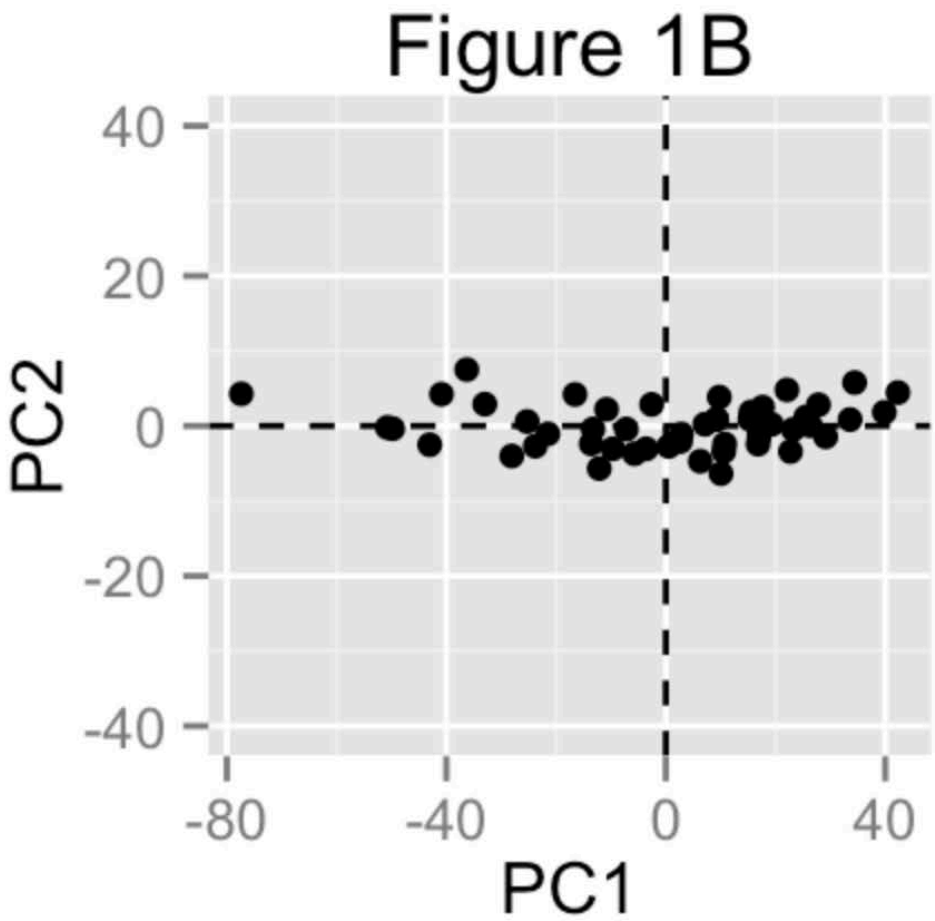
Suppose we have a population measured on p random variables $X_1,\ldots,X_p$. Note that these random variables represent the p-axes of the Cartesian coordinate system in which the population resides. Our goal is to develop a new set of p axes (linear combinations of the original p axes) in the directions of greatest variability:



This is accomplished by rotating the axes.

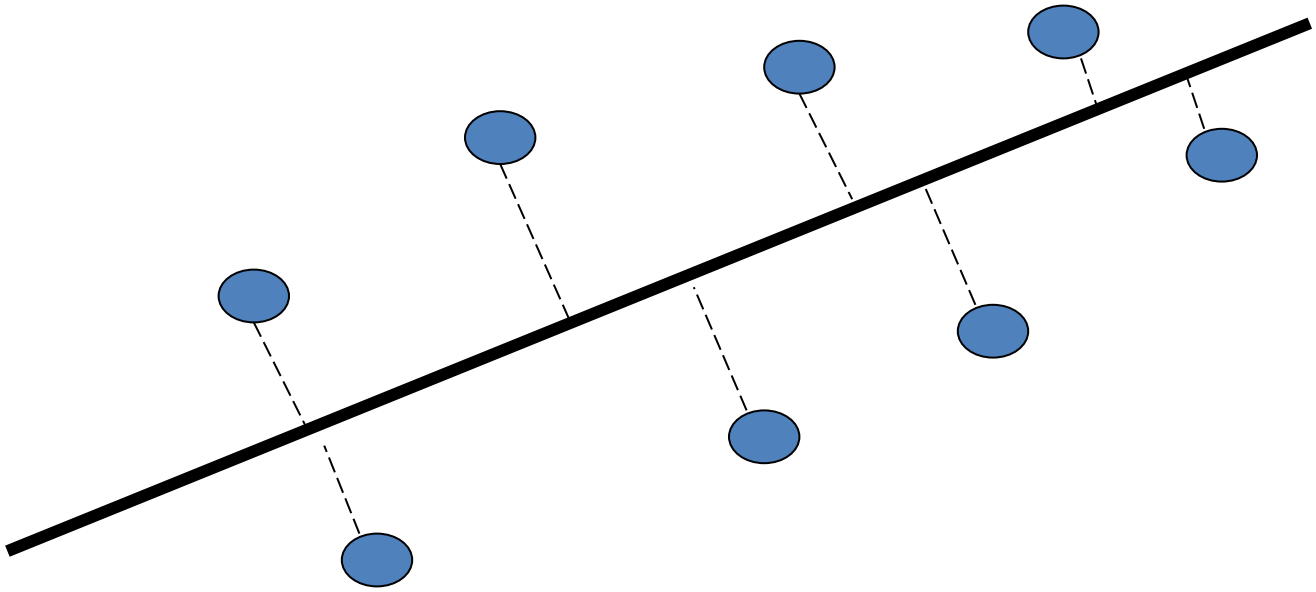
Data projected onto PC1





Selecting Principal Components

- Given m points in a n dimensional space, for large n, how does one project on to a 1 dimensional space?
- Formally, minimize sum of squares of distances to the line.



- Why sum of squares? Because it allows fast minimization, assuming the line passes through 0

Linear Algebra Review

- **Eigenvectors** (for a square $m \times m$ matrix $\mathbf{S}$)

$$\mathbf{S}\mathbf{v} = \lambda \mathbf{v}$$

(right) eigenvector $\mathbf{v} \in \mathbb{R}^m \neq \mathbf{0}$

eigenvalue $\lambda \in \mathbb{R}$

Example

$$\begin{pmatrix} 6 & -2 \\ 4 & 0 \end{pmatrix} \begin{pmatrix} 1 \\ 2 \end{pmatrix} = \begin{pmatrix} 2 \\ 4 \end{pmatrix} = 2 \begin{pmatrix} 1 \\ 2 \end{pmatrix}$$

- How many eigenvalues are there at most?

$$\mathbf{S}\mathbf{v} = \lambda \mathbf{v} \iff (\mathbf{S} - \lambda \mathbf{I})\,\mathbf{v} = \mathbf{0}$$

only has a non-zero solution if $|\mathbf{S} - \lambda \mathbf{I}| = 0$

this is a m-th order equation in λ which can have **at most m distinct solutions** (roots of the characteristic polynomial) – can be complex even though **S** is real.

Eigenvalues & Eigenvectors

- For symmetric matrices, eigenvectors for distinct eigenvalues are **orthogonal**

$$Sv_{\{1,2\}} = \lambda_{\{1,2\}} v_{\{1,2\}}, \text{ and } \lambda_1 \neq \lambda_2 \Rightarrow v_1 \bullet v_2 = 0$$

- All eigenvalues of a real symmetric matrix are **real**.

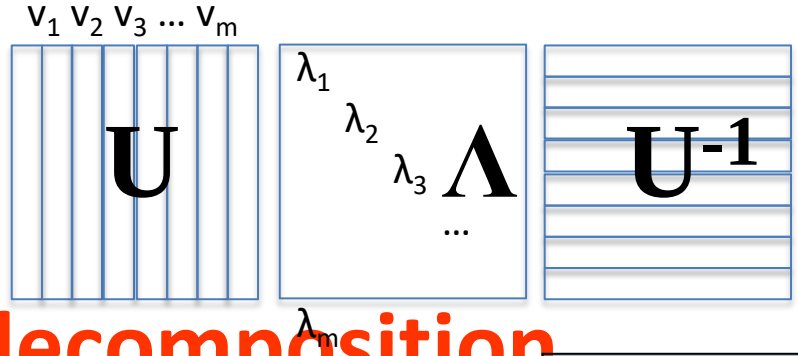
$$\text{for complex } \lambda, \text{ if } \left|S - \lambda I\right| = 0 \text{ and } \mathrm{S} = \mathrm{S}^{\mathrm{T}} \Rightarrow \lambda \in \Re$$

- All eigenvalues of a positive semidefinite matrix are **non-negative**

$$\forall w \in \Re^n, w^T S w \geq 0, \text{ then if } \mathrm{Sv} = \lambda \mathrm{v} \Rightarrow \lambda \geq 0$$

Eigen/diagonal Decomposition

- Let $\mathbf{S} \in \mathbb{R}^{m \times m}$ be a **square** matrix with ***m*** **linearly independent eigenvectors** (a "non-defective" matrix)



- **Theorem**: Exists an **eigen decomposition**

$$\mathbf{S} = \mathbf{U}\mathbf{\Lambda}\mathbf{U}^{-1}$$

diagonal

Unique for distinct eigen-values

  - (cf. matrix diagonalization theorem)

- Columns of ***U*** are **eigenvectors** of ***S***
- Diagonal elements of $\mathbf{\Lambda}$ are **eigenvalues** of $\mathbf{S}$

$$\mathbf{\Lambda} = \mathrm{diag}(\lambda_1, \ldots, \lambda_m), \quad \lambda_i \geq \lambda_{i+1}$$

Symmetric Eigen Decomposition

- If $\mathbf{S} \in \mathbb{R}^{m \times m}$ is a **symmetric** matrix:
- **Theorem**: Exists a (unique) **eigen decomposition** $S = Q \Lambda Q^T$
- where ***Q*** is **orthogonal:**
  - $Q^{-1} = Q^T$
  - Columns of ***Q*** are normalized eigenvectors
  - Columns are orthogonal.
  - (everything is real)

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  - Building intuition: Playing with t-SNE parameters
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  - Autoencoders

5. Singular value decomposition (general m x n matrices)

Singular Value Decomposition

For an $m \times n$ matrix $\mathbf{A}$ of rank r there exists a factorization (Singular Value Decomposition = **SVD**) as follows:

$$A = U\Sigma V^T$$

$m \times m$ $\quad$ $m \times n$ $\quad$ V is $n \times n$

The columns of $\boldsymbol{U}$ are orthogonal eigenvectors of $\boldsymbol{AA^T}$.

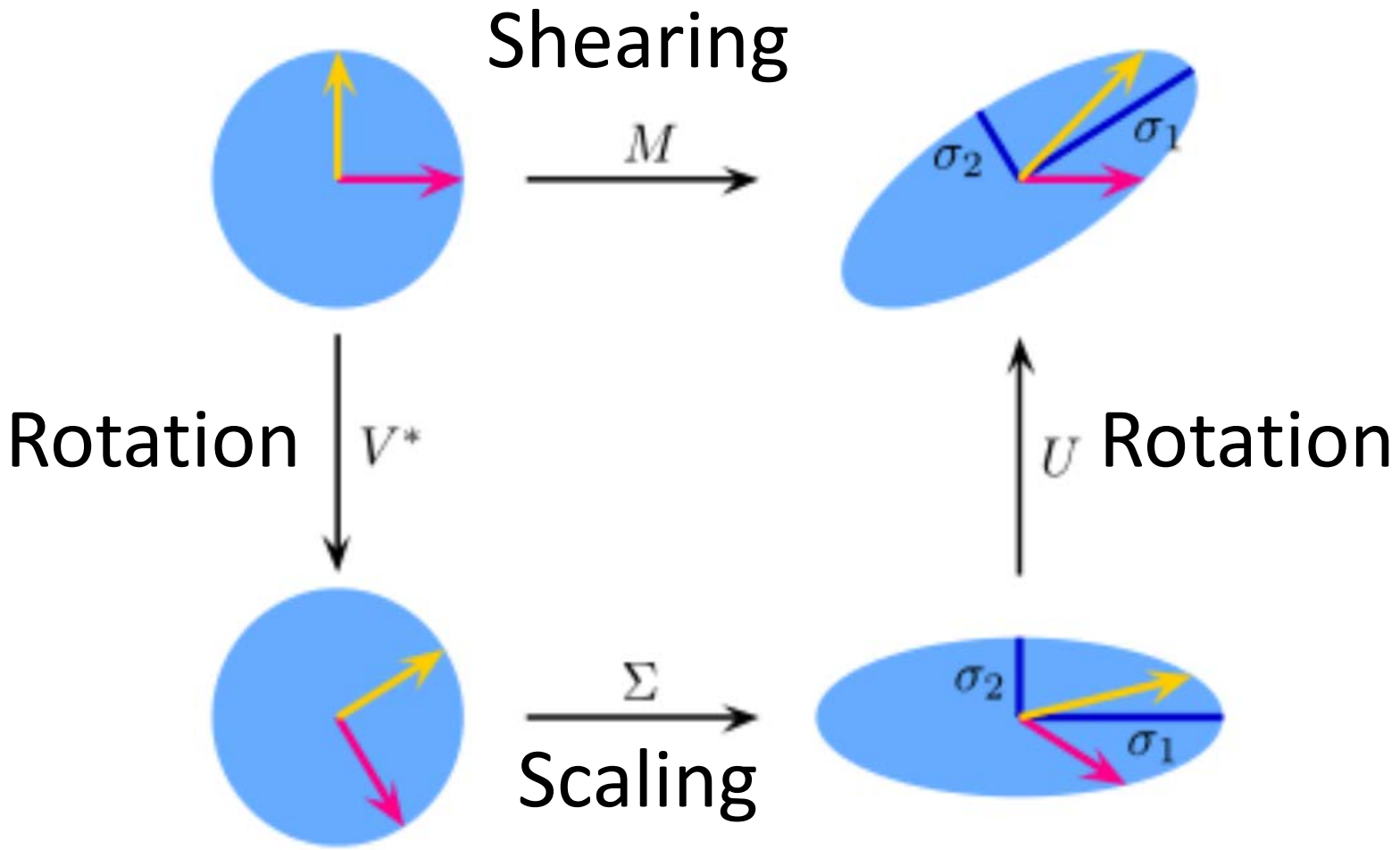
The columns of $\boldsymbol{V}$ are orthogonal eigenvectors of $\boldsymbol{A^TA}$.

Eigenvalues $\lambda_1 \ldots \lambda_r$ of $\boldsymbol{AA^T}$ are the eigenvalues of $\boldsymbol{A^TA}$.

$$\sigma_i = \sqrt{\lambda_i}$$

$$\Sigma = diag(\sigma_1 \ldots \sigma_r)$$ ← *Singular values.*

Geometric interpretation of SVD

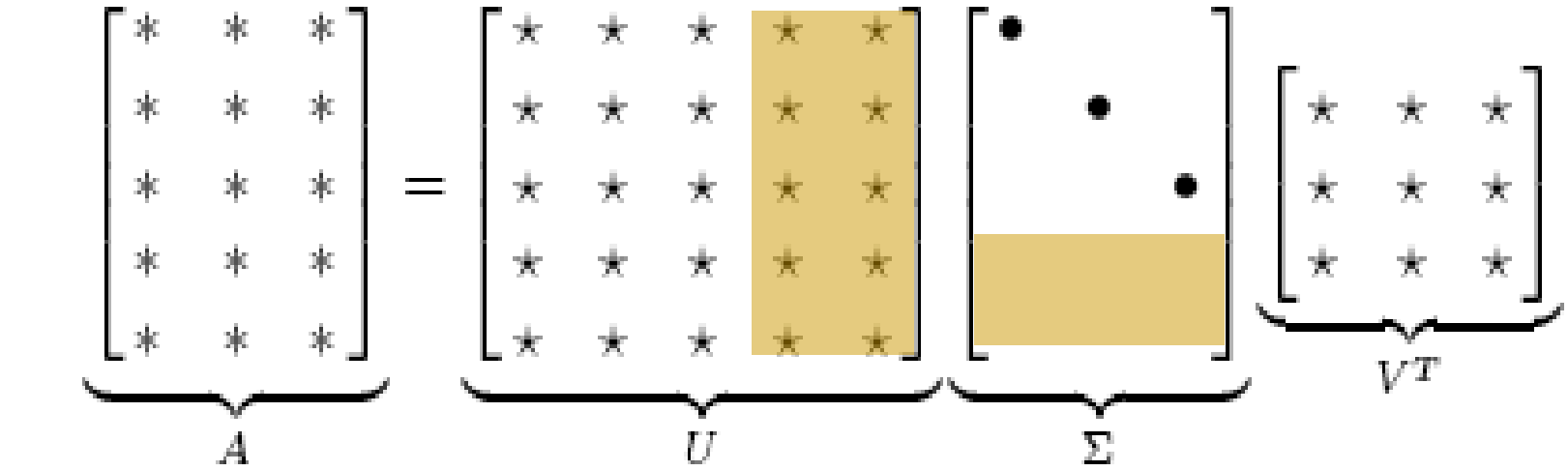


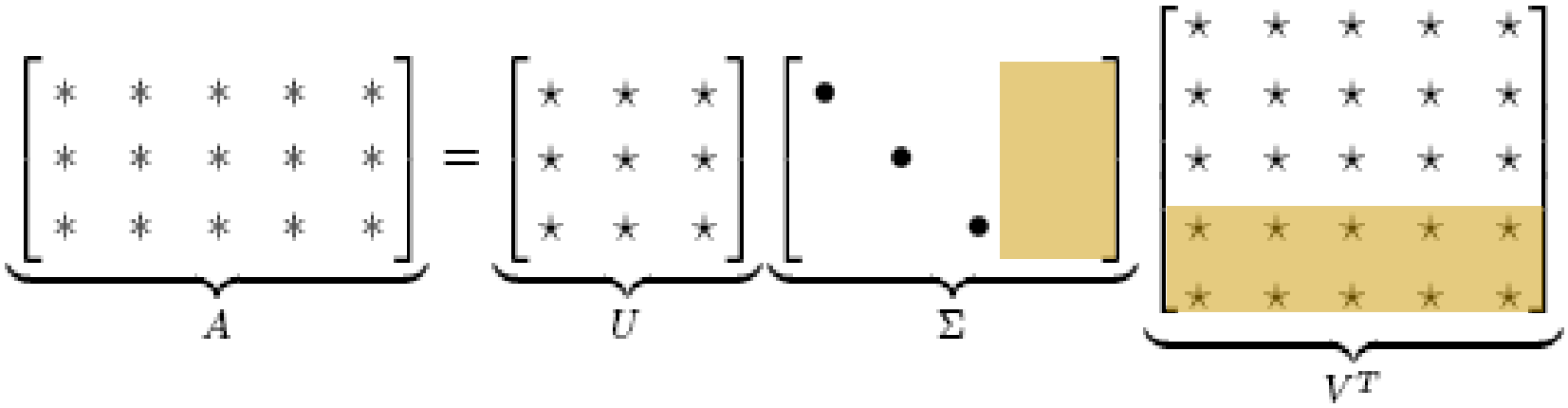
$$M = U \cdot \Sigma \cdot V^*$$

Mx = M(x) = U(S(V*(x)))

Singular Value Decomposition

- Illustration of SVD dimensions and sparseness





Singular Value Decomposition-example

- Let $A = \begin{bmatrix} 1 & -1 \\ 0 & 1 \\ 1 & 0 \end{bmatrix}$

Thus $m=3$, $n=2$. Its SVD is

$$\begin{bmatrix} 0 & 2/\sqrt{6} & 1/\sqrt{3} \\ 1/\sqrt{2} & -1/\sqrt{6} & 1/\sqrt{3} \\ 1/\sqrt{2} & 1/\sqrt{6} & -1/\sqrt{3} \end{bmatrix} \begin{bmatrix} 1 & 0 \\ 0 & \sqrt{3} \\ 0 & 0 \end{bmatrix} \begin{bmatrix} 1/\sqrt{2} & 1/\sqrt{2} \\ 1/\sqrt{2} & -1/\sqrt{2} \end{bmatrix}$$

Typically, the singular values arranged in decreasing order.

Low-rank Approximation

- SVD can be used to compute optimal **low-rank approximations**.
- Approximation problem: Find $\boldsymbol{A_k}$ of rank $\boldsymbol{k}$ such that

$$A_k = \min_{X:rank(X)=k} \|A - X\|_F$$

Frobenius norm (aka Euclidian norm)

$$\|A\|_F \equiv \sqrt{\sum_{i=1}^{m}\sum_{j=1}^{n} |a_{ij}|^2}.$$

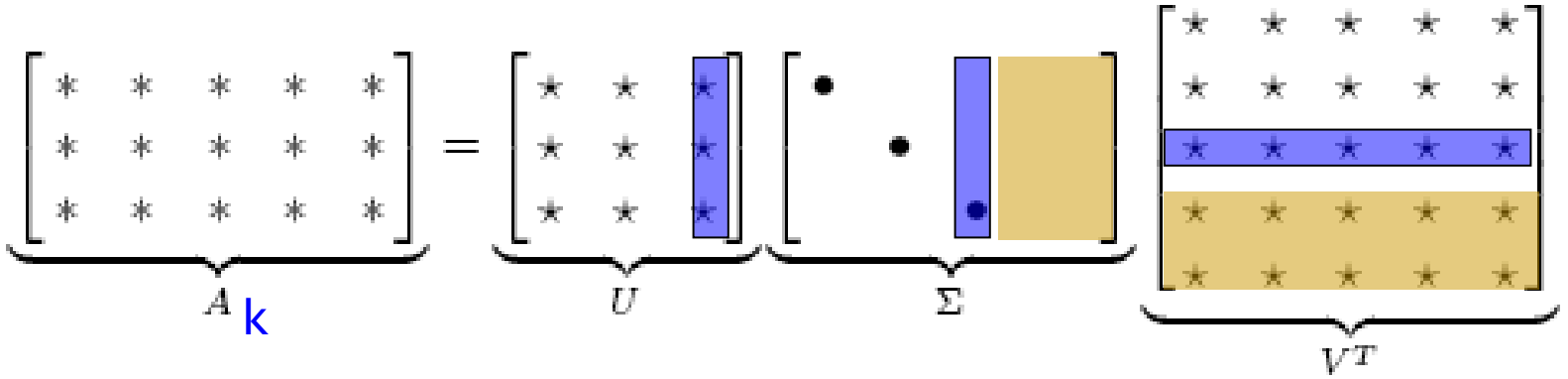
A_k and X are both $m \times n$ matrices.

Typically, want $k << r$.

Low-rank Approximation

- Solution via SVD

$$A_k = U\,\mathrm{diag}(\sigma_1,\ldots,\sigma_k,\underbrace{0,\ldots,0}_{\text{set smallest r-k singular values to zero}})V^T$$



$$A_k = \sum_{i=1}^{k} \sigma_i u_i v_i^T$$

column notation: sum of rank 1 matrices

- Error: $\min_{X:rank(X)=k} \|A - X\|_F = \|A - A_k\|_F = \sigma_{k+1}$

Principle Component Analysis (PCA)

- How do we find the eigenvectors v_i?
- We use singular value decomposition to decompose Σ into an orthogonal rotation matrix U and a diagonal scaling matrix S:

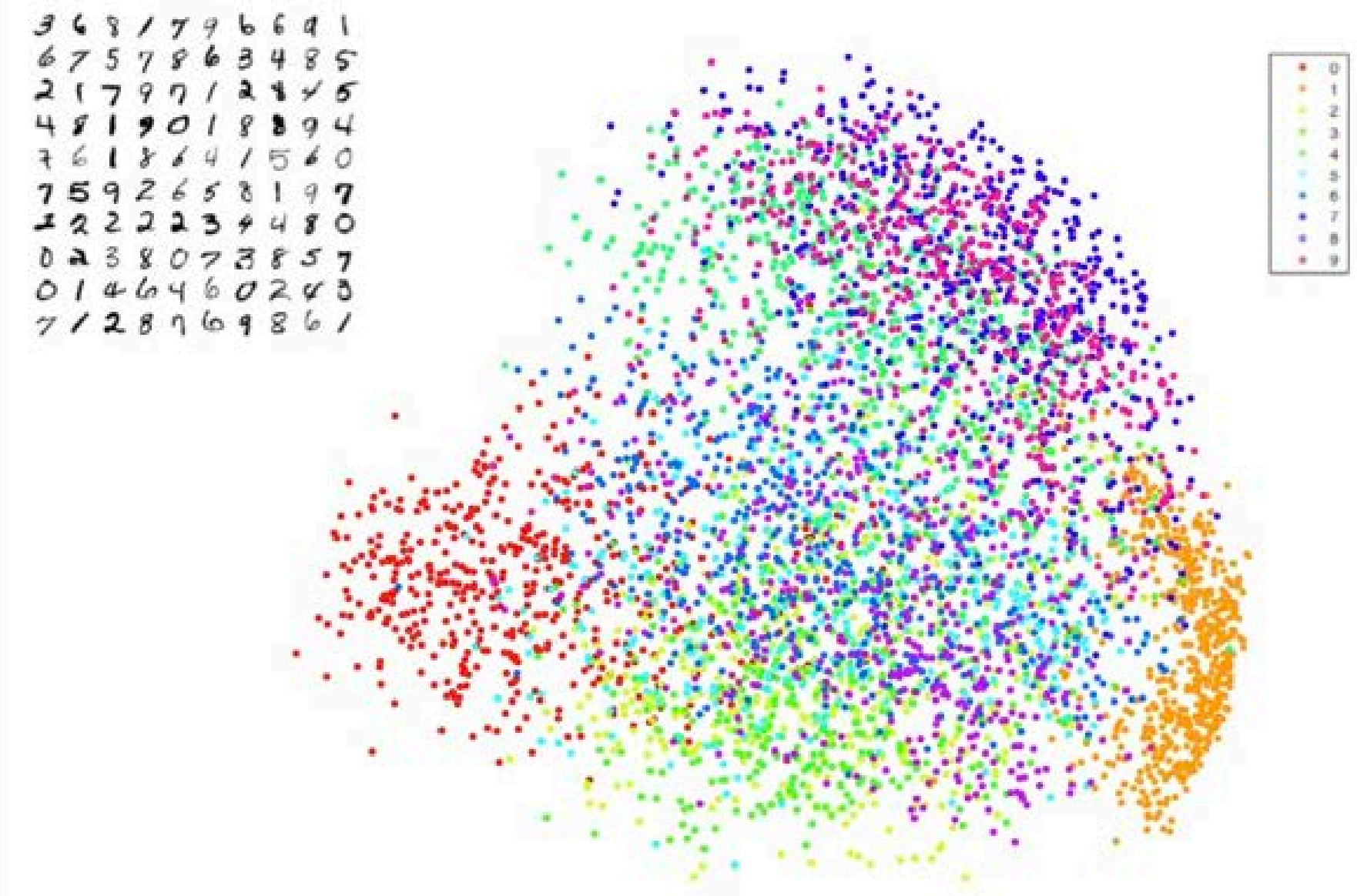
$$\Sigma = USU^T \tag{22}$$

$$\Sigma U = (USU^T)U \tag{23}$$

$$= US \tag{24}$$

- The columns of U are the v_i, and S is the diagonal matrix of eigenvalues λ_i^2

PCA of MNIST digits



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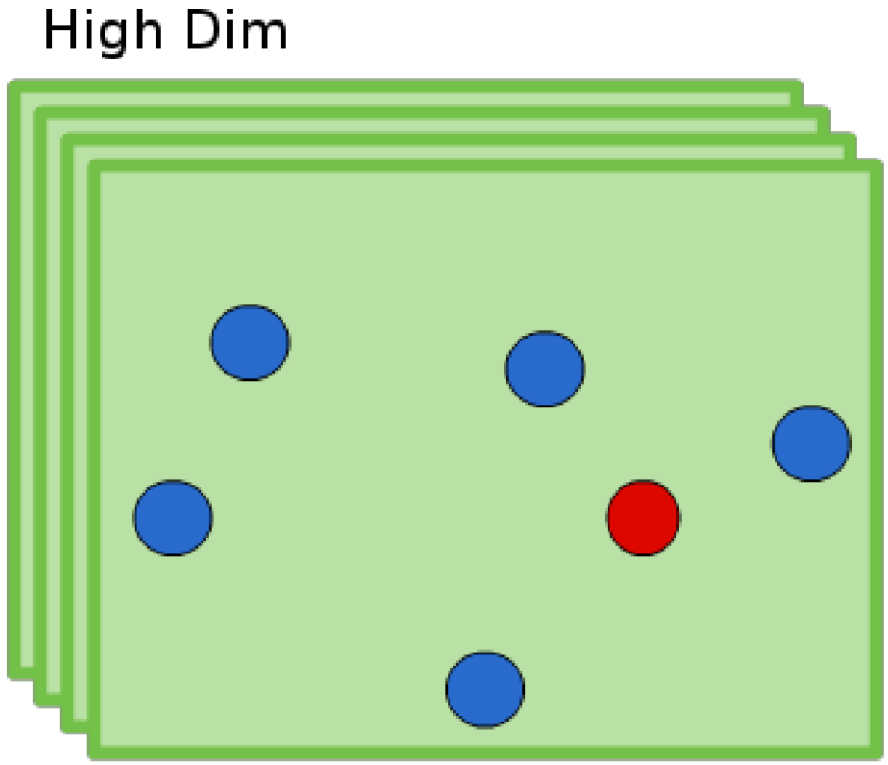
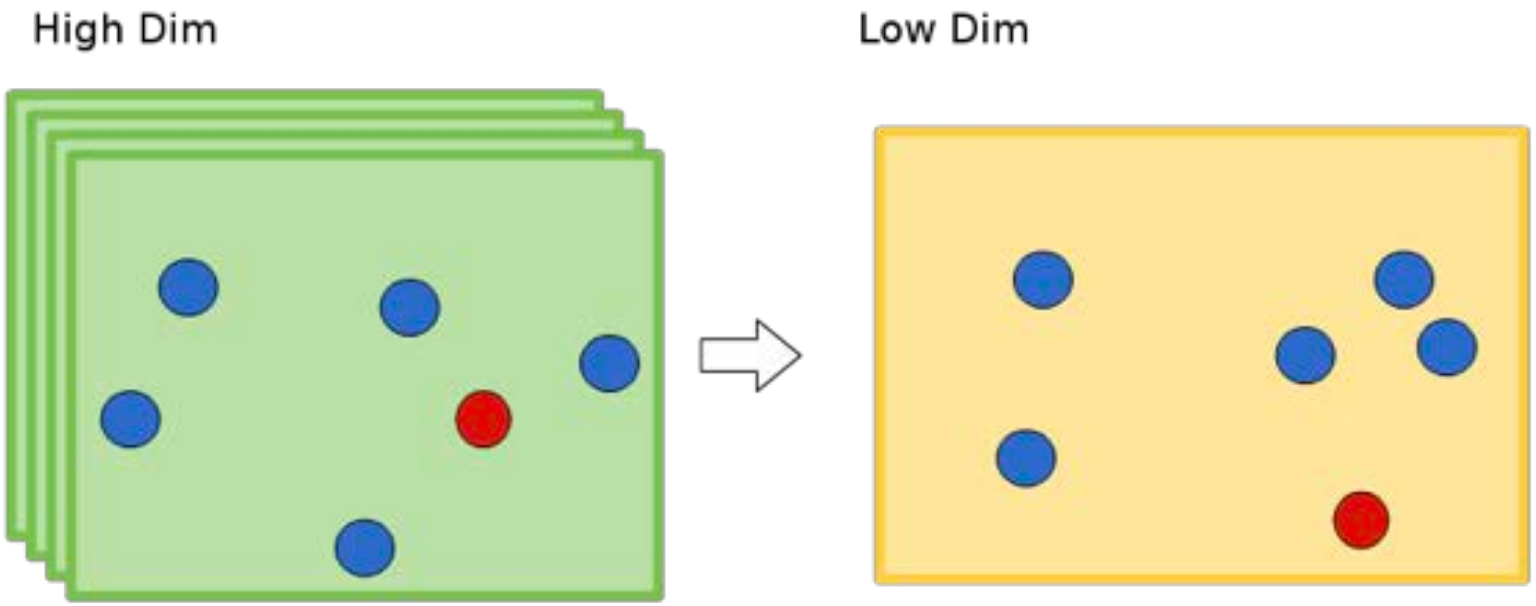
6. Non-linear embeddings: t-SNE

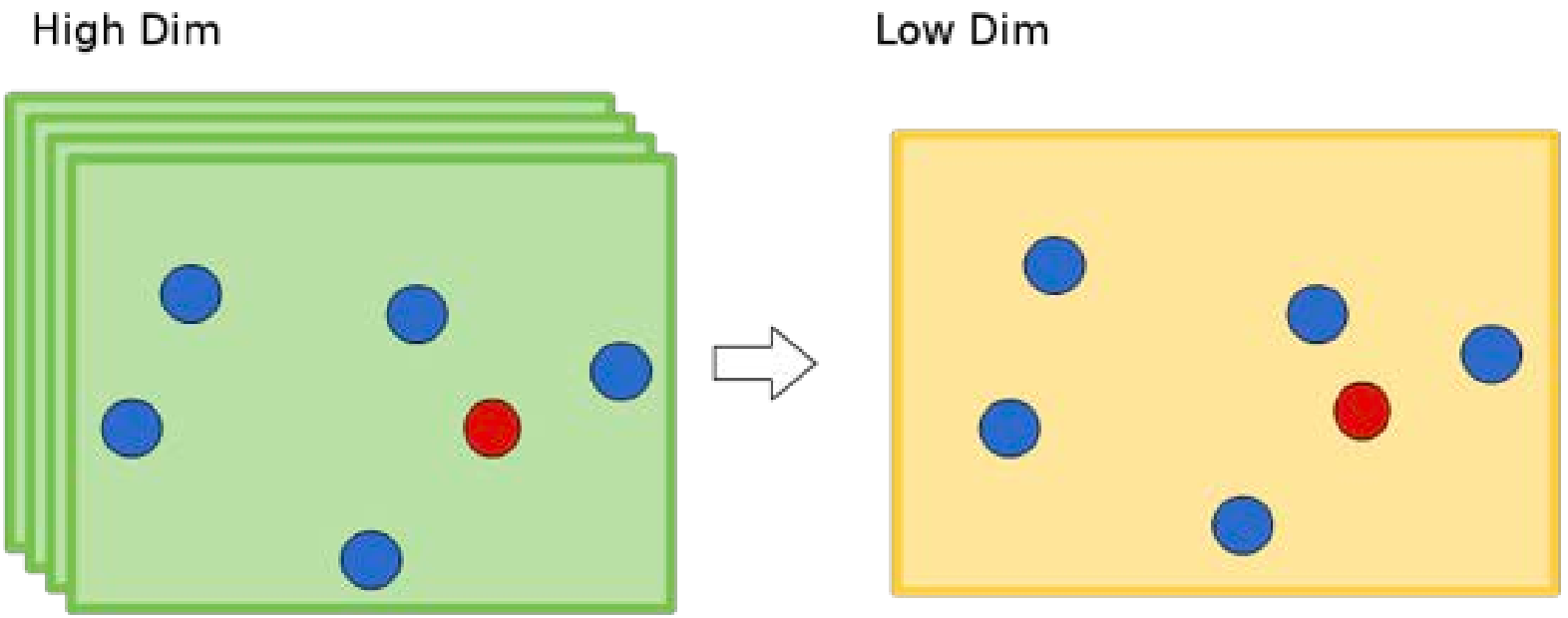
Distance Preservation Neighbor Preservation



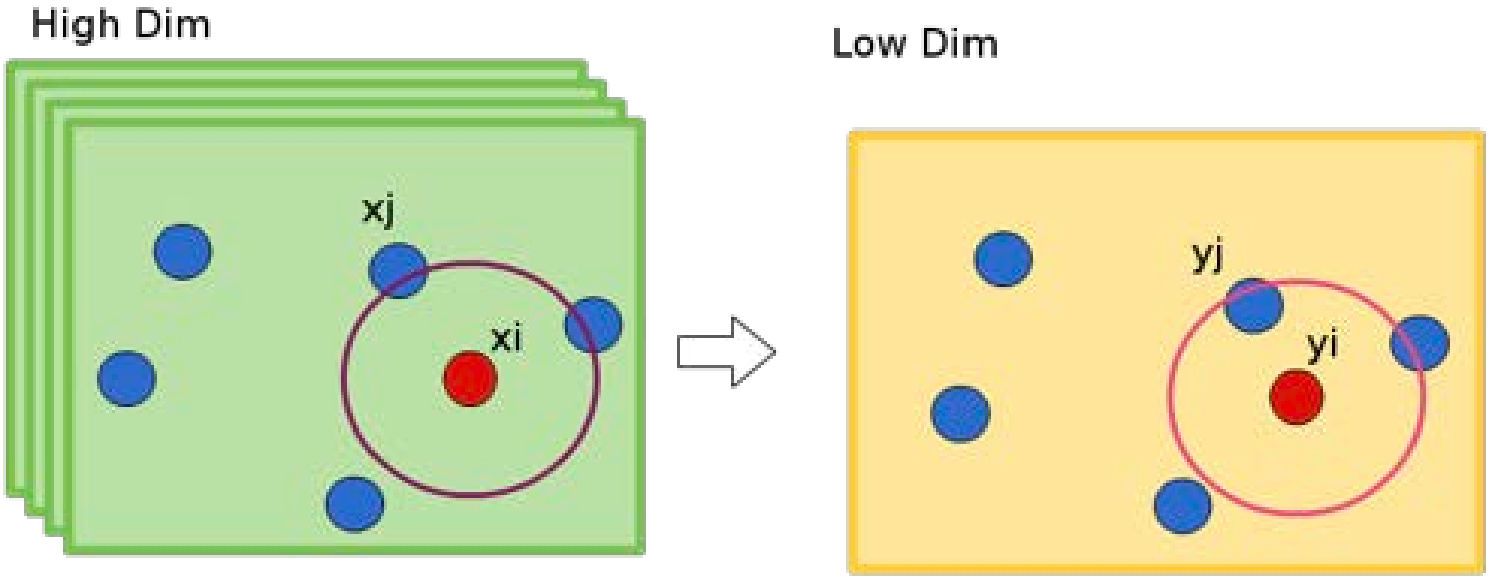
Neighborhood not preserved



Neighborhood preserved



Measure pairwise distances in high dimensional space



$$p_{j|i} = \frac{exp(-||x_i - x_j||^2/2\sigma_i^2)}{\sum_{k \neq i} exp(-||x_i - x_k||^2/2\sigma_i^2)}$$

Set the bandwidth σ_i such that the conditional has a fixed perplexity (effective number of neighbors) $Perp(P_i) = 2^{H(P_i)}$, typical value is about 5 to 50

Shannon entropy of P_i

We want to choose an embedding that minimizes divergence between low and high dimension similarities

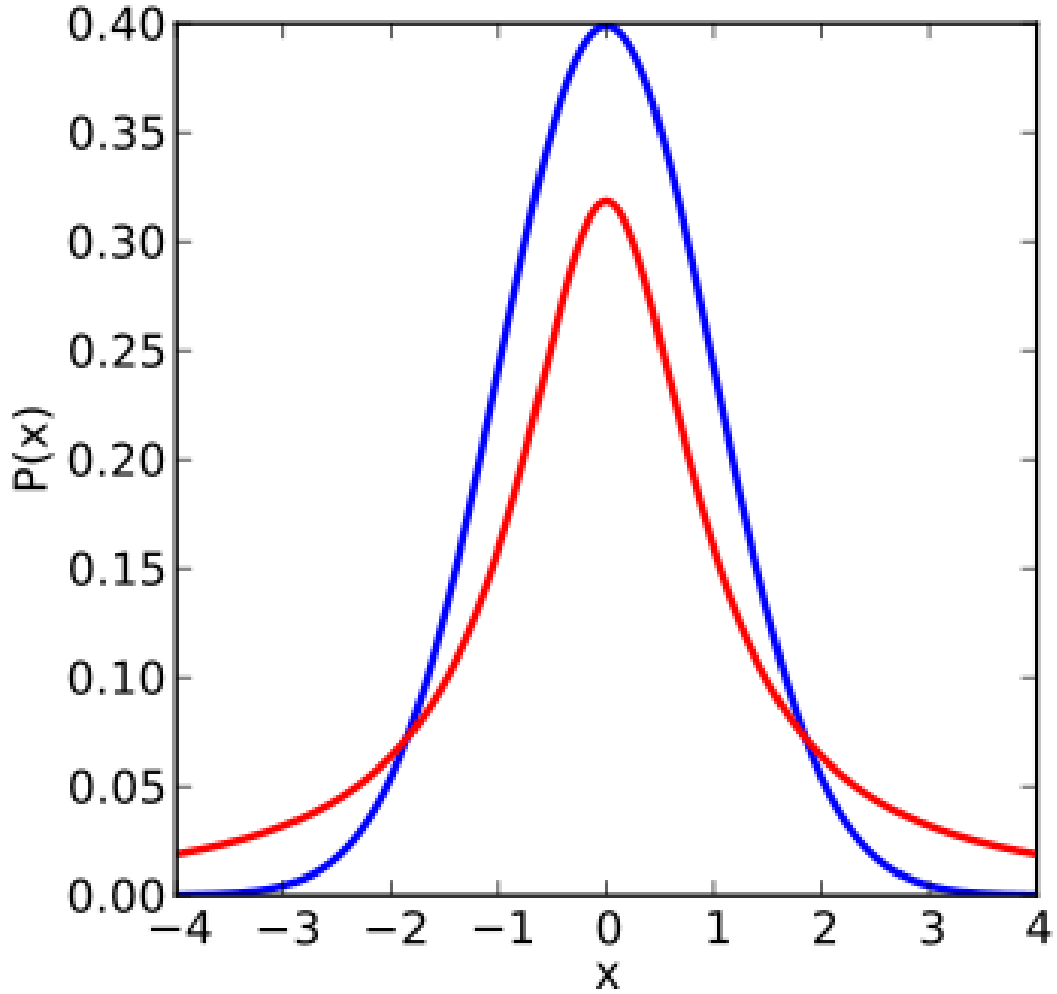
- Similarity of datapoints in High Dimension

$$p_{ij} = \frac{exp(-||x_i - x_j||^2/2\sigma^2)}{\sum_{k \neq l} exp(-||x_l - x_k||^2/2\sigma^2)}$$

- Similarity of datapoints in Low Dimension

$$q_{ij} = \frac{(1 + ||y_i - y_j||^2)^{-1}}{\sum_{k \neq l}(1 + ||y_k - y_l||^2)^{-1}}$$

Low dimensional embedding using a Student t-distribution to avoid overcrowding



Red – Student t-distribution (1 degree of freedom)

Blue - Gaussian

We can use gradient methods to find an embedding

- Cost function

p_{ij} = New (low) dimension distance

$$C = KL(P||Q) = \sum_i \sum_j p_{ij} log \frac{p_{ij}}{q_{ij}}$$

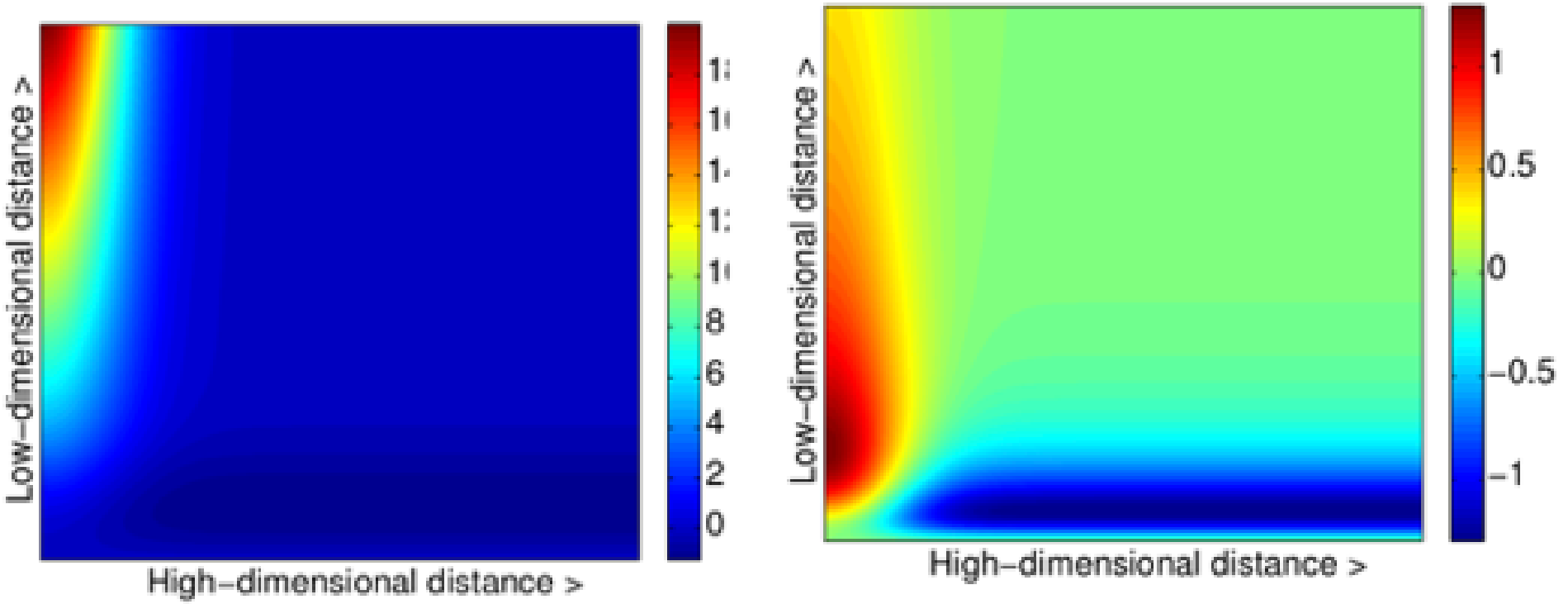
q_{ij} = Original (high) dimension D

  - Large p_{ij} modeled by small q_{ij}: Large penalty (not okay to bring distant points closer)
  - Small p_{ij} modeled by large q_{ij}: Small penalty (okay to separate nearby points)
  - t-SNE mainly preserves local similarity structure of the data

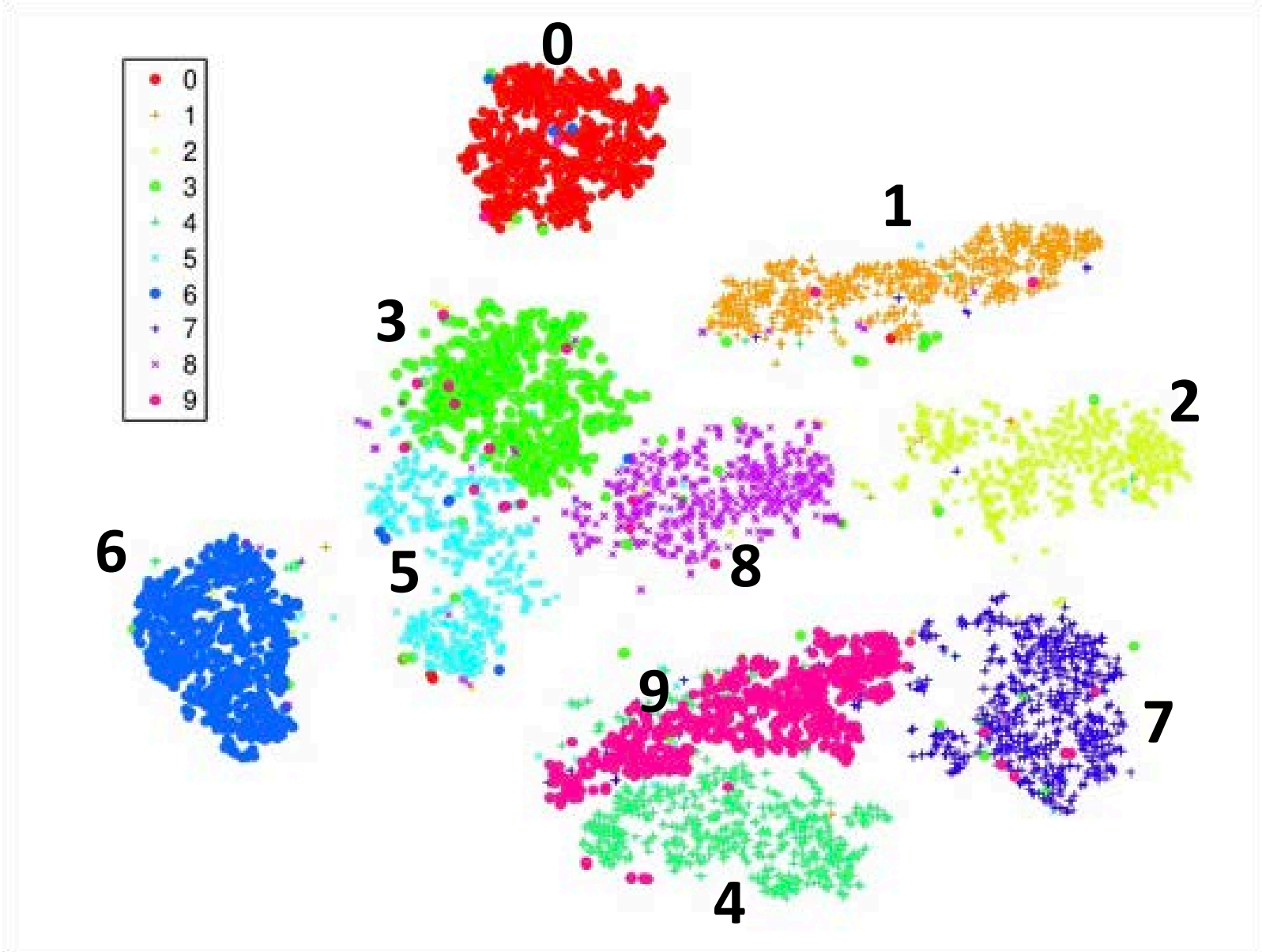
- Gradient

$$\frac{\partial C}{\partial y_i} = 4 \sum_{j \neq i} (p_{ij} - q_{ij})(1 + ||y_i - y_j||^2)^{-1}(y_i - y_j)$$

Interpretation of SNE (left) and t-SNE (right) gradients



t-SNE of MNIST digits



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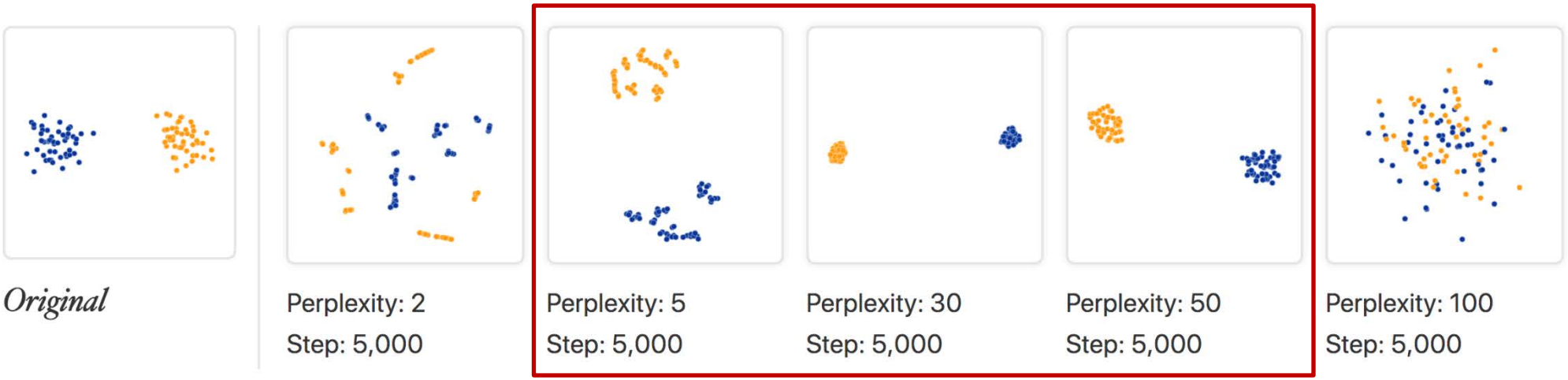
7. Playing with t-SNE parameters

Perplexity matters



Recommended range by Van Der Maaten and Hinton

https://distill.pub/2016/misread-tsne/

Number of steps matter

"pinched": Not enough steps

Too tight

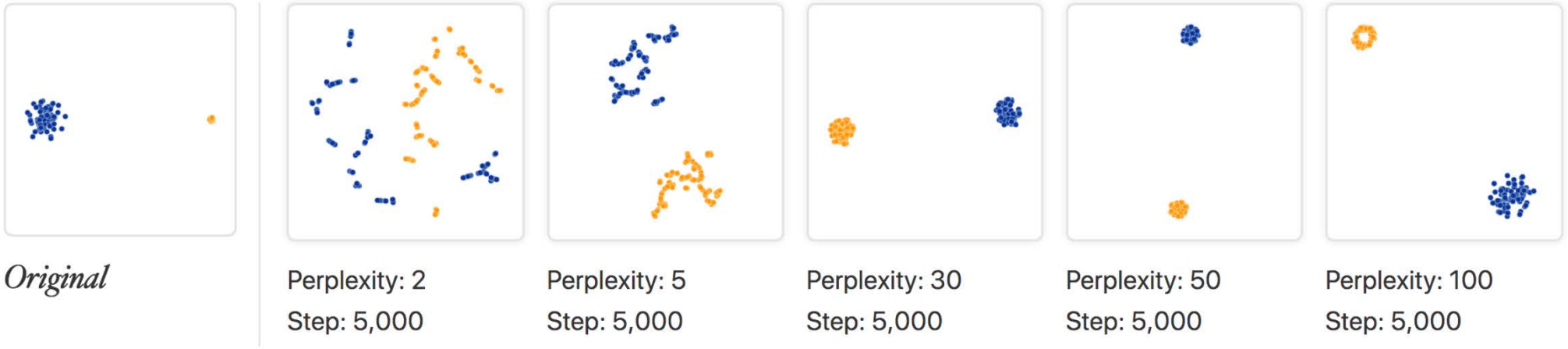
Spread again

Tight again

https://distill.pub/2016/misread-tsne/

Cluster sizes are not meaningful

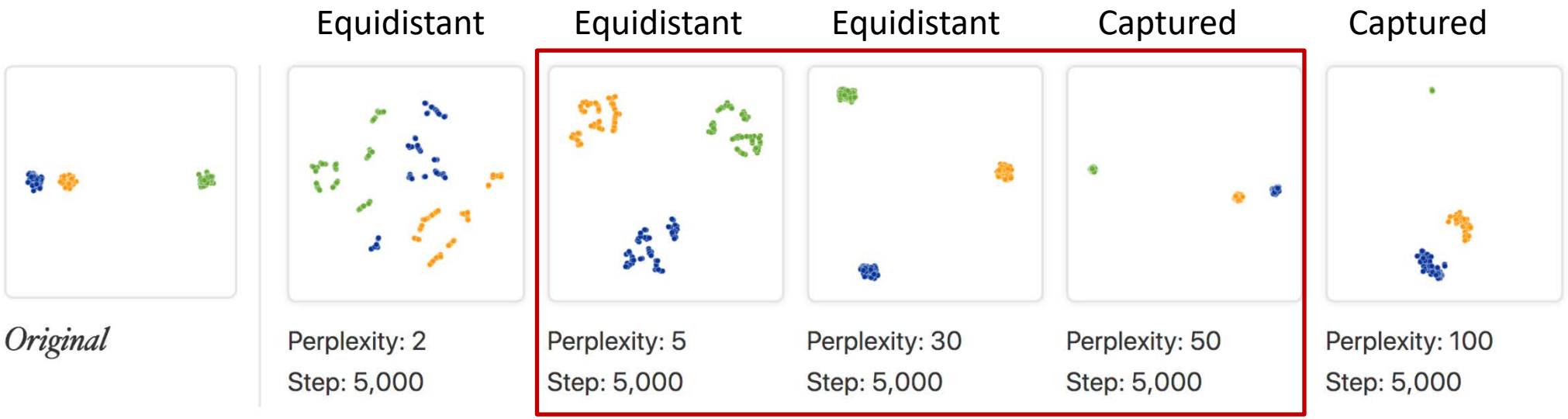
Original data: 2 Gaussians
Widely different (10-fold) dispersion



t-SNE loses that notion of distance.
By design, it adapts to regional variations in distance.

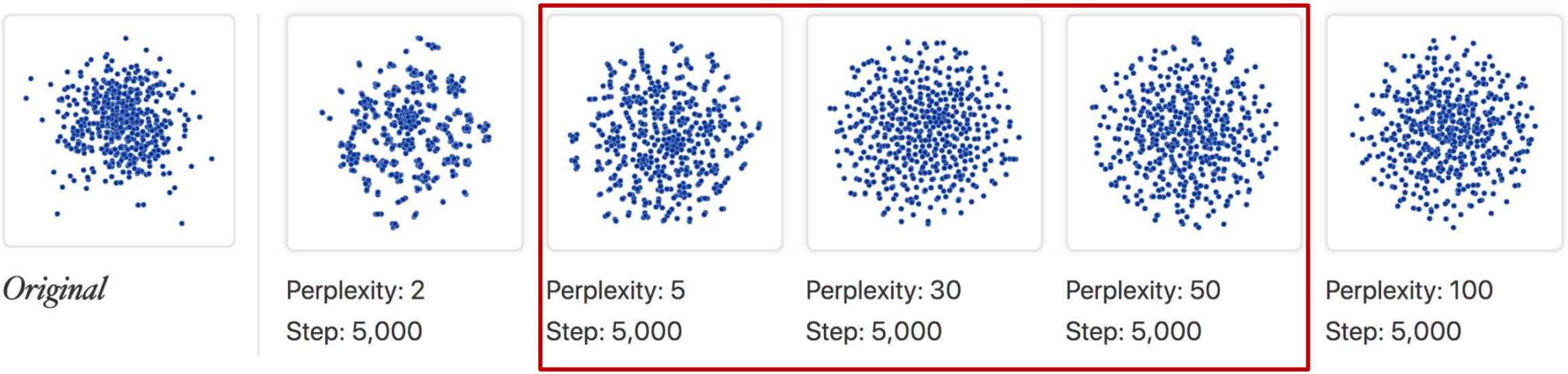
https://distill.pub/2016/misread-tsne/

Between-cluster distance is not always preserved



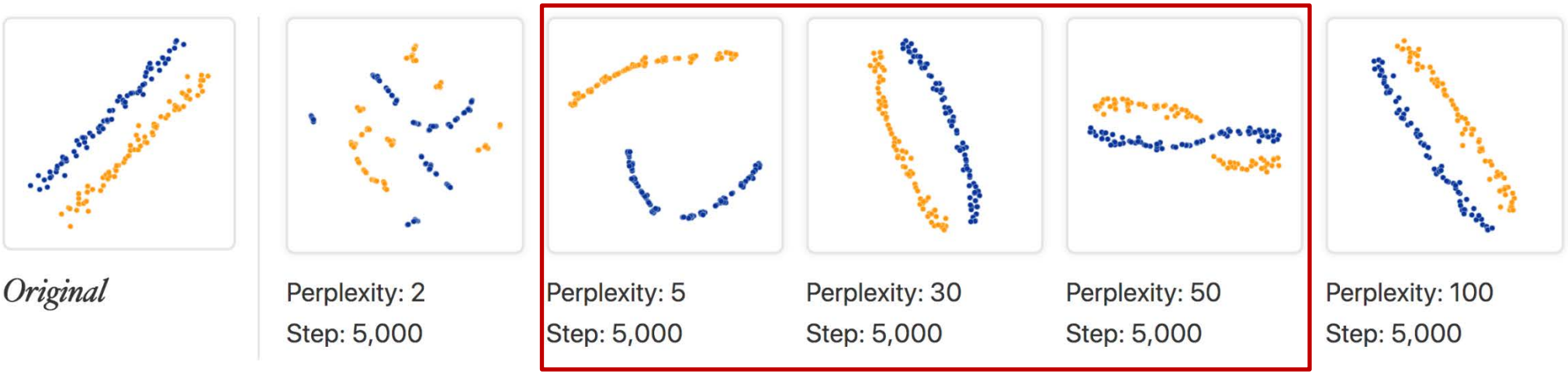
https://distill.pub/2016/misread-tsne/

False clusters may appear



https://distill.pub/2016/misread-tsne/

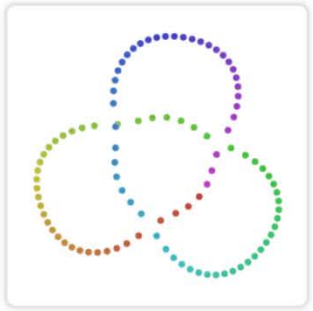
Relationships are not always preserved



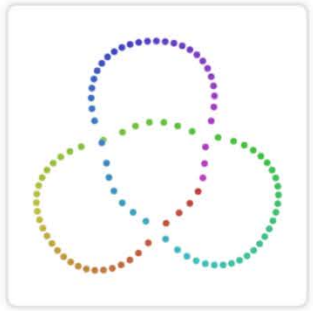
https://distill.pub/2016/misread-tsne/

Different runs may produce similar results…

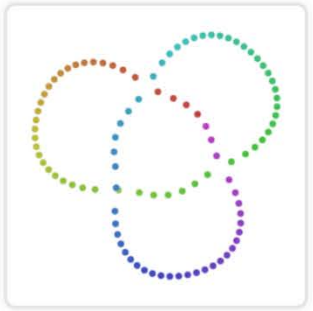
Original



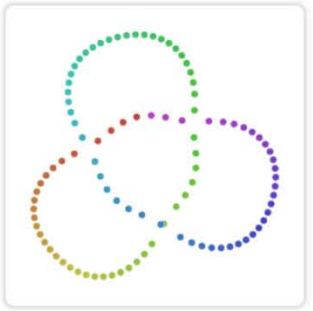
Perplexity: 50
Step: 5,000



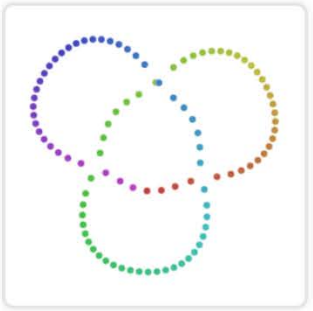
Perplexity: 50
Step: 5,000



Perplexity: 50
Step: 5,000

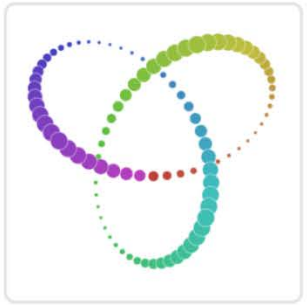


Perplexity: 50
Step: 5,000



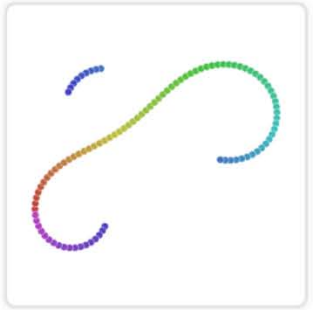
Perplexity: 50
Step: 5,000

(but not at very low perplexity)

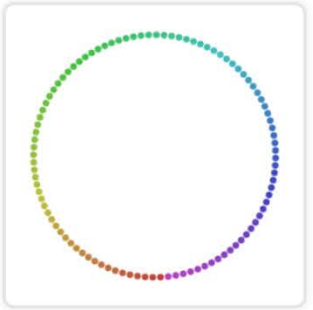


Original

Perplexity: 2
Step: 5,000



Perplexity: 2
Step: 5,000



Perplexity: 2
Step: 5,000

Perplexity: 2
Step: 5,000

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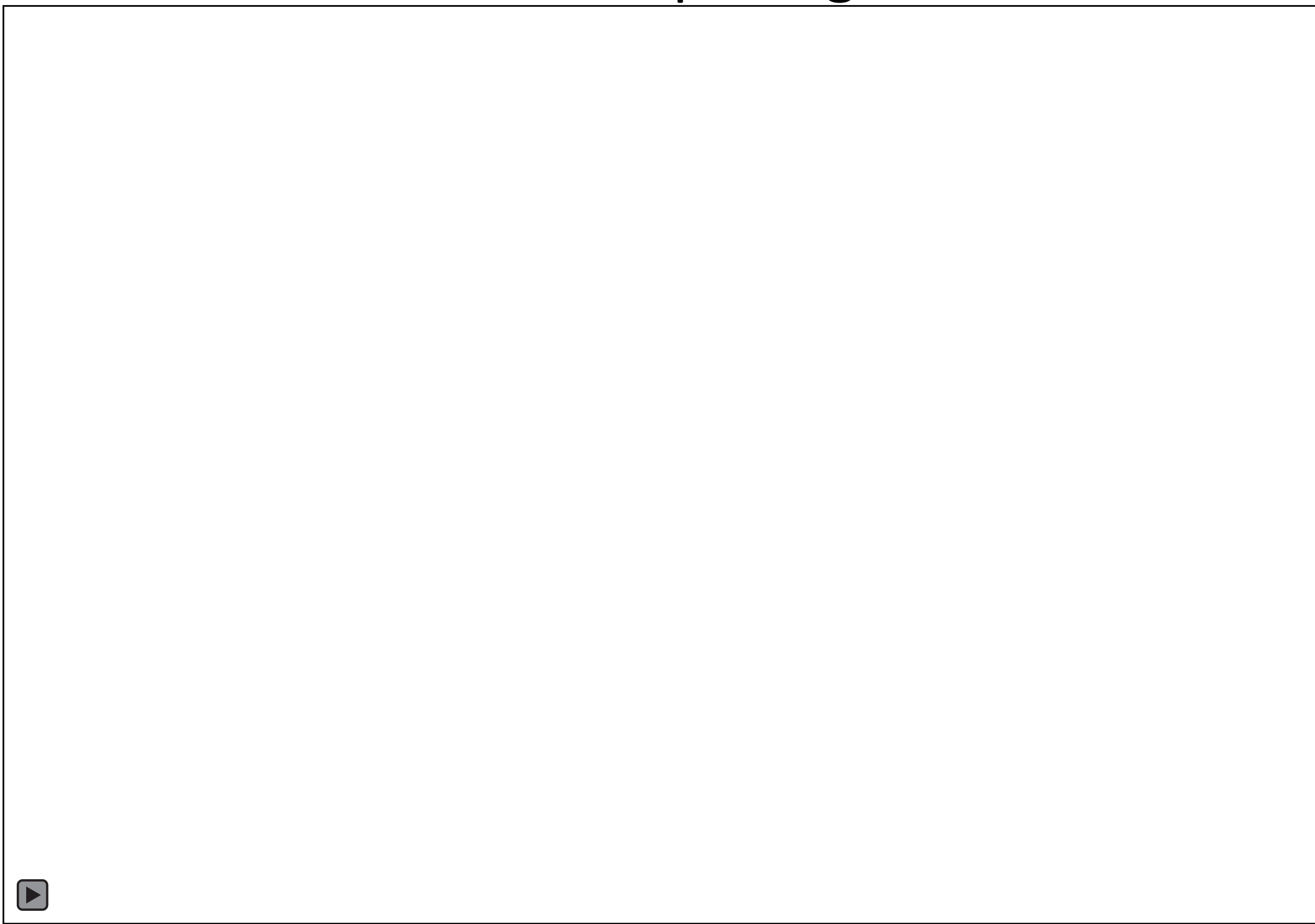
Step: 5,000

https://distill.pub/2016/misread-tsne/

t-SNE of equidistant points

t-SNE of square grid



t-SNE of 3D Knot

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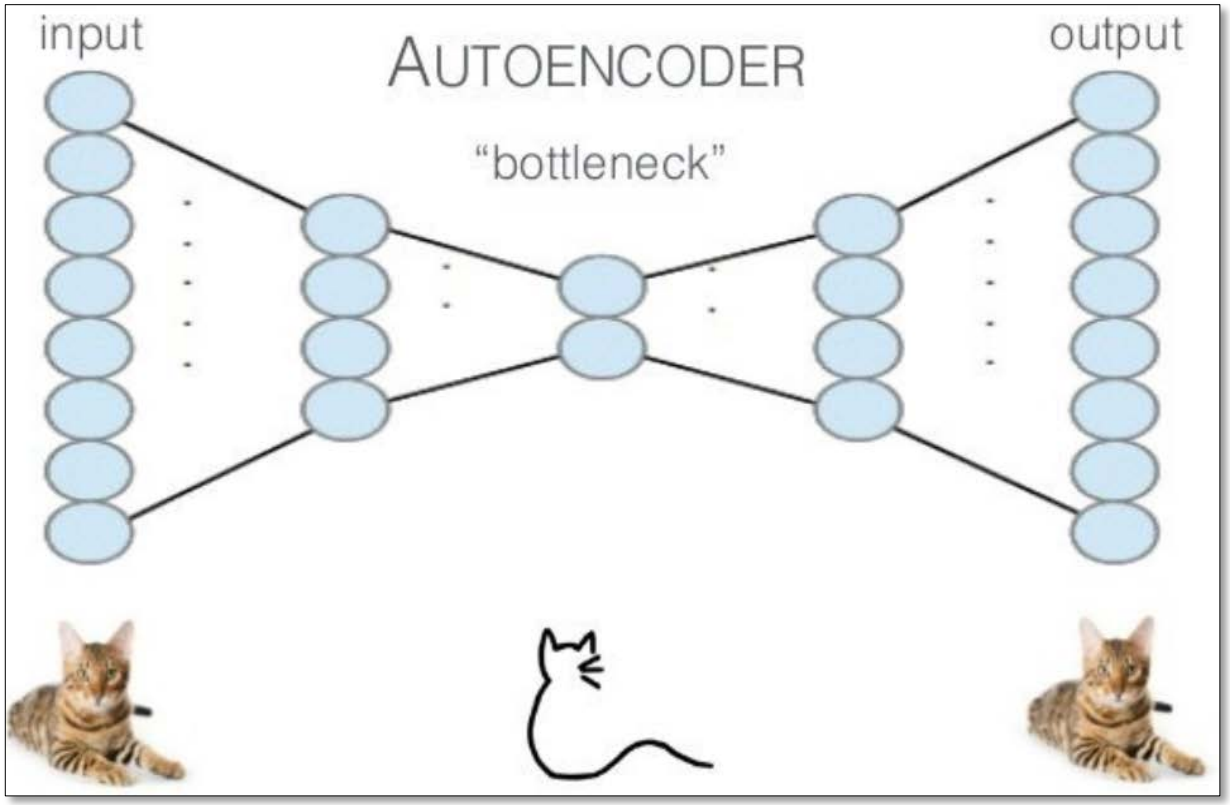
8. Embedding with Deep learning: Auto-encoders

Autoencoder: dimensionality reduction with neural net

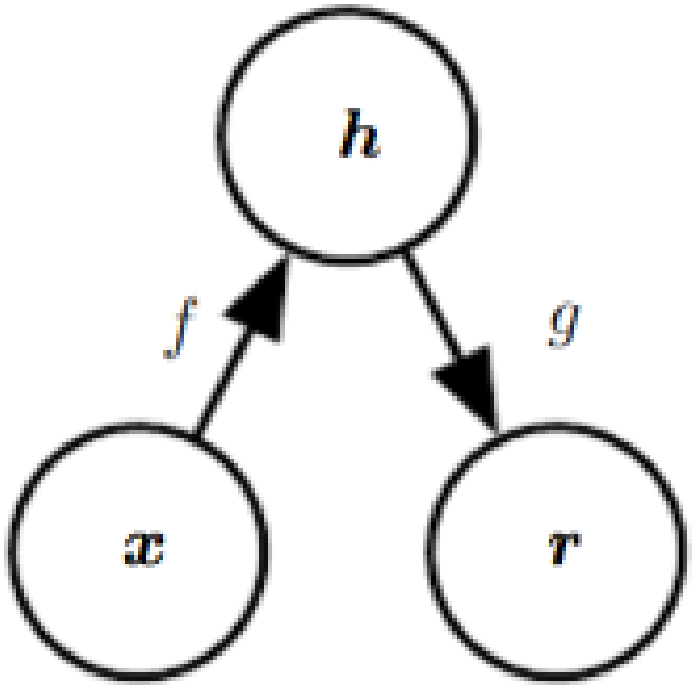


- Tricking a **supervised** learning algorithm to work in **unsupervised** fashion
- Feed input as output function to be learned. **But!** Constrain model complexity

- **Pretraining** with RBMs to learn representations for future supervised tasks. Use RBM output as "data" for training the next layer in stack
- After pretraining, "unroll" RBMs to create deep autoencoder
- Fine-tune using backpropagation

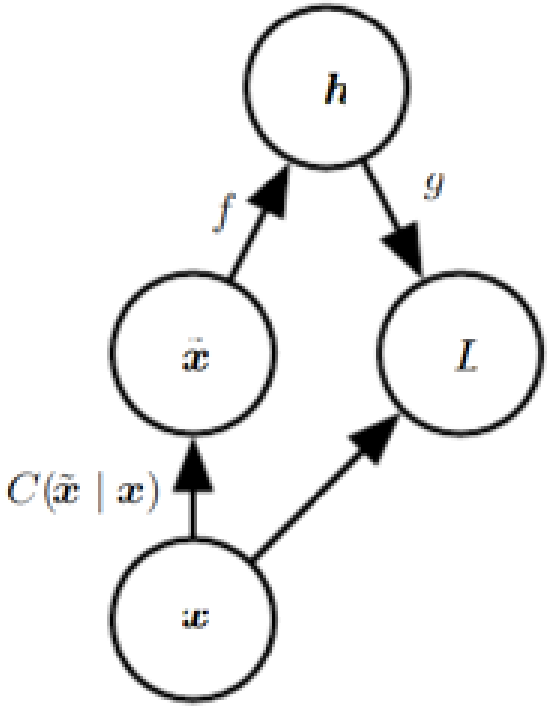
[Hinton *et al*, 2006]

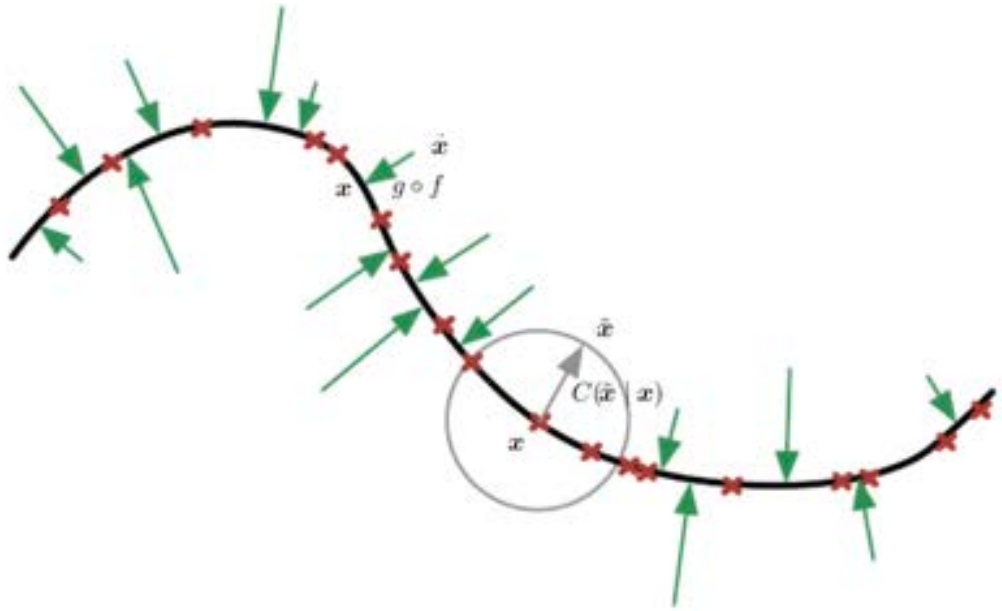
Autoencoders learn a latent representation of data



$$L(\boldsymbol{x}, g(f(\boldsymbol{x})))$$

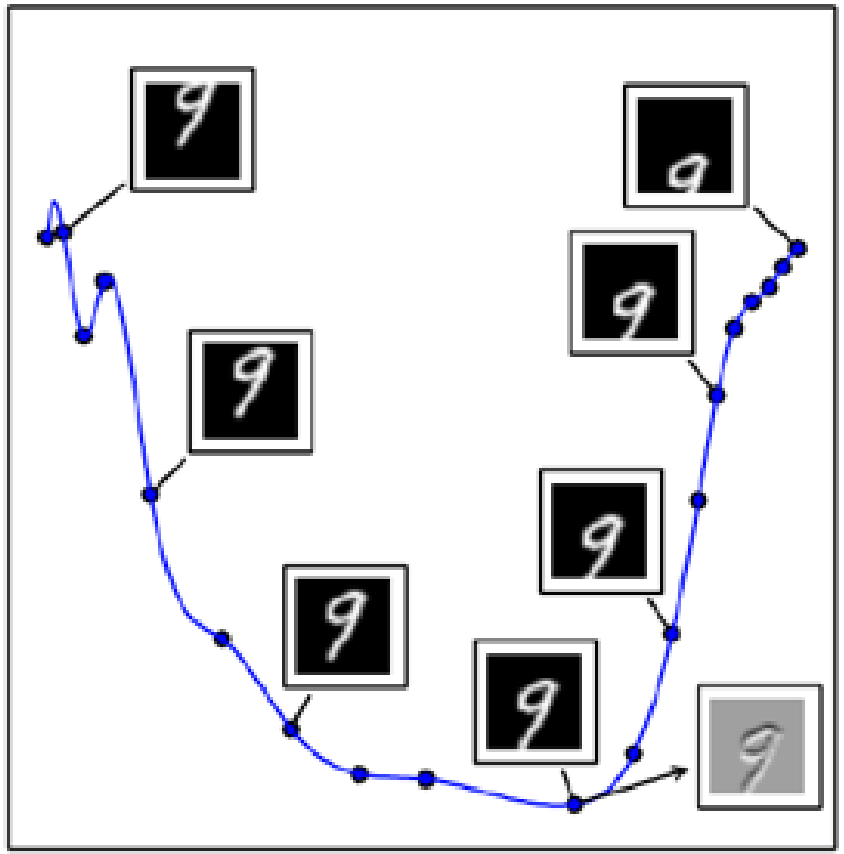
Denoising autoencoders recover signal corrupted by noise

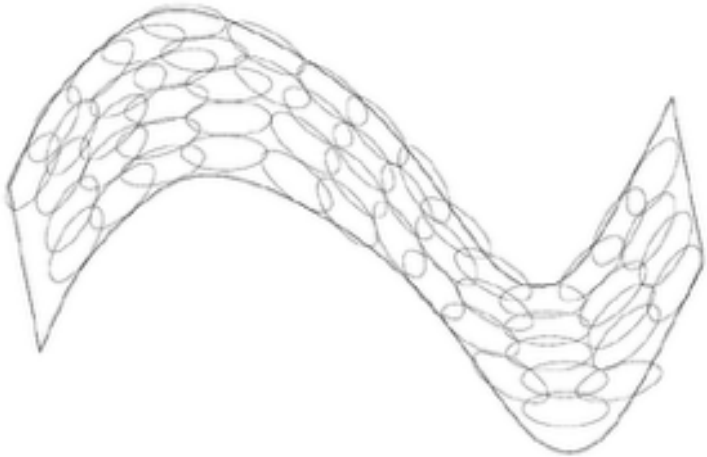




$$L(\boldsymbol{x}, g(f(\tilde{\boldsymbol{x}}))),$$

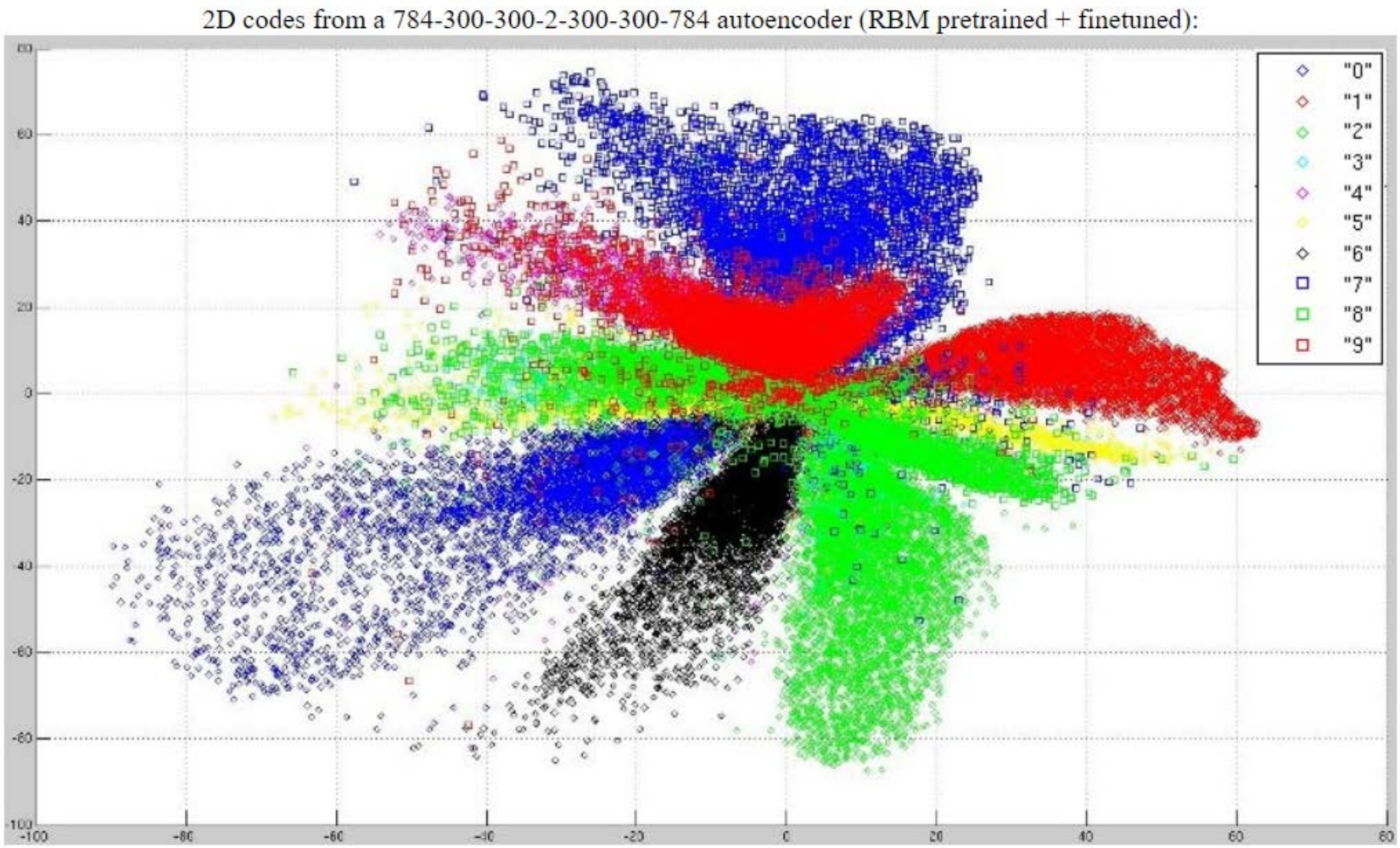
We can learn manifolds with autoencoders



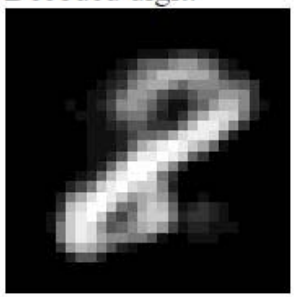


Auto-encoder learning of MNIST digit data

Autoencoder - MNIST



Decoded digit:



Pos X|Y: 77.28 -79.6000

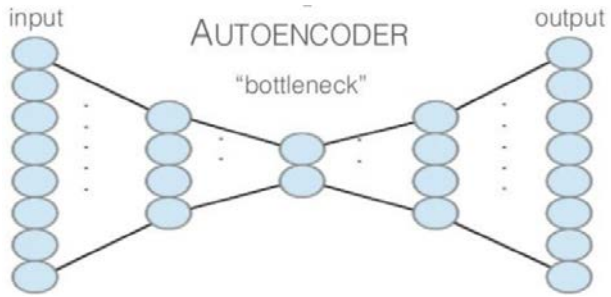
Mouse X|Y: 789 408

Offset X|Y: -453 -209

Scale X|Y: 0.23 -0.4

PosX=(MouseX+OffsetX)*ScaleX

PosY=(MouseY+OffsetY)*ScaleY



http://elf-project.sourceforge.net/autoencoder.html

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FIN - Thank You

Interesting on-line demos

http://dpkingma.com/sgvb_mnist_demo/demo_old.html
http://elf-project.sourceforge.net/autoencoder.html
http://vdumoulin.github.io/morphing_faces/online_demo.html