Clustering

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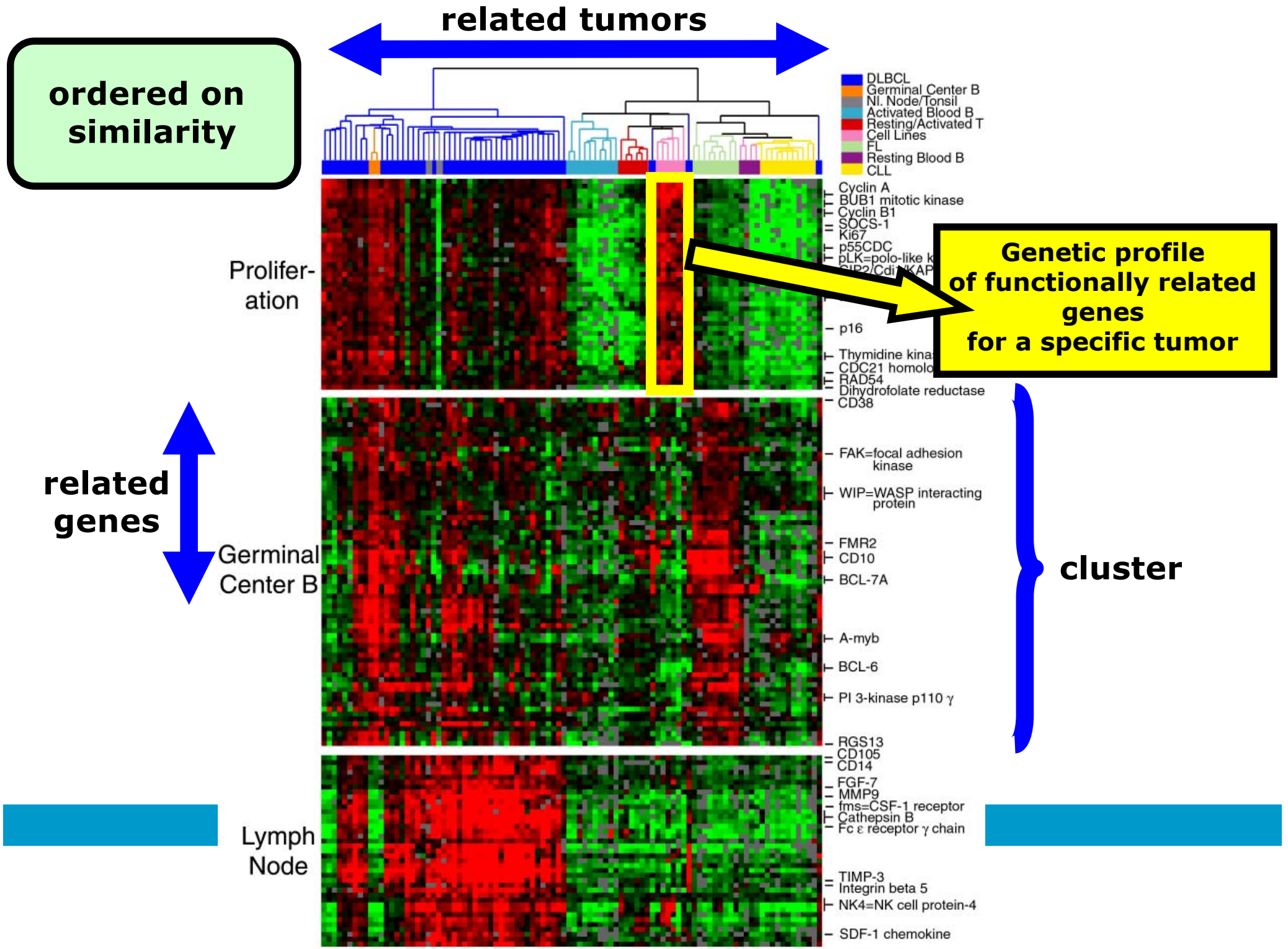
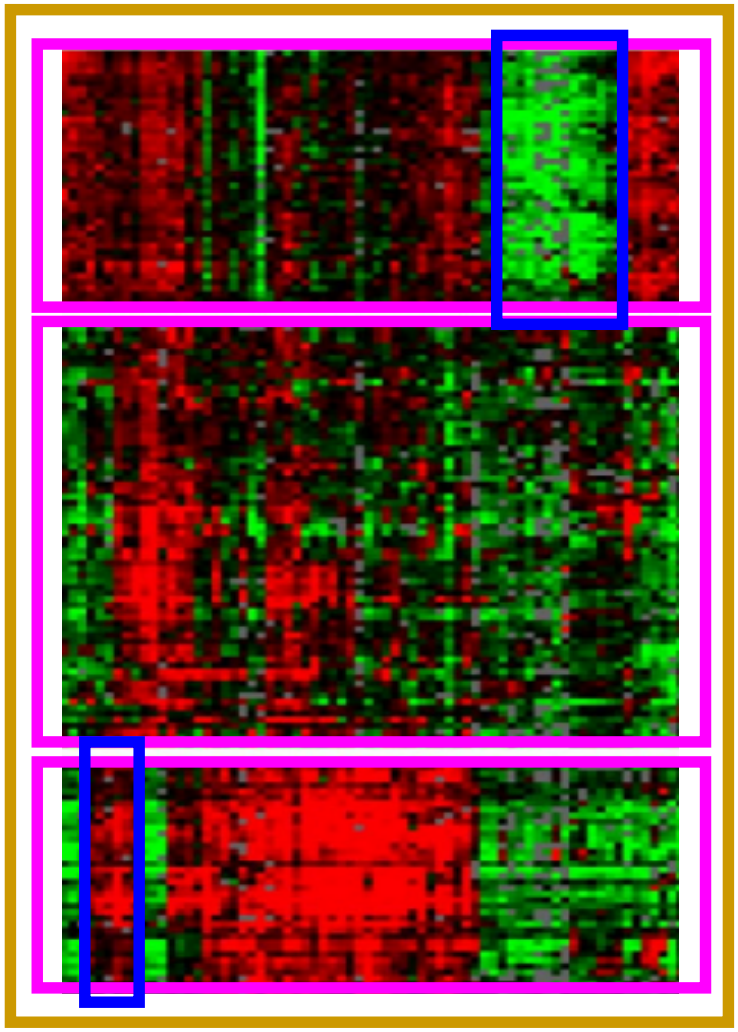
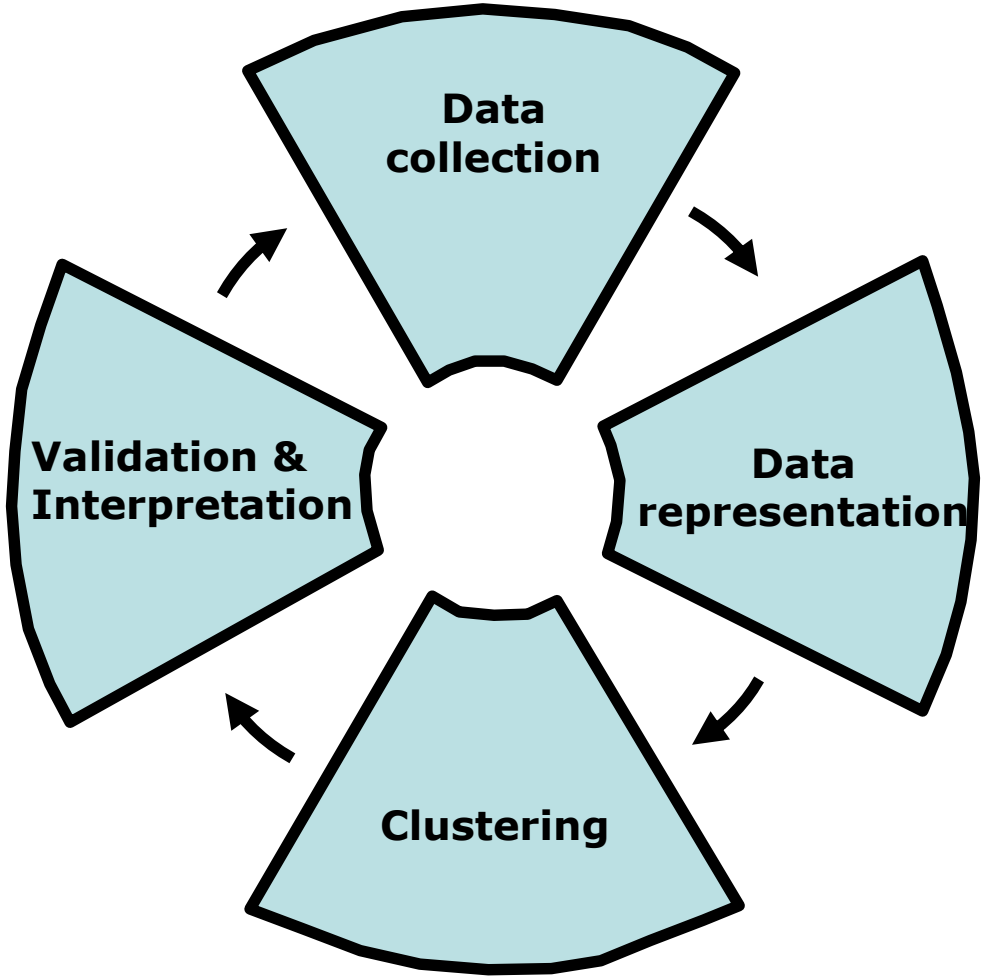

related tumors
ordered on similarity
DLBCL
Germinal Center B
NI. Node/Tonsil
Activated Blood B
Resting/Activated T
Cell Lines
FL
Resting Blood B
CLL
Cyclin A
BUB1 mitotic kinase
Cyclin B1
SOCS-1
Ki67
p55CDC
Proliferation
p16
Thymidine kina
CDC21 homolo
RAD54
Dihydrofolate reductase
CD38
Genetic profile of functionally related genes for a specific tumor
related genes
FAK=focal adhesion kinase
WIP=WASP interacting protein
FMR2
CD10
BCL-7A
Germinal Center B
A-myb
BCL-6
PI 3-kinase p110 γ
cluster
RGS13
CD105
CD14
FGF-7
MMP9
fms=CSF-1 receptor
Cathepsin B
Fc ε receptor γ chain
Lymph Node
TIMP-3
Integrin beta 5
NK4=NK cell protein-4
SDF-1 chemokine

Cluster analysis

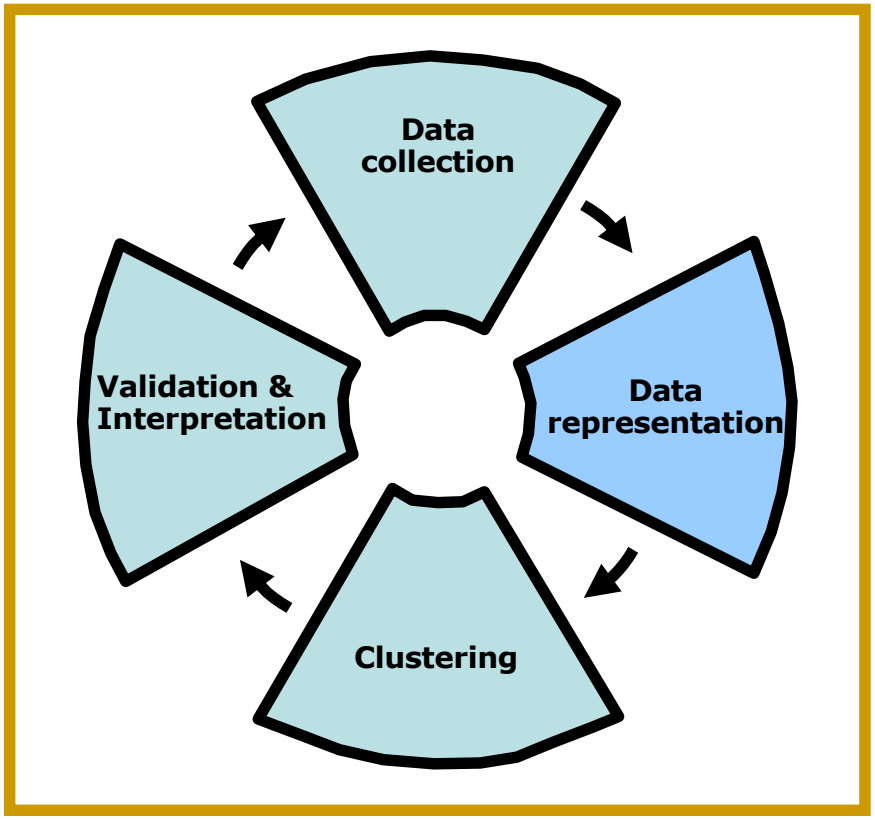


- **Group similar profiles**
- **Finding structure in the data**
- **Requisites:**
  - Measure of similarity
  - Grouping method
- **Subjective measures:**
  - Validation
  - Clustering is a process

Cluster analysis: The process



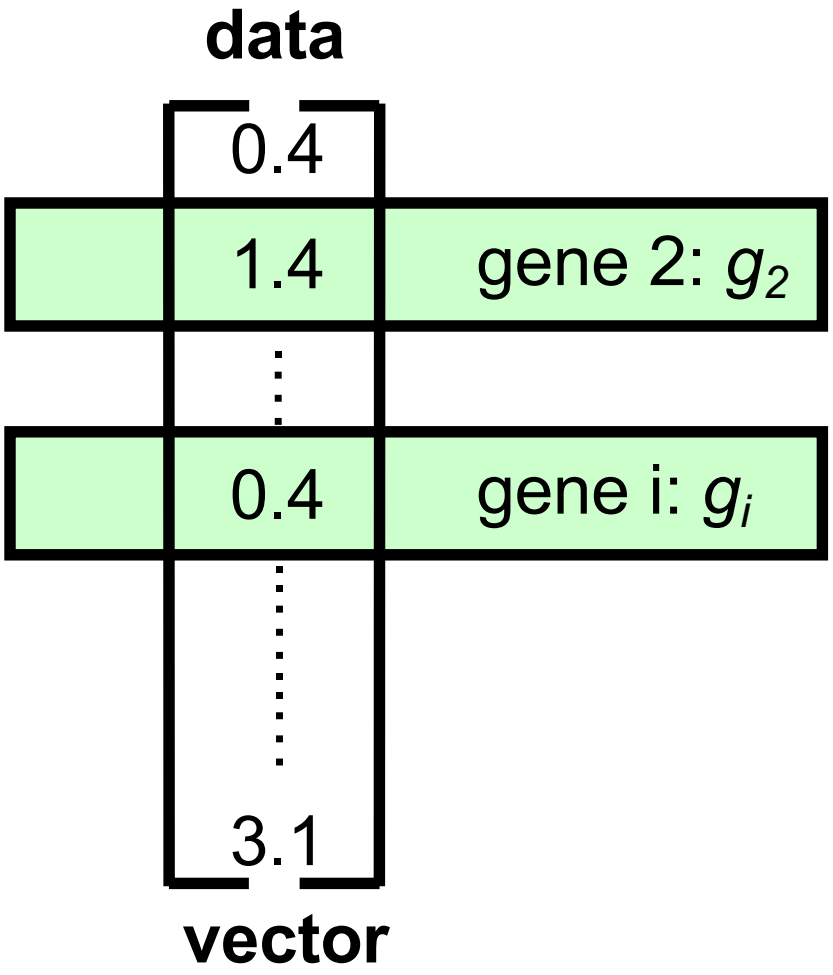
Data representation



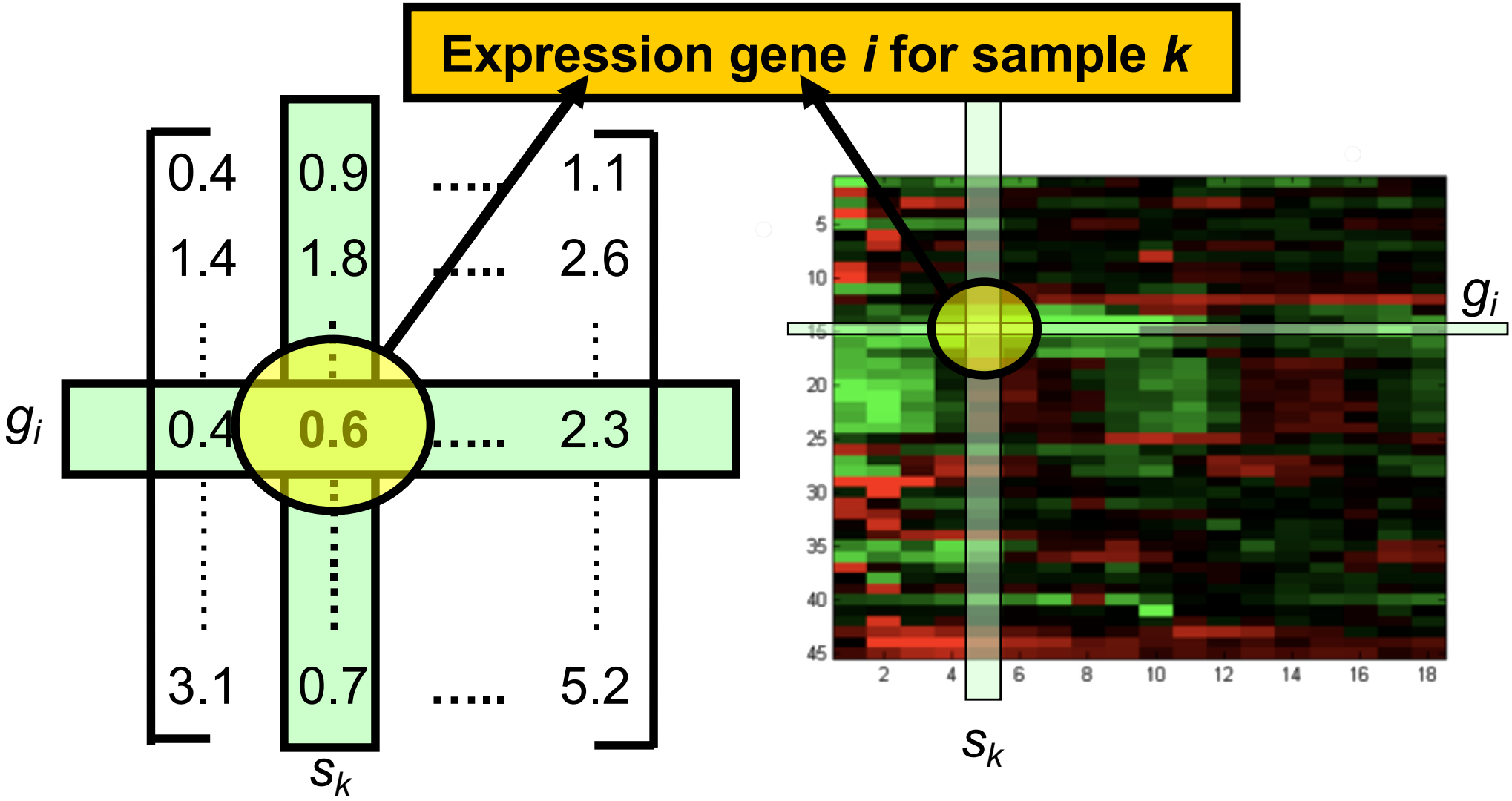
TOPICS

- **Data representation**
- **Data spaces:**
  - Sample-space
  - Gene-space
- **Clustering**

Data representation, one sample



Data representation, multiple samples



The Delft Bioinformatics Lab

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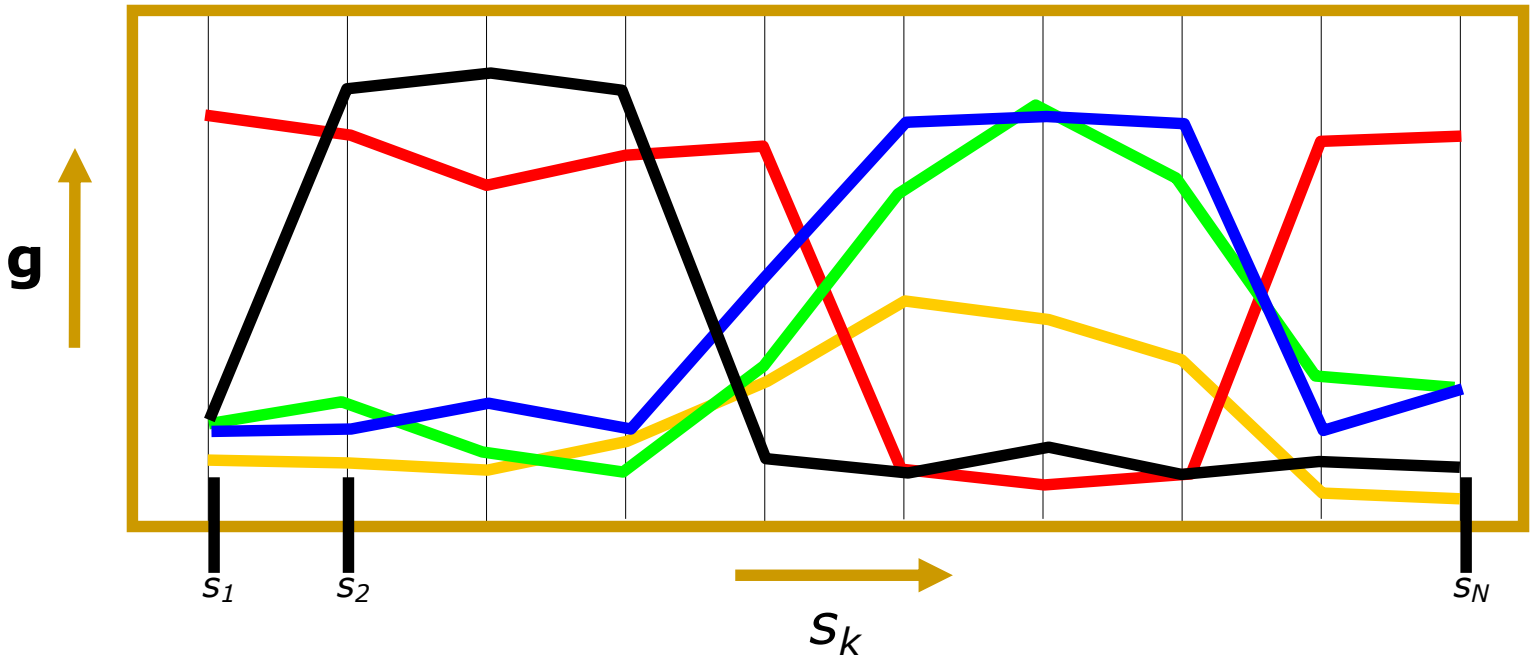
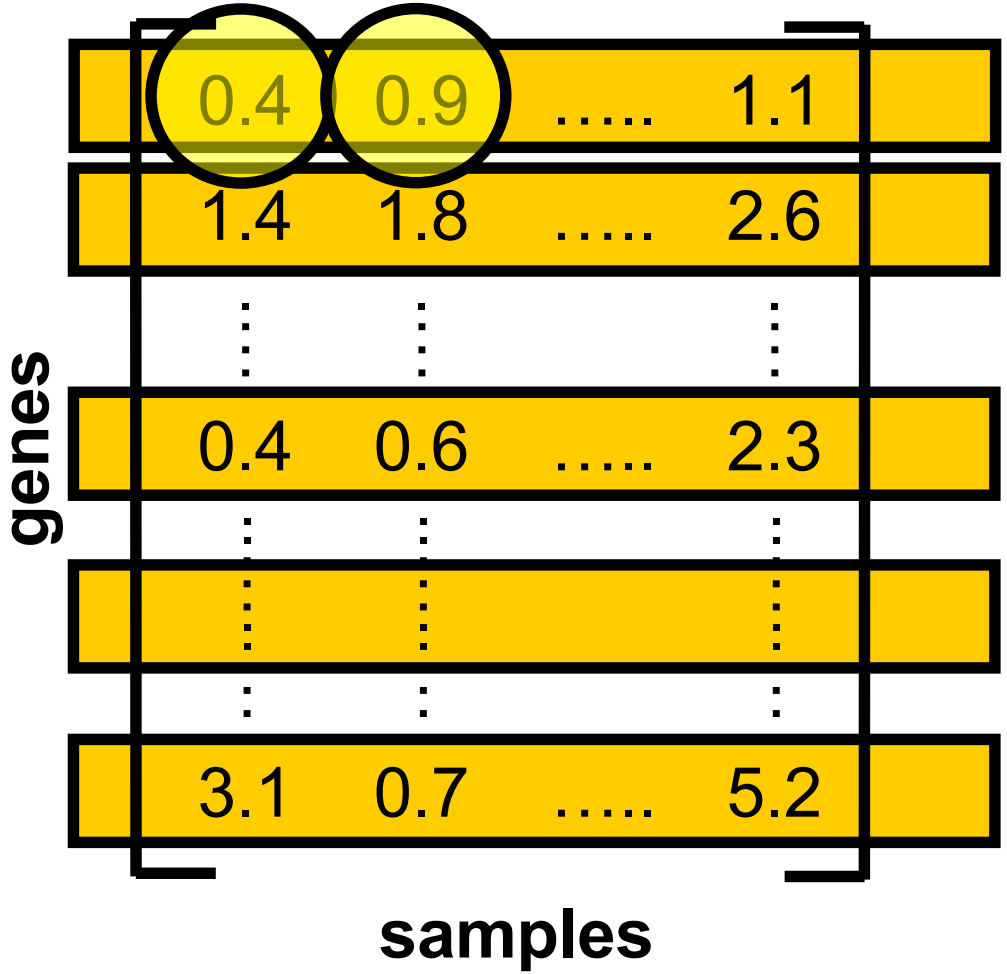
View as profiles

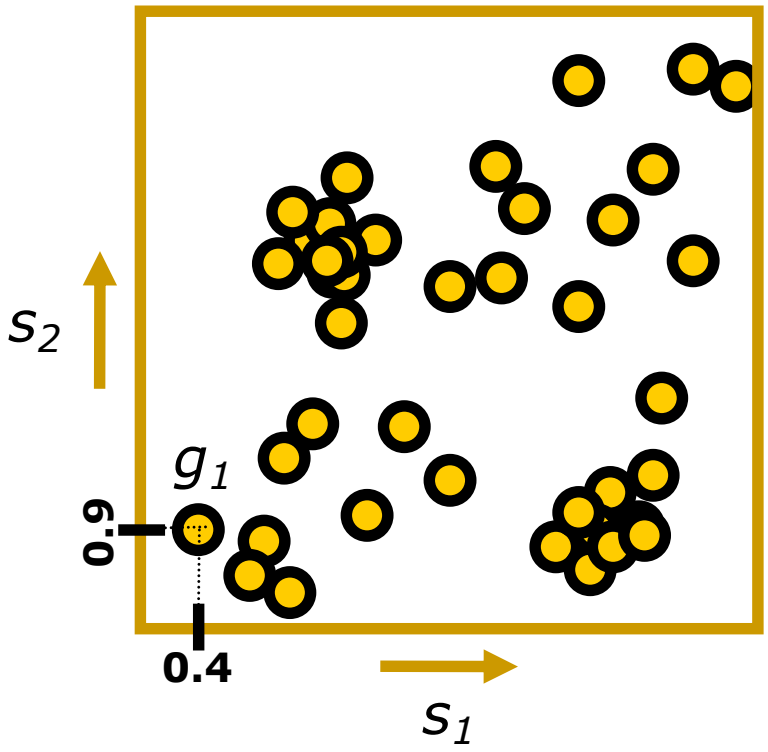


Profile for each gene

Represents gene activity across all samples

Sample-space (1/2)

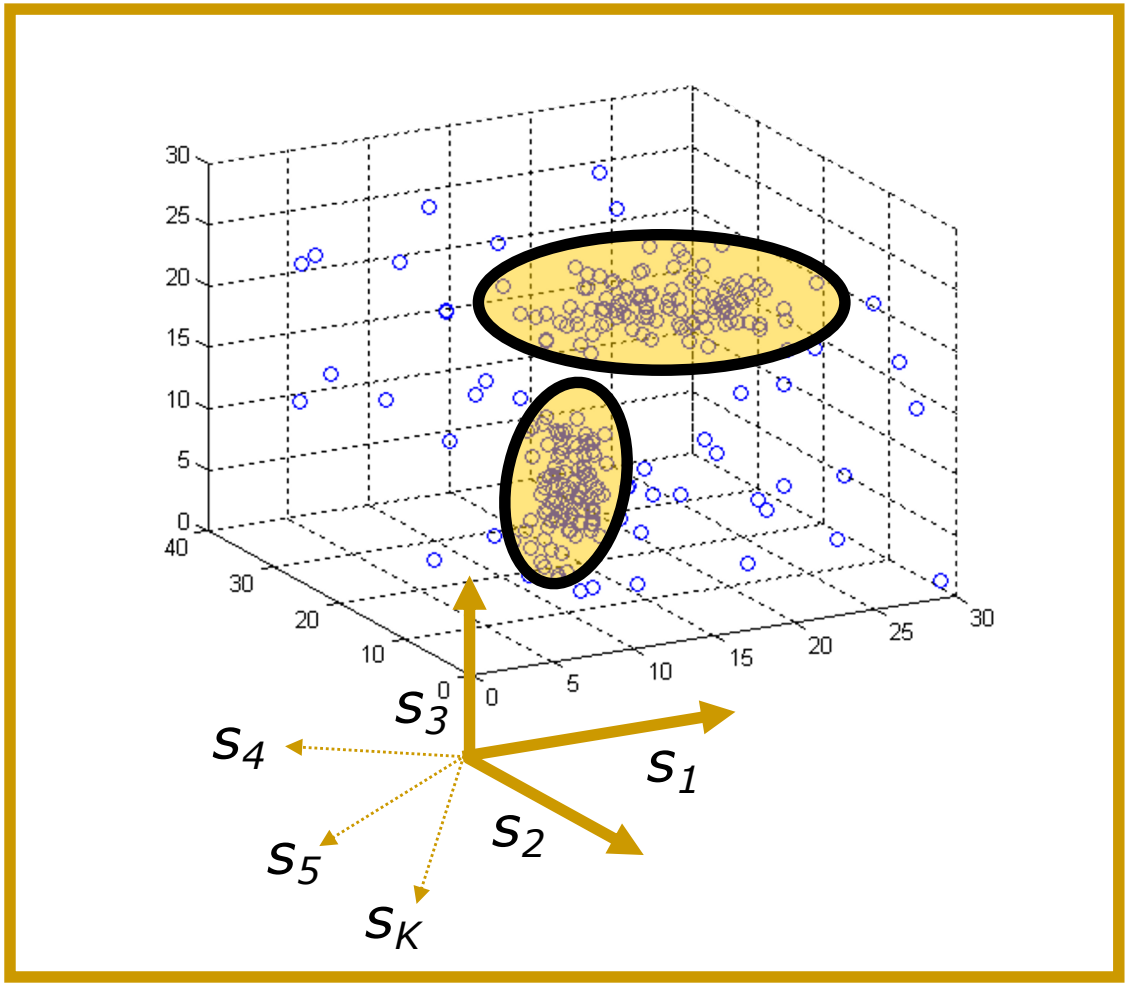




Sample-space

Genes are data points

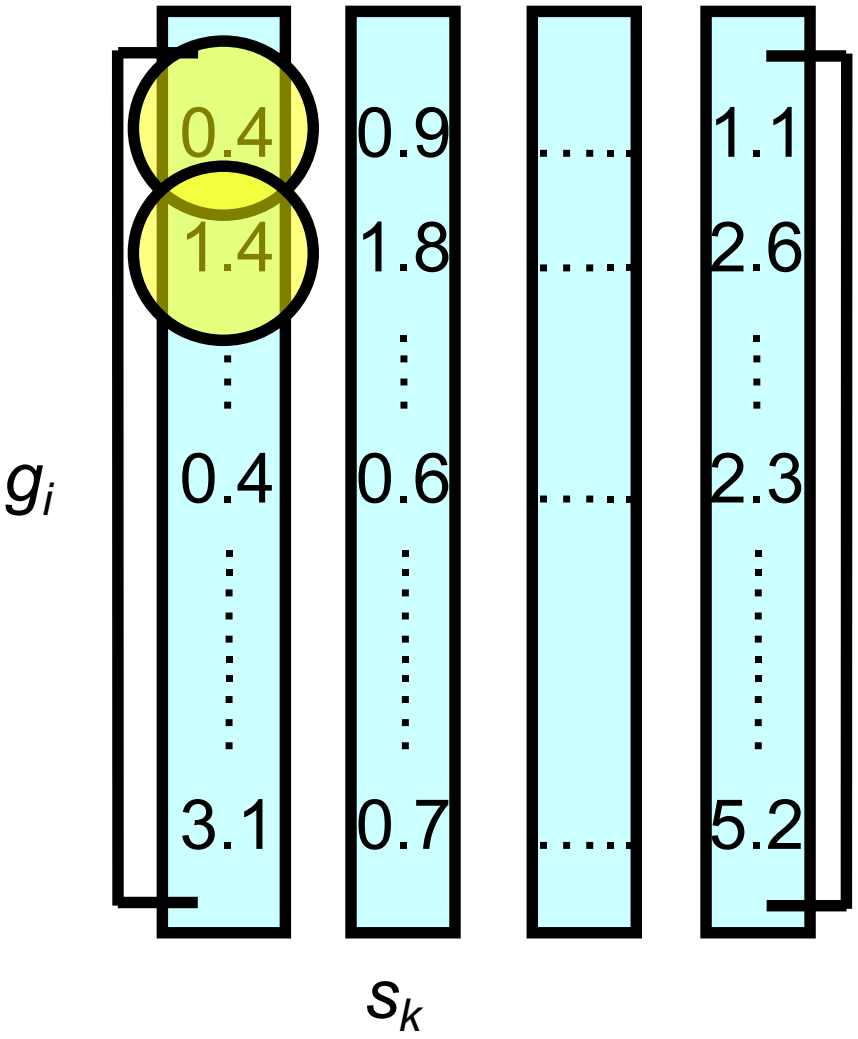
Sample-space (2/2)

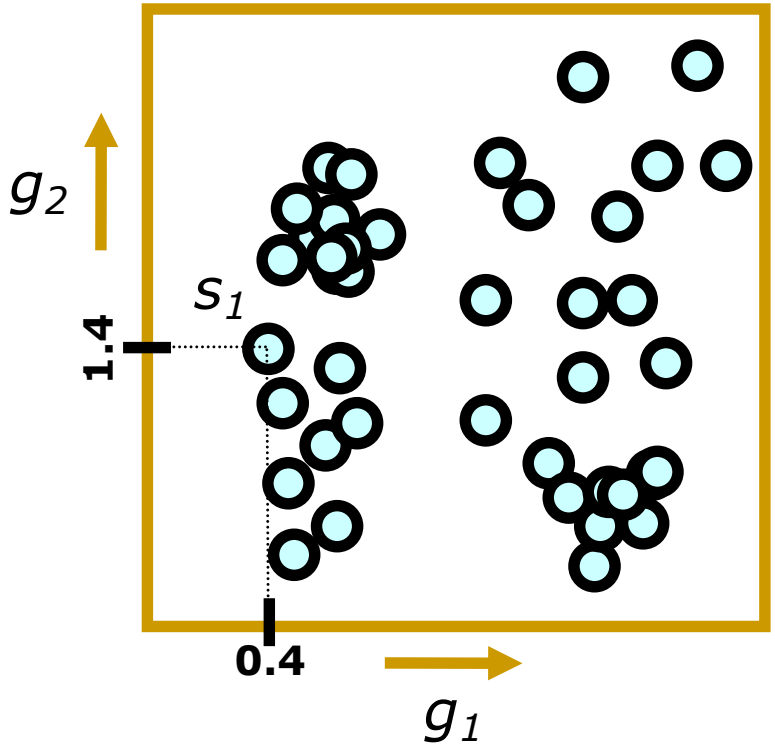


Note!

Sample-space is high dimensional

Gene-space

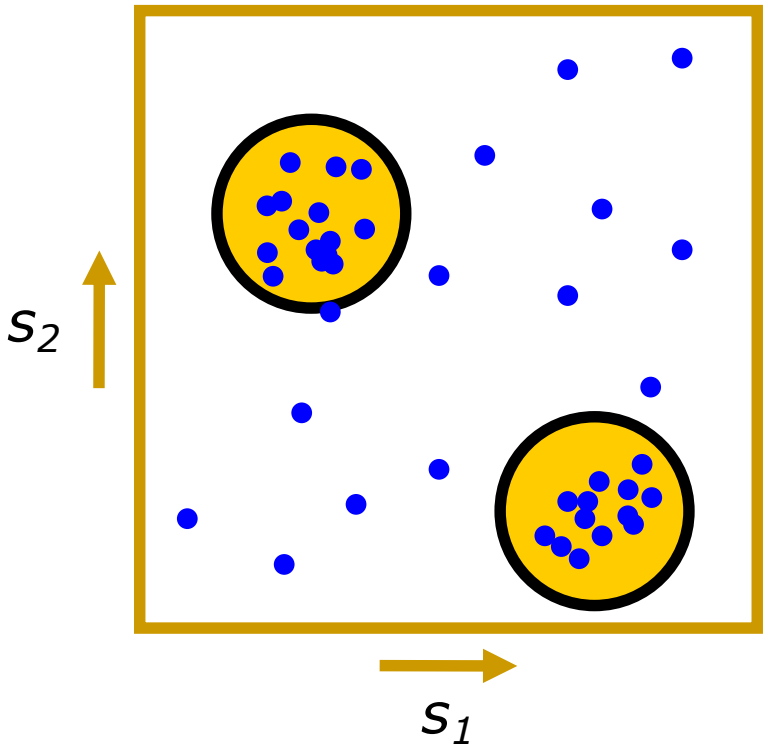




Gene-space

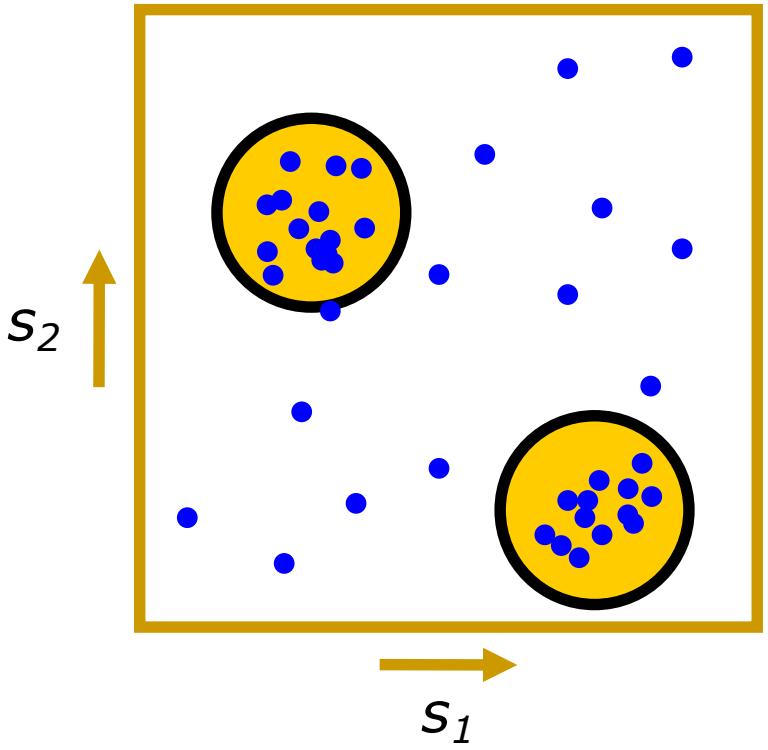
Samples are data points

Genes in *sample-space*

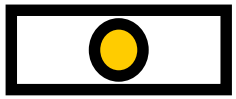


Gene g_i: activity level in Samples s_1 and s_2
(each point represents one gene)

Genes in *experiment-space*



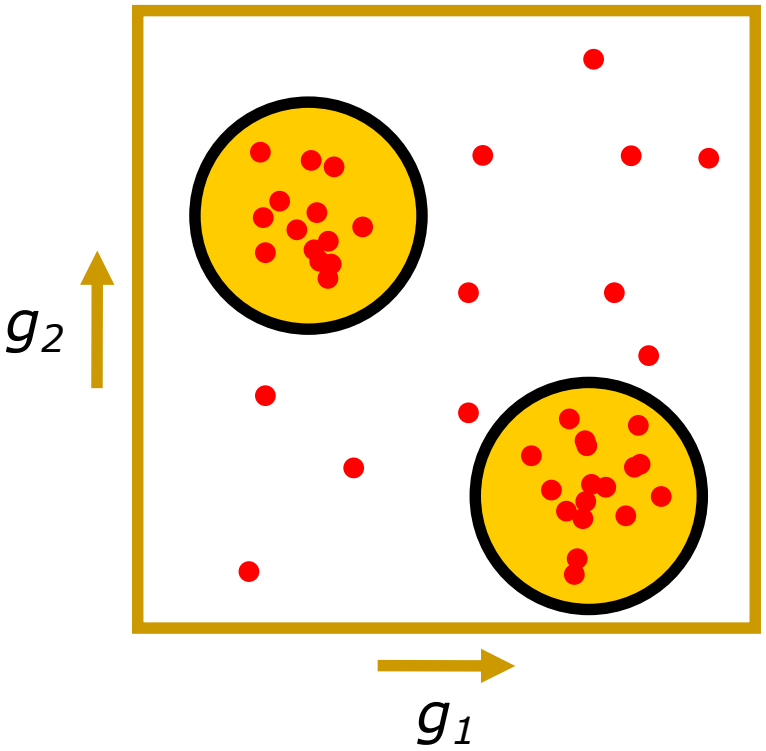
Gene g_i: activity level in samples s_1 and s_2
(each point represents one gene)

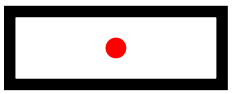


Group of genes that have the same activity levels across"all" samples

Cluster: Genes functionally related
Characterization of unknown genes
Hypothesis testing!

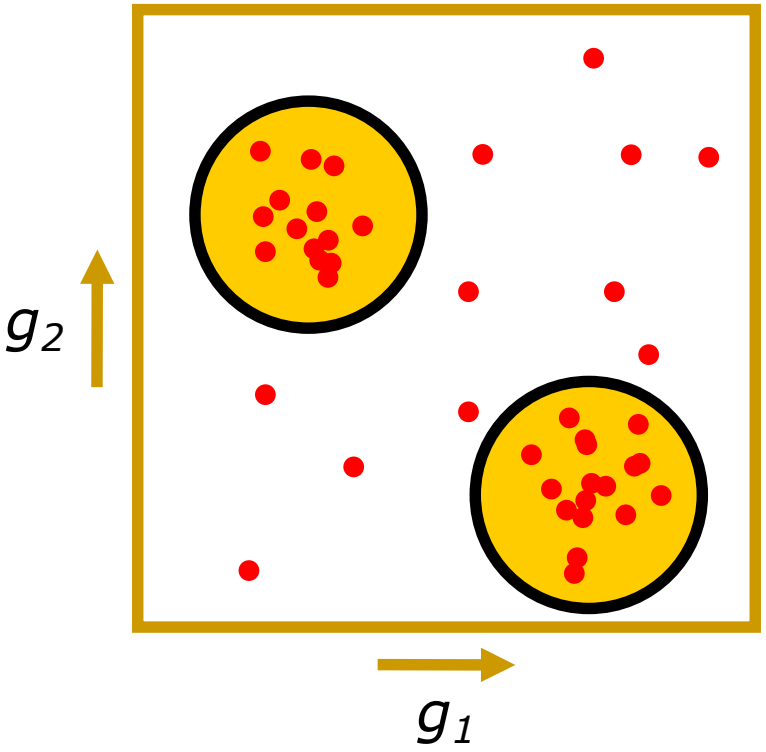
Samples in *gene-space*

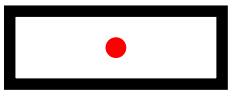




Sample s_k: activity of genes g_1 and g_2
(each point represents one sample)

Samples in *gene-space*



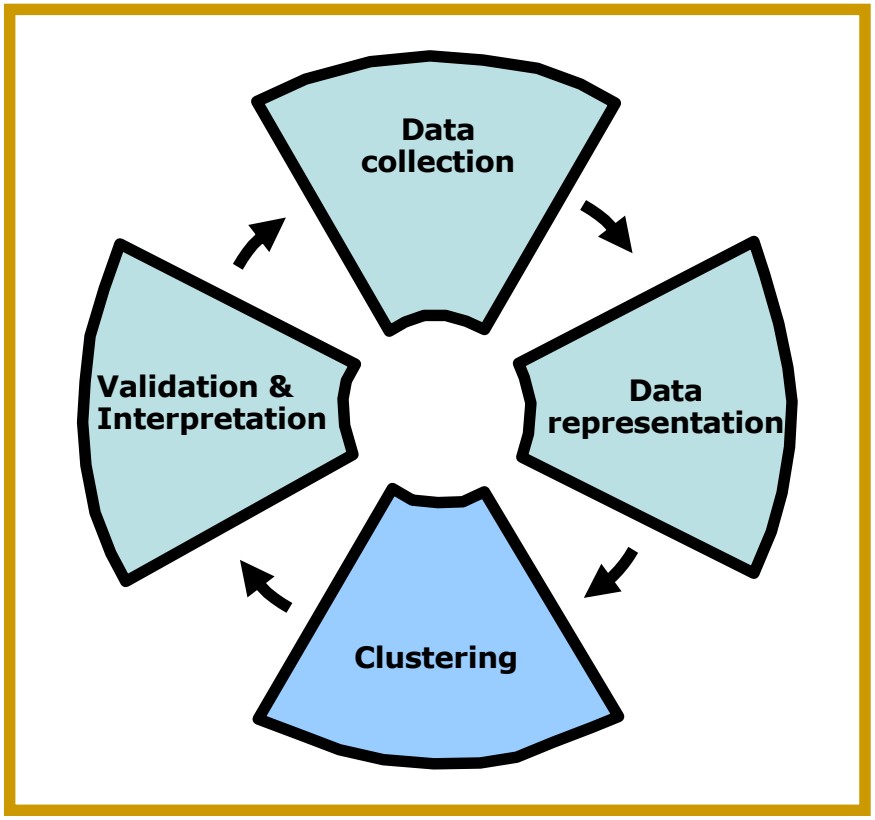


Sample s_k: activity of genes g_1 and g_2
(each point represents one sample)

Group of samples in which genes have the same activity levels across samples

Cluster: Genetic profile for related samples
Characterization of related diseases

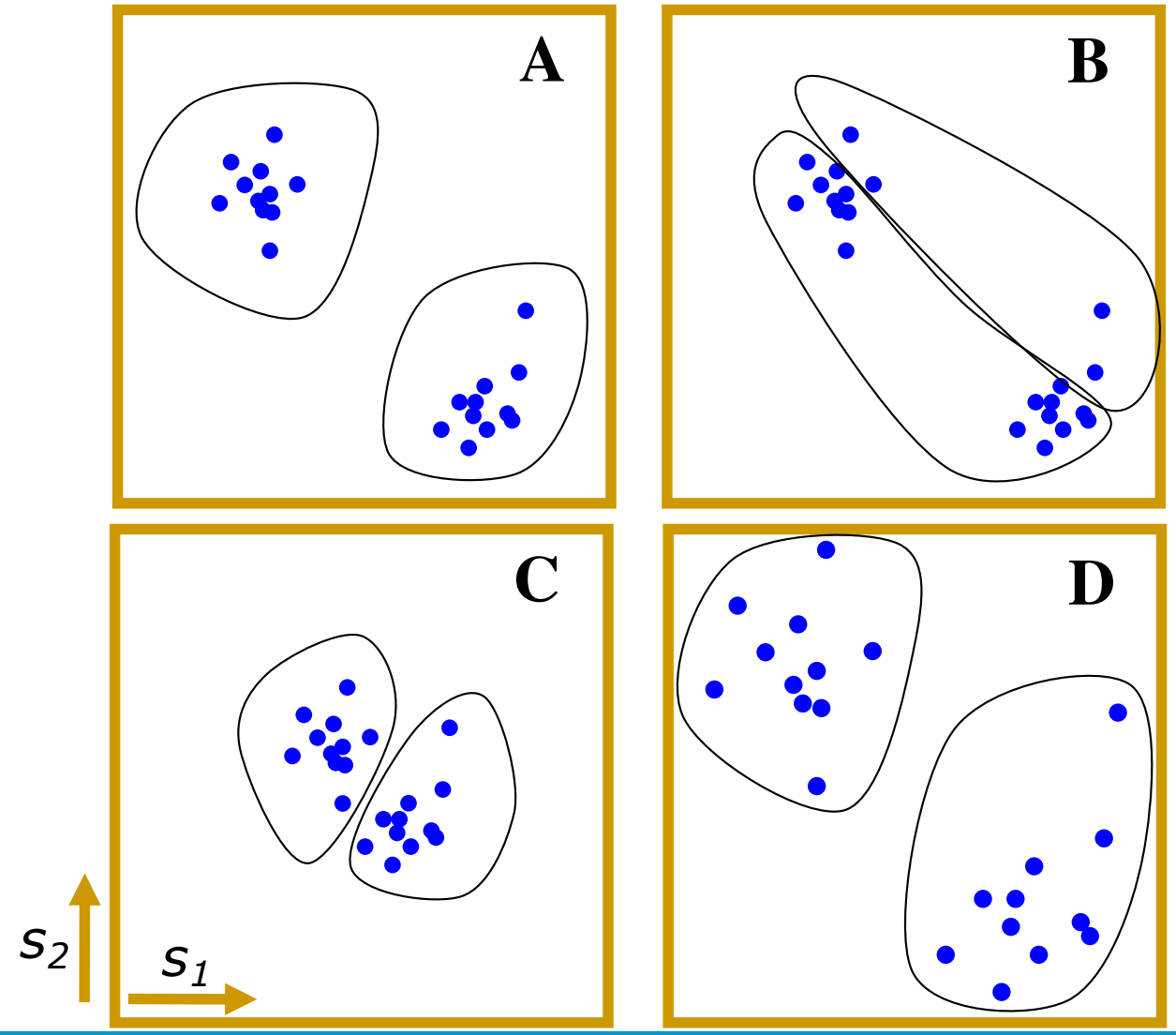
Clustering methods



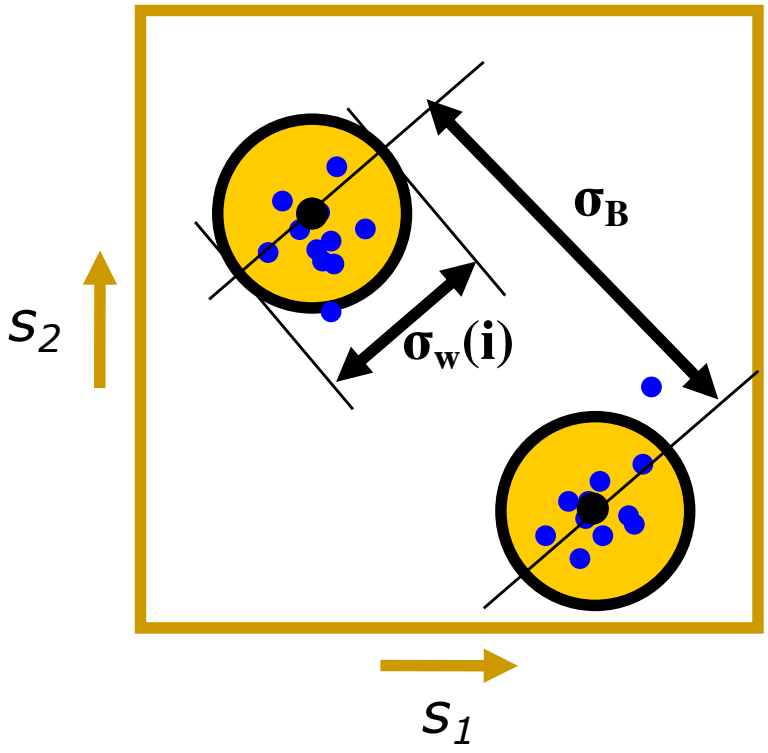
TOPICS

- Finding structure
- Hierarchical clustering
- Similarity & Linkage
- K-means clustering
- Graph-based clustering

Finding structure: better grouping?



Finding structure: better grouping?



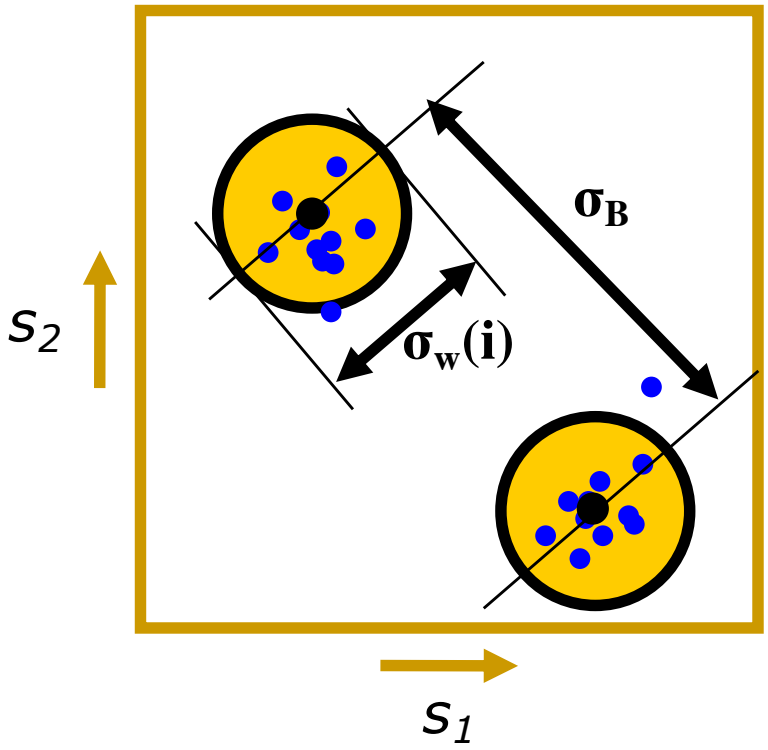
- **Structure when:**
  1) **Points within cluster resemble each other**

     (within variance, $\sigma_W(i)$)
  2) **Clusters deviate from each other *(between variance, σ_B)***

- **Group points such that**

$$\textbf{MIN}\left[\frac{\sum \textbf{within variance}}{\textbf{between variance}}\right] \rightarrow \sigma_W\textbf{: small \&}\ \sigma_B\textbf{ : large}$$

General approaches



- **Agglomerative**

  (building trees)

  hierarchical clustering (Mike Eisen's Cluster), Louvain graph clustering

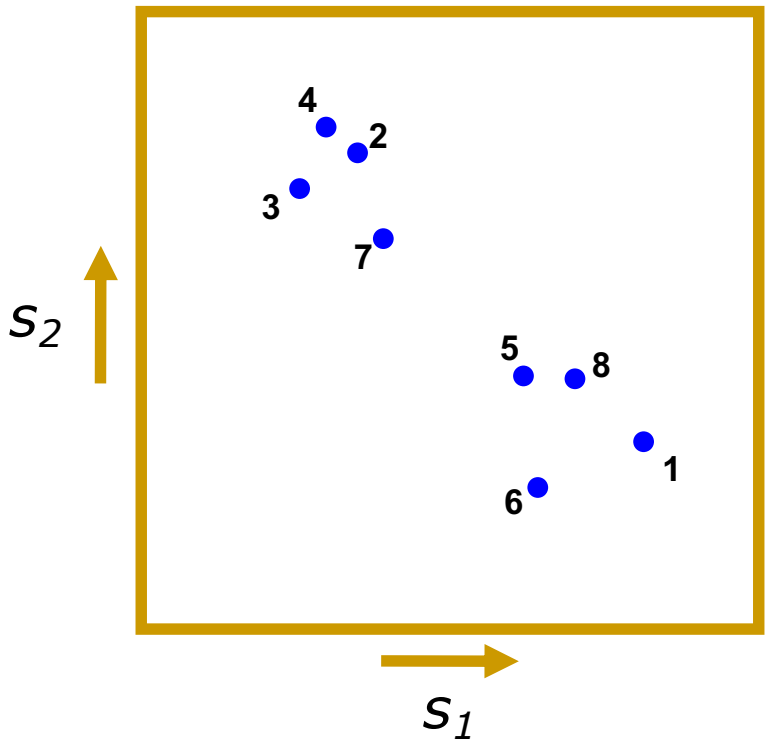
- **Partitional**

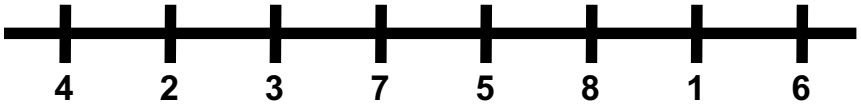
  (finding prototypes)

  k-means, spectral-based graph-based clustering, som-mapping

  gene shaving

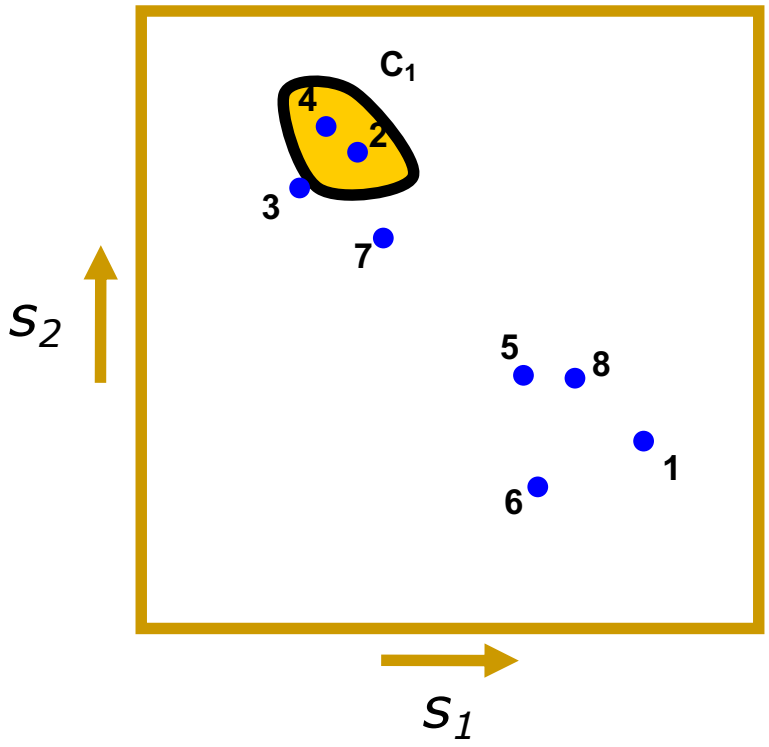
Hierarchical clustering



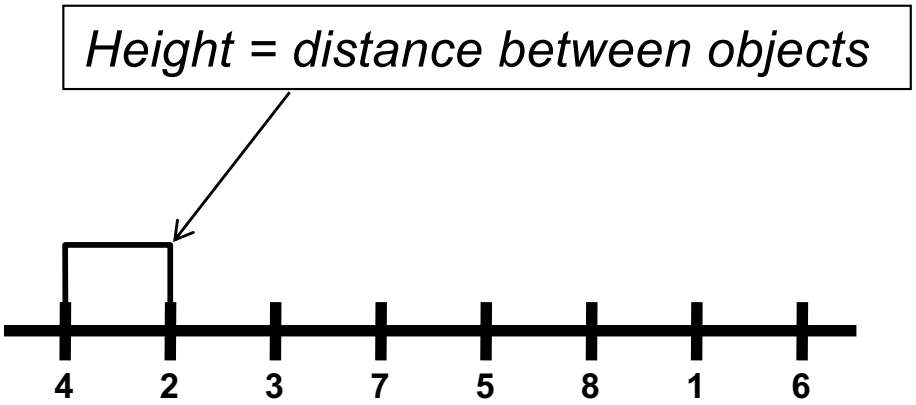


Find most similar objects (points/genes) and group them

Hierarchical clustering



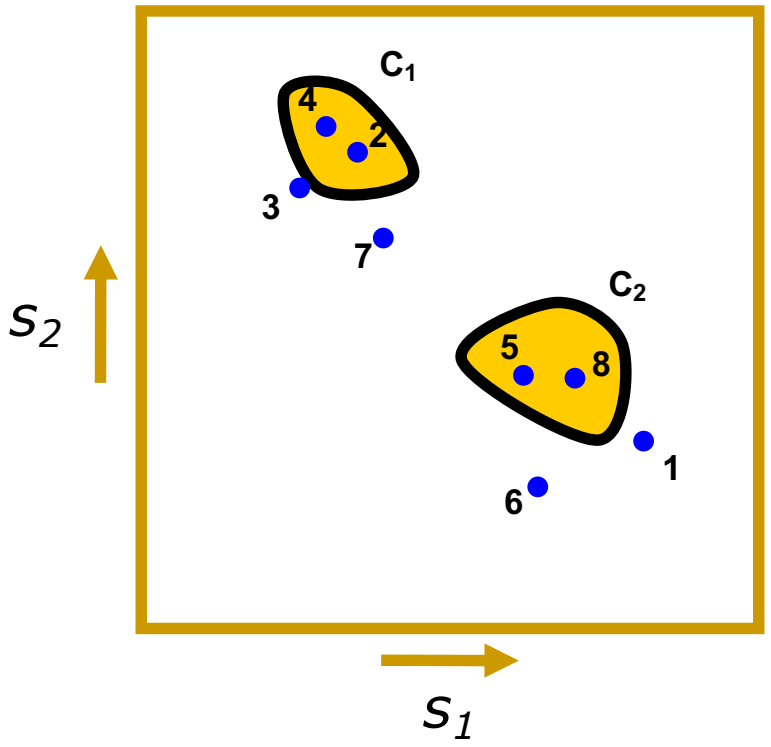
dendrogram

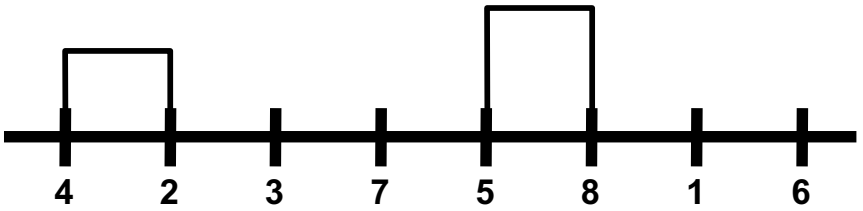


These are: objects 4 and 2
Again, find most similar objects (genes or clusters) and group them

Hierarchical clustering

dendrogram



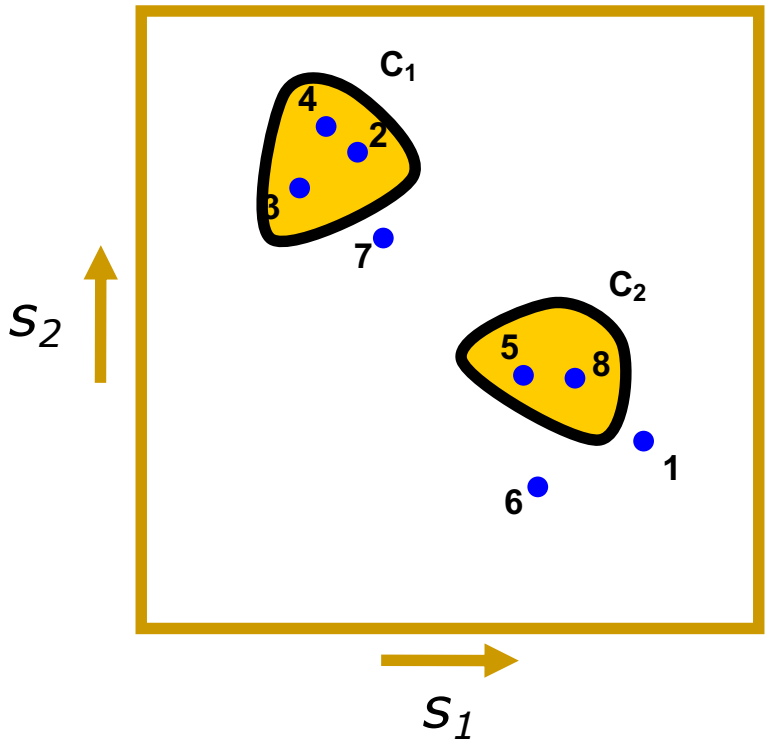


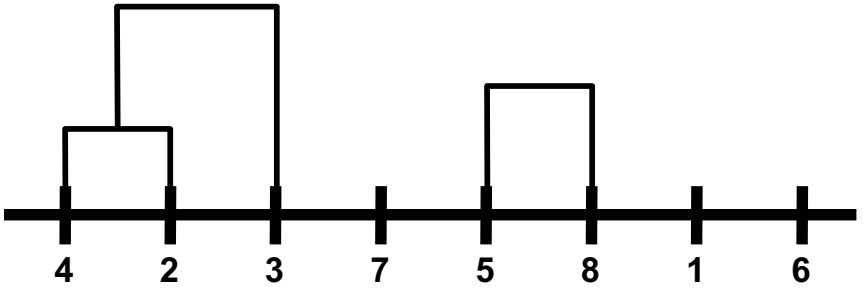
These are: objects 5 and 8

Repeat finding most similar objects (genes or clusters) and grouping them

Hierarchical clustering

dendrogram

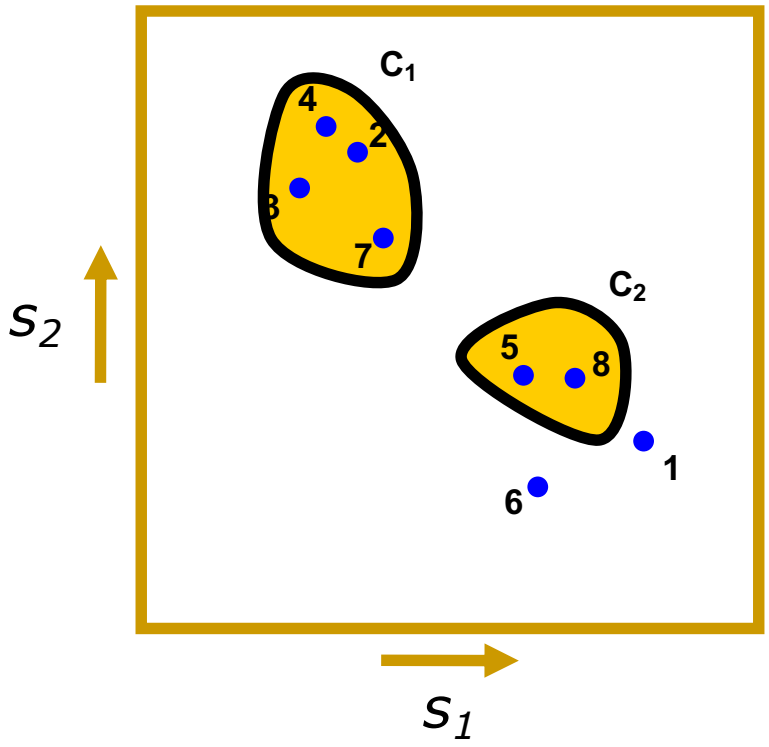


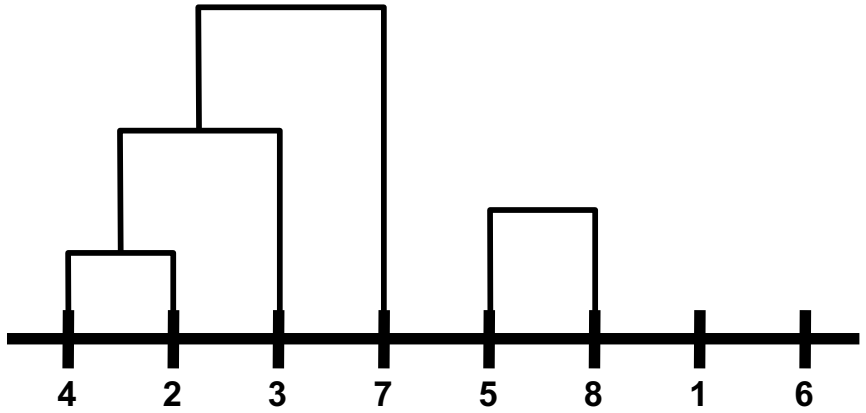


Join object 3 and cluster 1
Repeat process

Hierarchical clustering

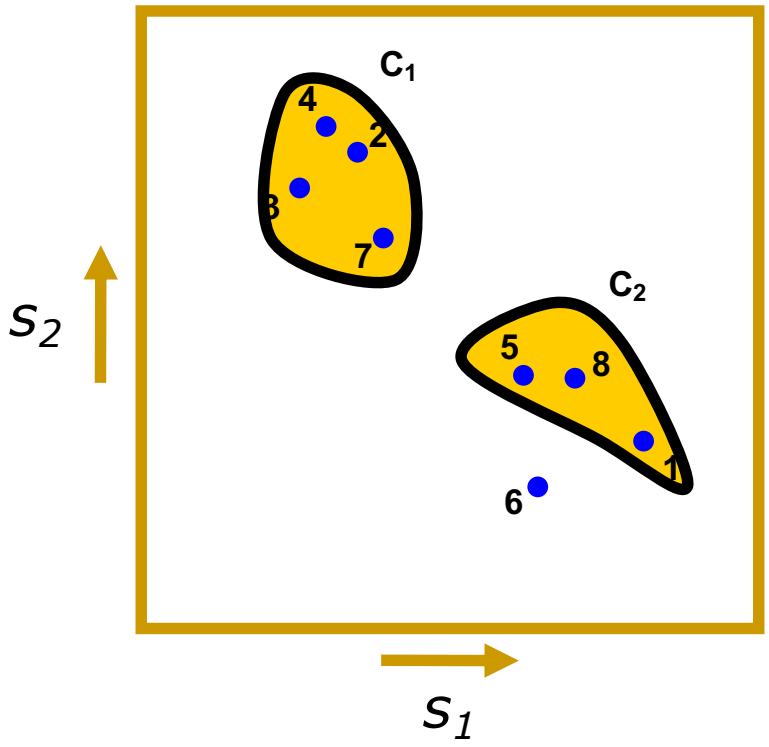
dendrogram



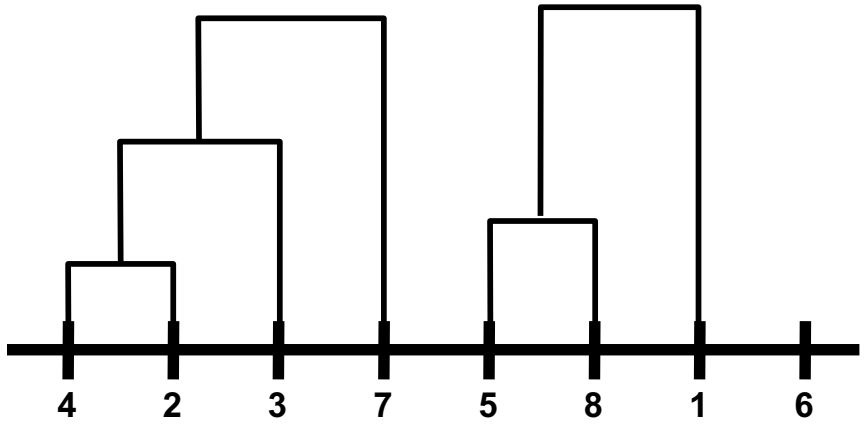


Join [object 7 and cluster 1] into [cluster 1]
Repeat process

Hierarchical clustering

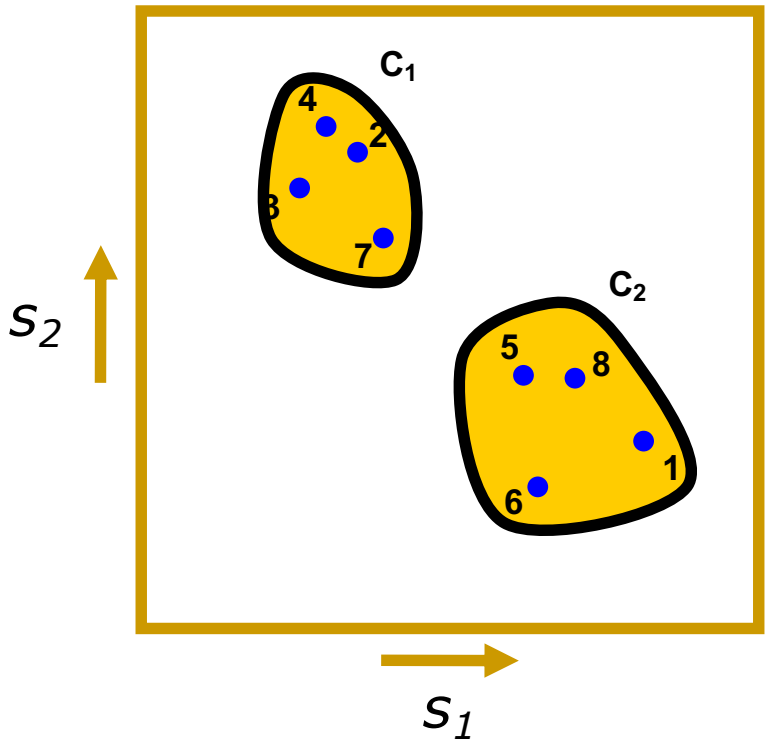


dendrogram

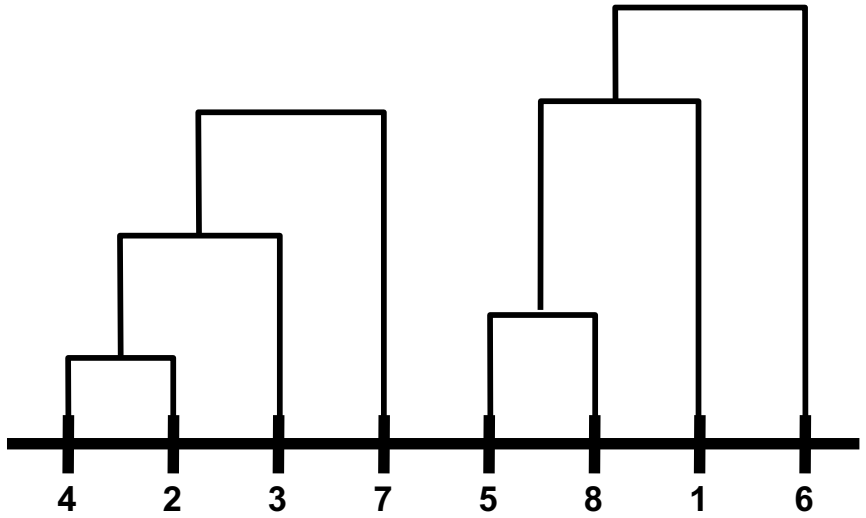


Join [object 1 and cluster 2] ➔ [cluster 2]
Repeat process

Hierarchical clustering

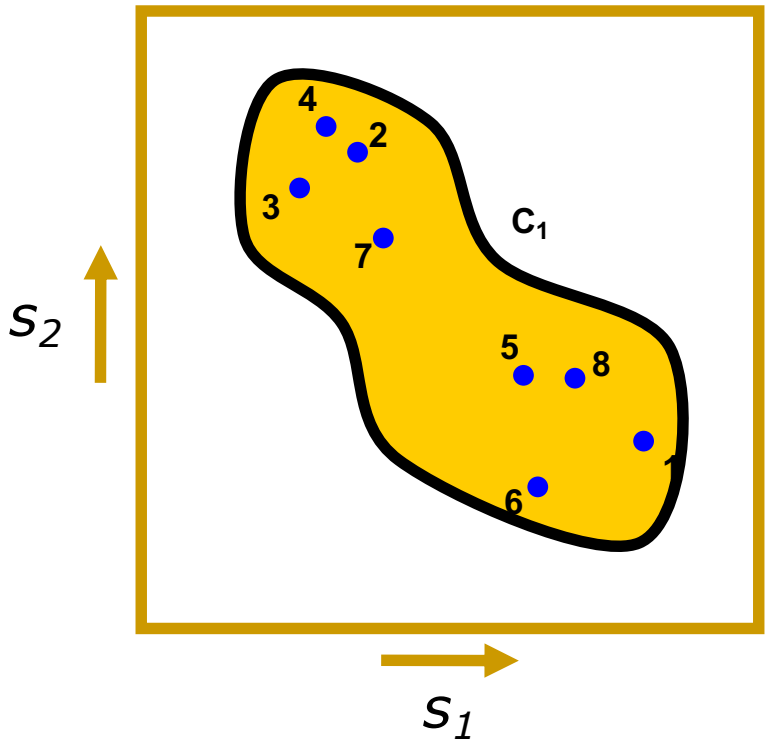


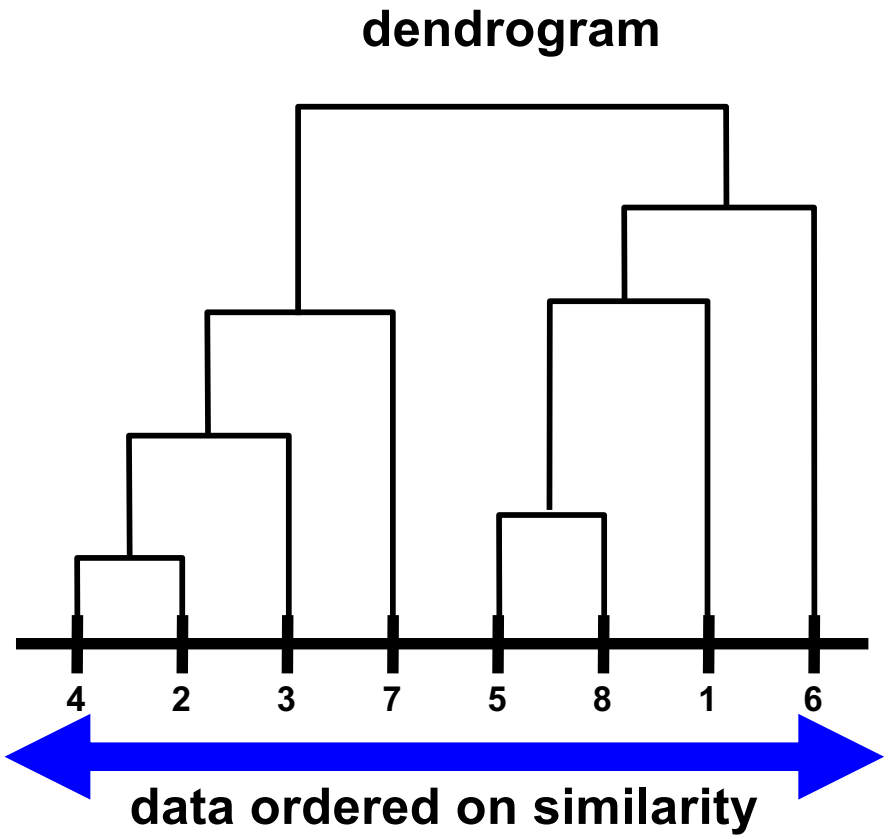
dendrogram



Join [object 6 and cluster 2] ➔ [cluster 2]
Repeat process

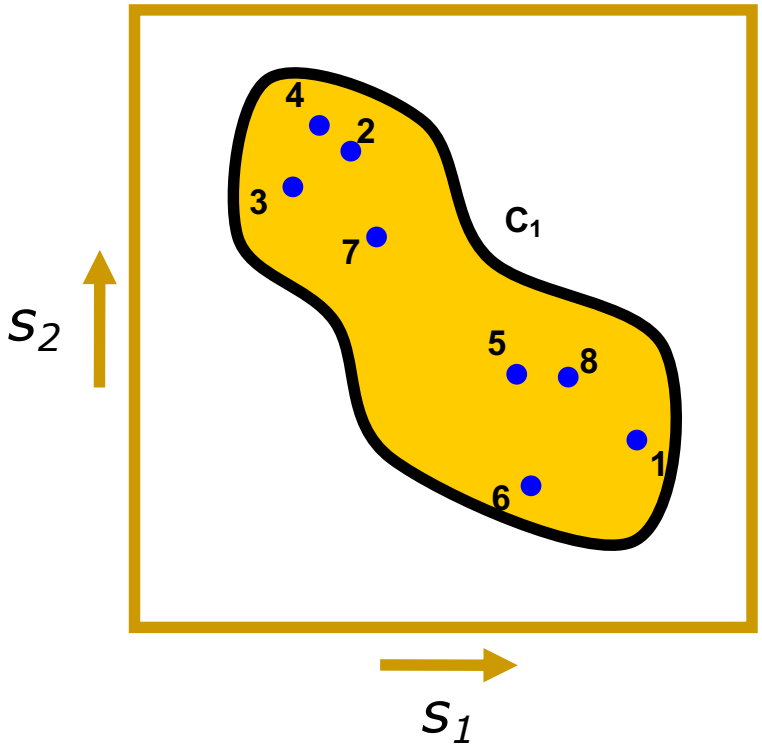
Hierarchical clustering





Join [cluster 1 and cluster 2] → [cluster 1]
All in one cluster: FINISHED!

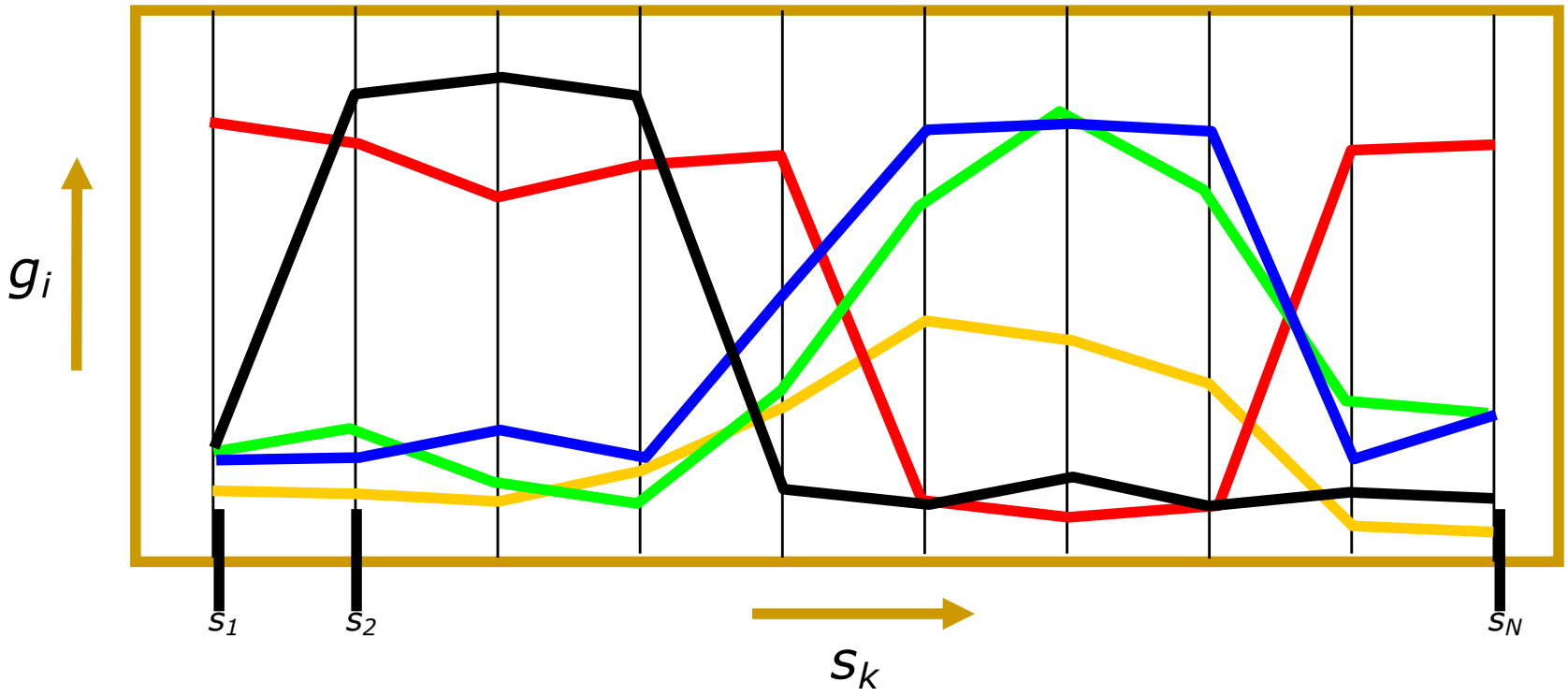
Hierarchical clustering: Choices

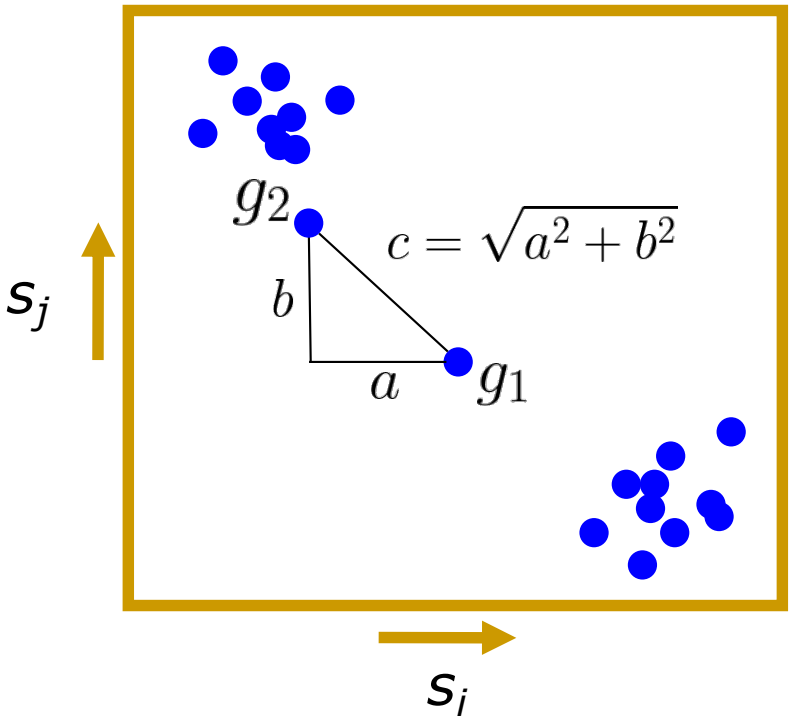


Need to know:

- **Similarity between objects**
- **Similarity between clusters**

Hierarchical clustering: Similarity between objects





Euclidean distance

$$a = g_1(s_i) - g_2(s_i)$$

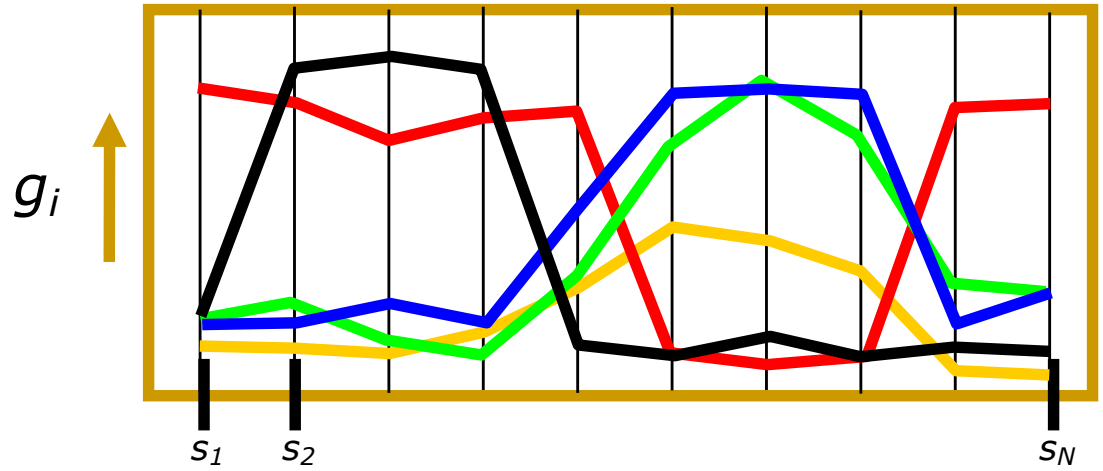
$$b = g_1(s_j) - g_2(s_j)$$

$$c = \sqrt{a^2 + b^2}$$

$$c = \sqrt{(g_1(s_i)) - g_2(s_i))^2 + (g_1(s_j) - g_2(s_j))^2}$$

$$d(g_1, g_2) = c = \sqrt{\sum_{k=1}^{K} (g_1(s_k) - g_2(s_k))^2}$$

Similarity between objects



Euclidean distance

$$d(g_1, g_2) = \sqrt{\sum_{k=1}^{K} (g_1(s_k) - g_2(s_k))^2}$$

d(●,●) < d(●,●)
d(●,●) << d(●,●)
d(●,●) << d(●,●)

Pearson correlation

$$1 - \rho_{g_1,g_2}$$

$$\rho_{g_1,g_2} = \frac{\sum_{k=1}^{K} g_1(s_k) * g_2(s_k)) - \mu_1 * \mu_2)}{(\sigma_1 * \sigma_2)}$$

d(●,●) ≈ d(●,●)
d(●,●) << d(●,●)
d(●,●) << d(●,●)

Mixed Pearson correlation

$$1 - |\rho_{g_1,g_2}|$$

d(●,●) ≈ d(●,●)
d(●,●) ≈ d(●,●)
d(●,●) << d(●,●)

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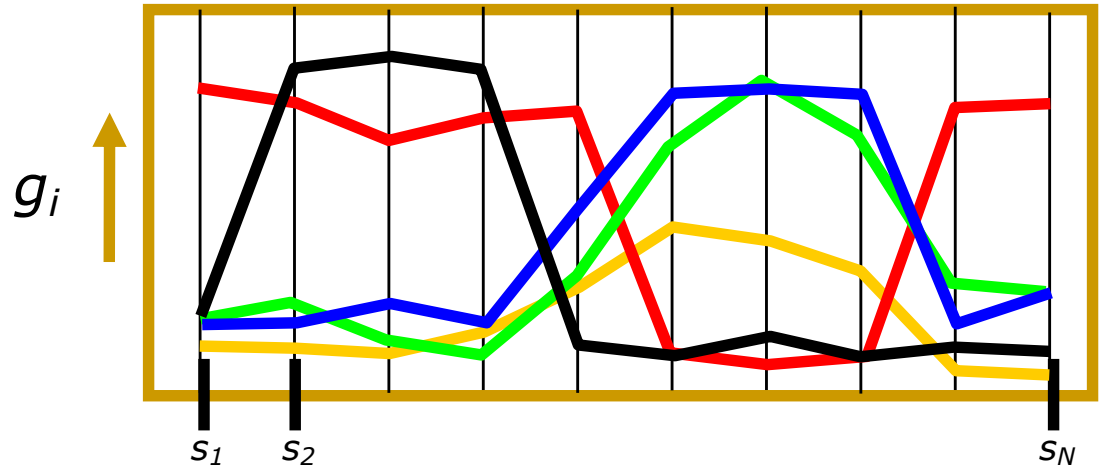
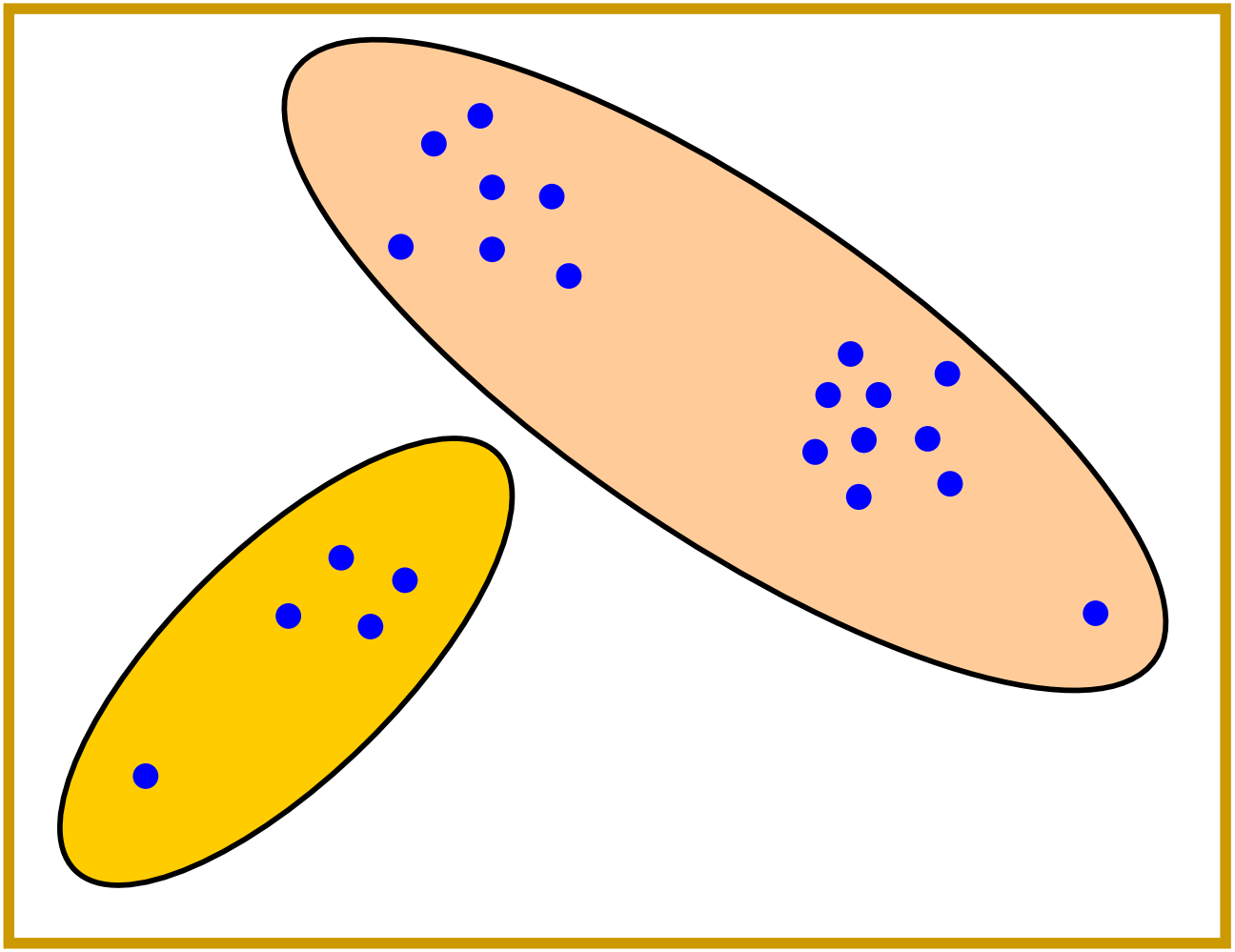
Similarity between objects

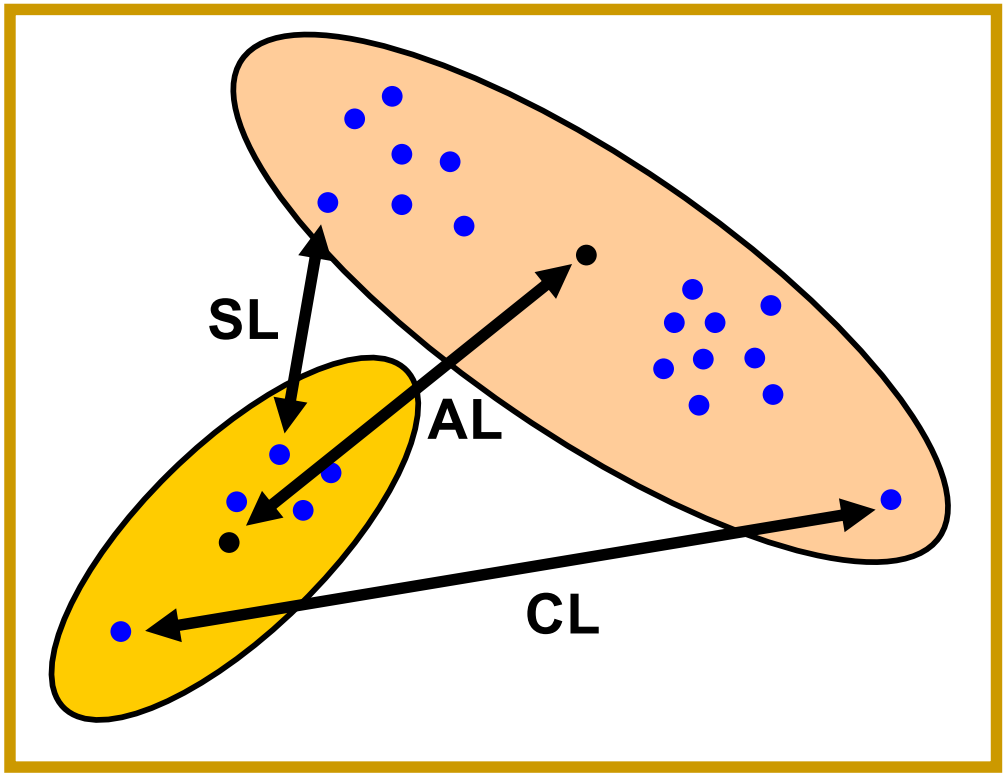


Euclidean distance	Pearson correlation	Mixed Pearson correlation
match exact shape	ignore amplitude	ignore amplitude & sign
d(●,●) < d(●,●)	d(●,●) ≈ d(●,●)	d(●,●) ≈ d(●,●)
d(●,●) << d(●,●)	d(●,●) << d(●,●)	d(●,●) ≈ d(●,●)
d(●,●) << d(●,●)	d(●,●) << d(●,●)	d(●,●) << d(●,●)

Similarity between clusters?

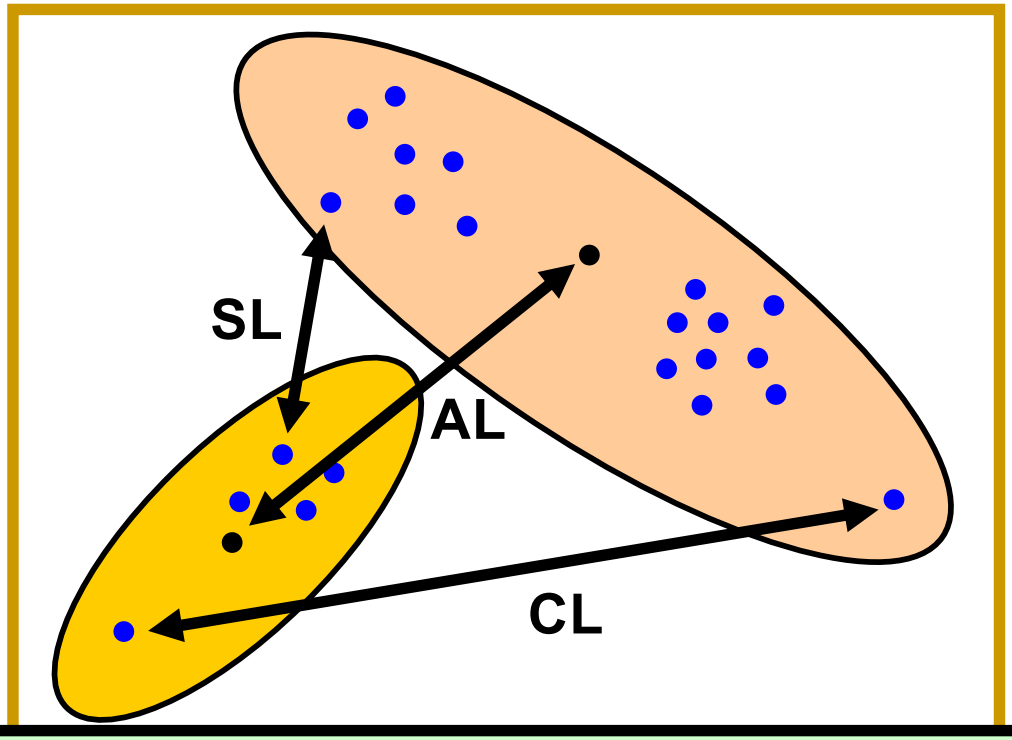


Similarity between clusters (linkage)



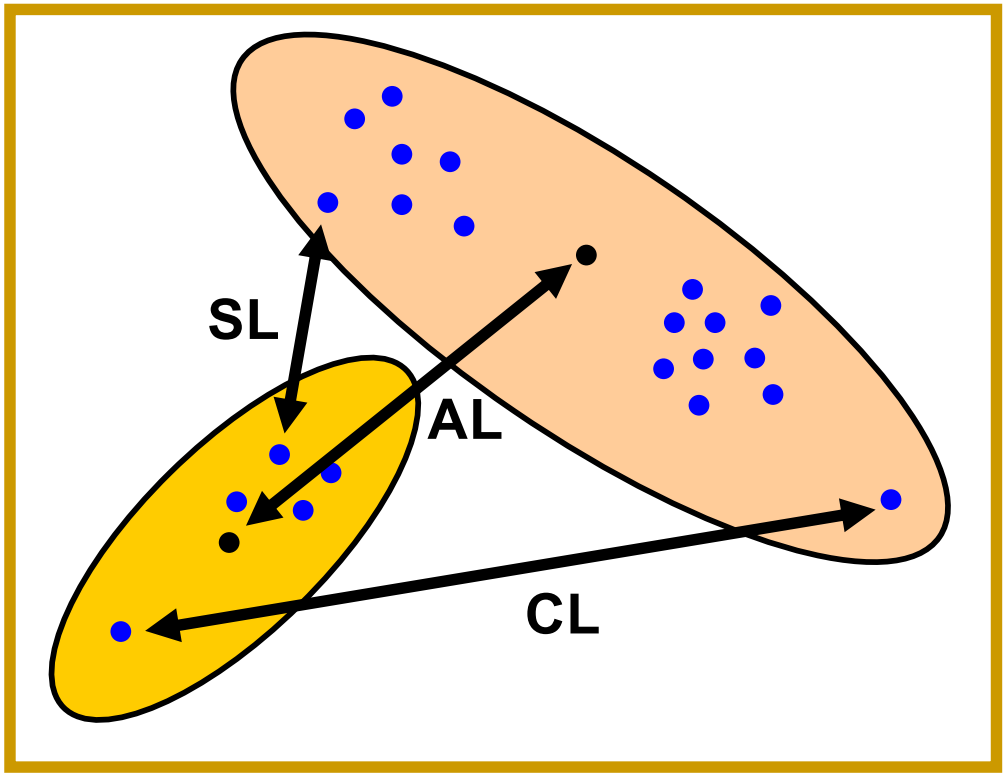
- **Single linkage:** Closest objects
- **Complete linkage:** Furthest objects
- **Average linkage:** Average dissimilarity

Similarity between clusters (linkage)



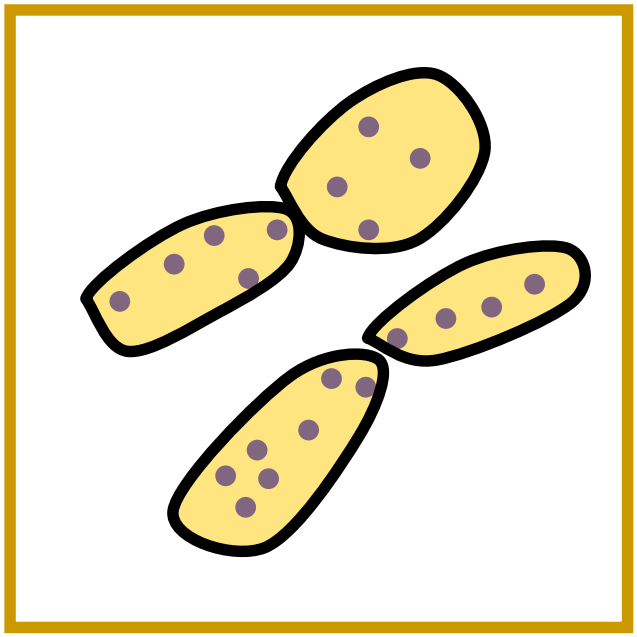
- **Single linkage:** $d(X_i, X_j) = min(d(a,b) : a \in X_i, b \in X_j)$
- **Complete linkage:** $d(X_i, X_j) = max(d(a,b) : a \in X_i, b \in X_j)$
- **Average linkage:** $d(X_i, X_j) = \frac{1}{|X_i||X_j|} \sum_{a \in X_i} \sum_{b \in X_j} d(a,b)$

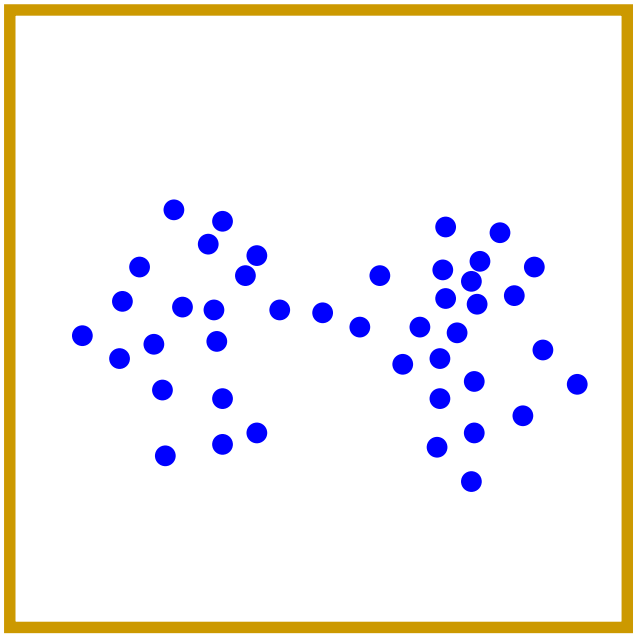
Similarity between clusters (2)

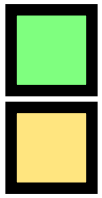


- **Ward's method:** $d(X_i, X_j) = \|X_i - X_j\|^2$ (total variance)
- **Centroid distance:** $d(X_i, X_j) = \|c_s - c_t\|$

SL vs CL: Shape influences



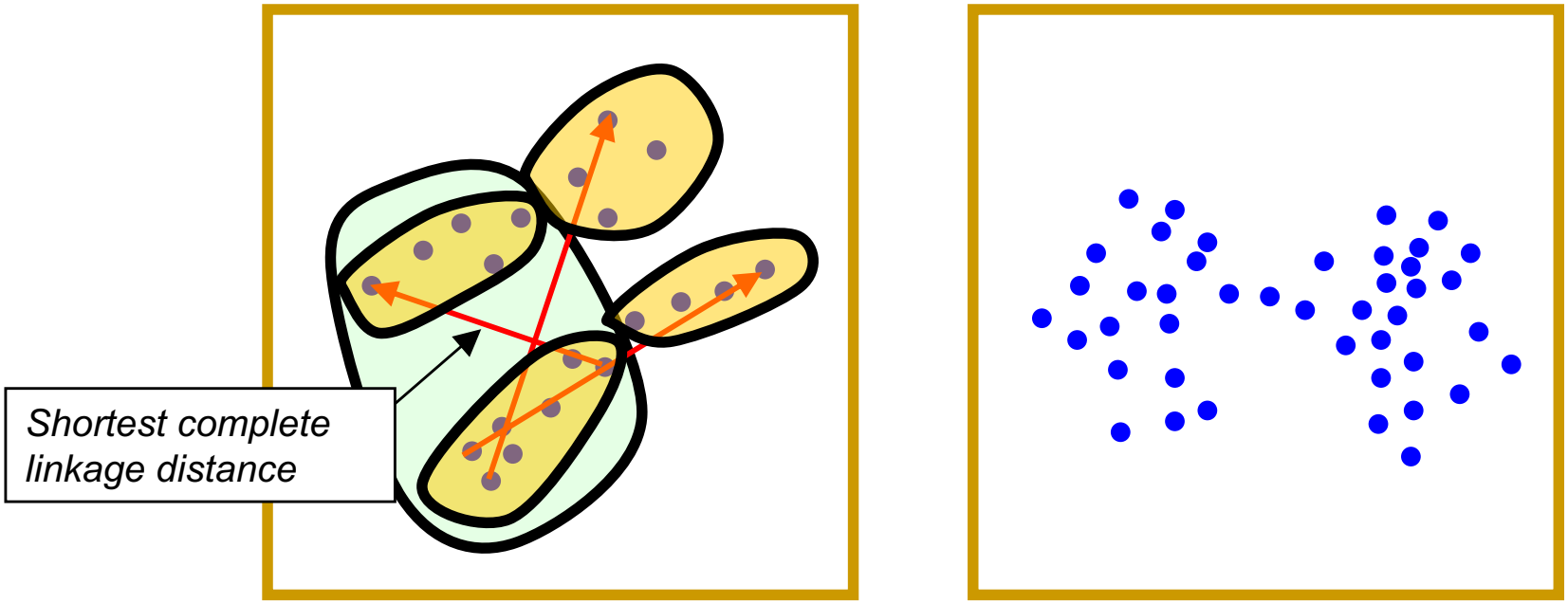




complete linkage ?

single linkage ?

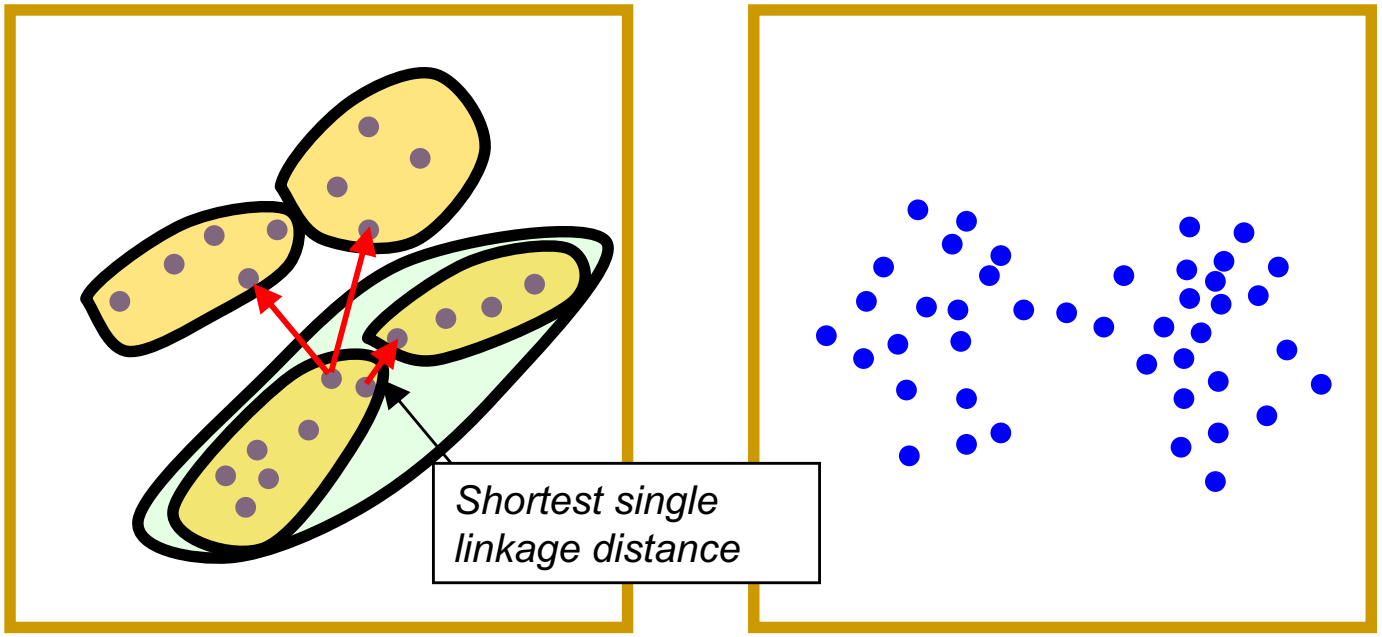
SL vs CL: Shape influences

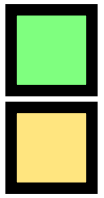


complete linkage ?

single linkage ?

SL vs CL: Shape influences

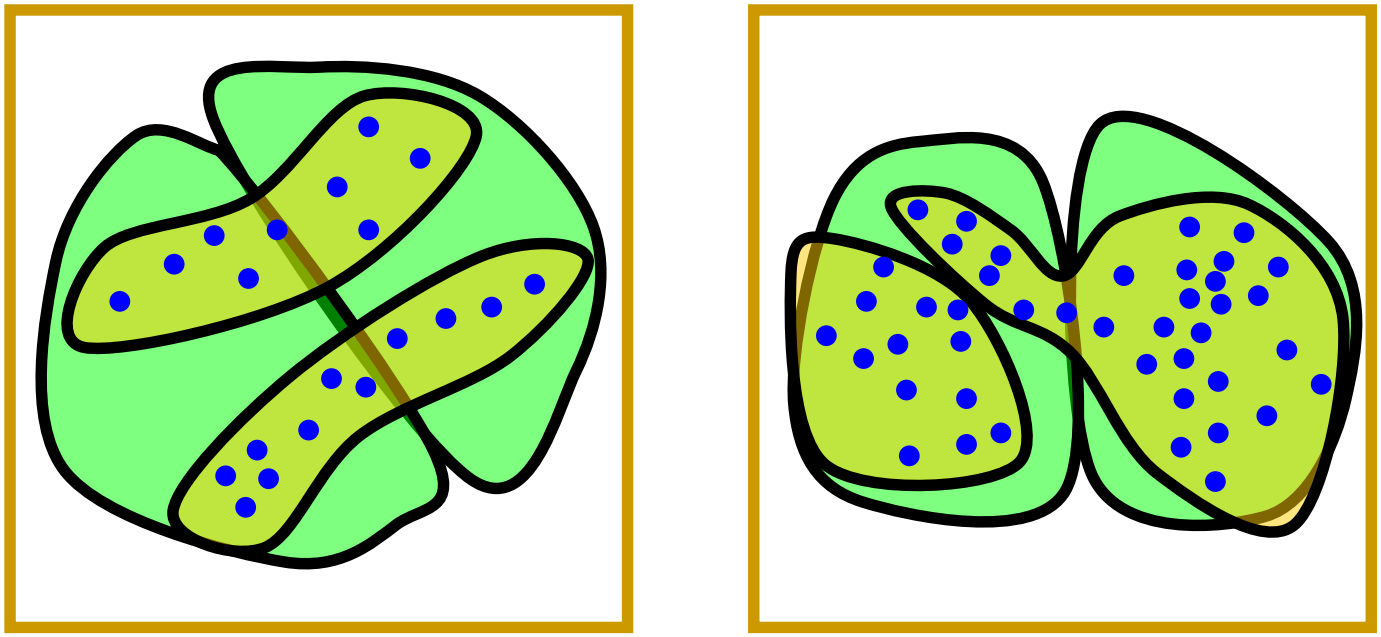




complete linkage ?

single linkage ?

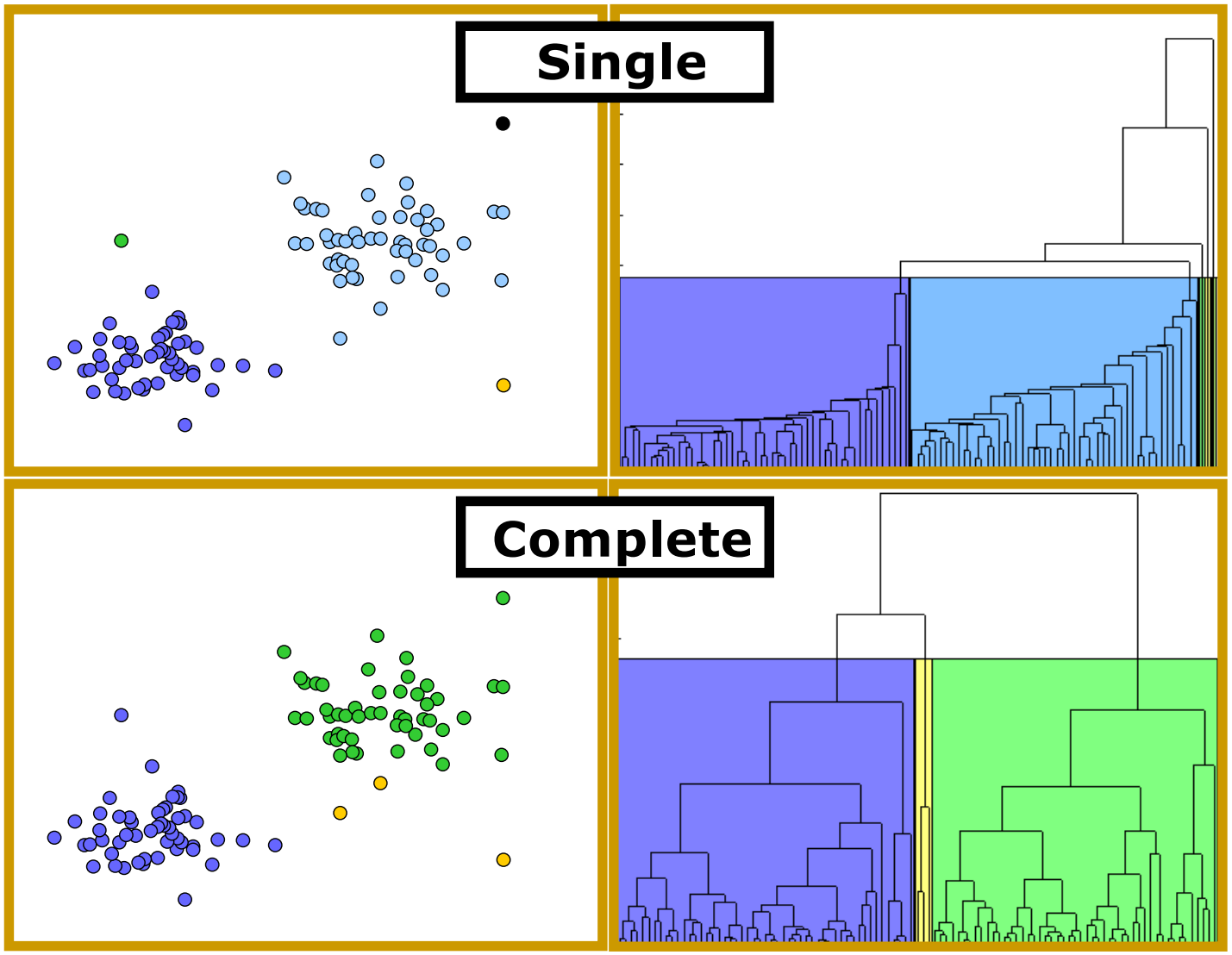
SL vs CL: Shape influences

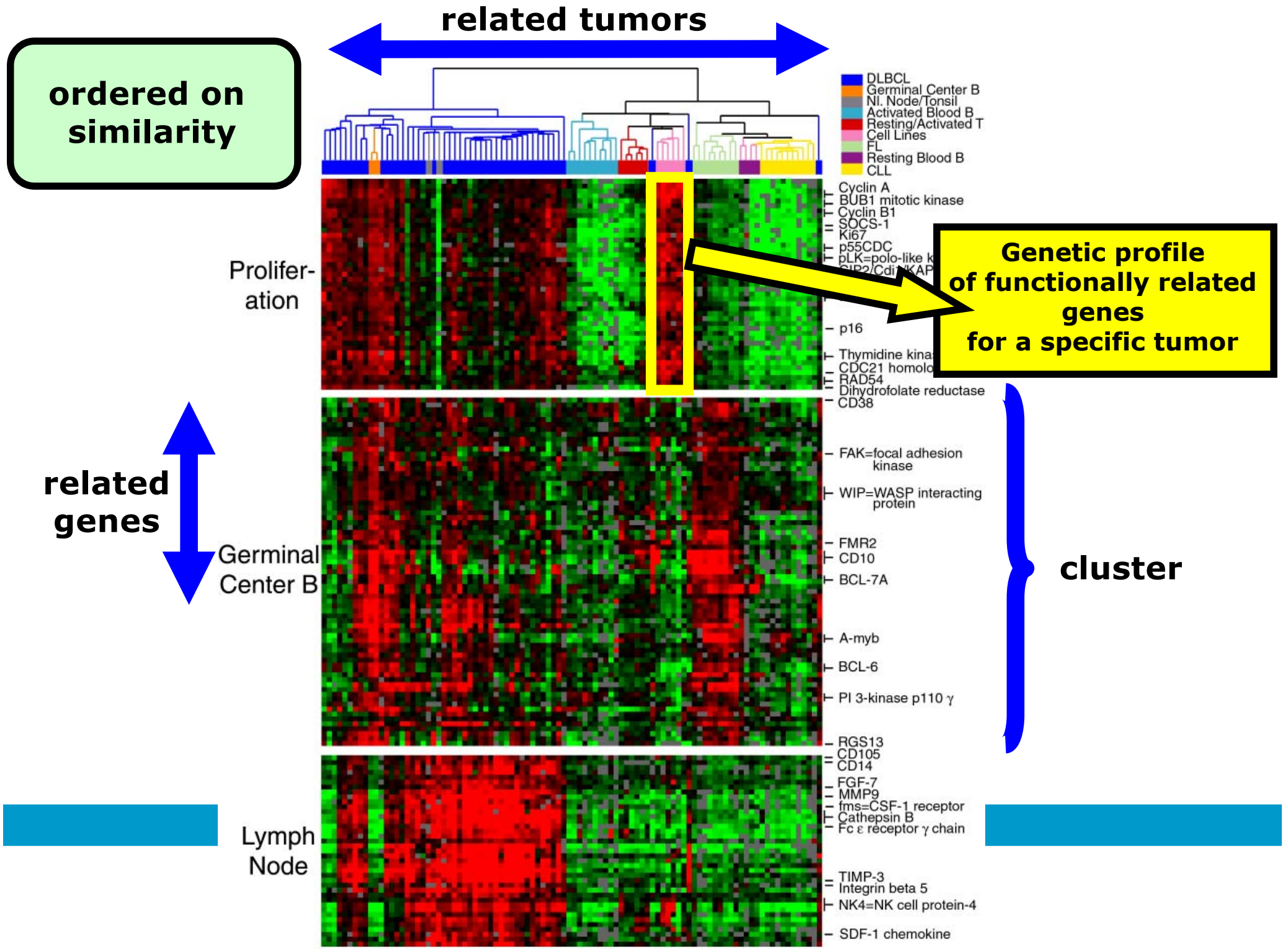


complete linkage

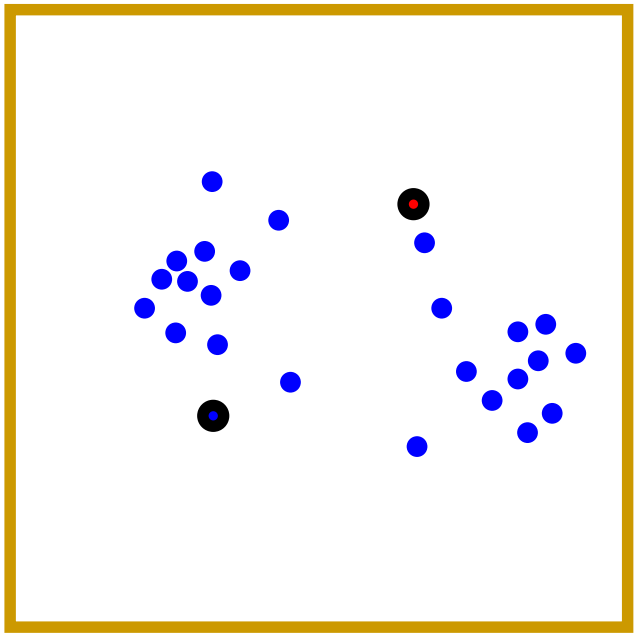
single linkage

SL vs CL: Outlier influences



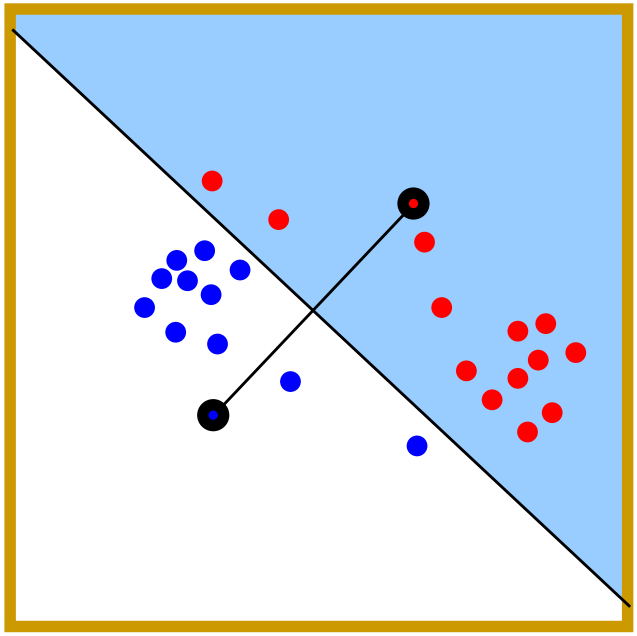

related tumors
ordered on similarity
DLBCL
Germinal Center B
NI. Node/Tonsil
Activated Blood B
Resting/Activated T
Cell Lines
FL
Resting Blood B
CLL
Cyclin A
BUB1 mitotic kinase
Cyclin B1
SOCS-1
Ki67
p55CDC
pLK=polo-like k
Prolifer-ation
p16
Thymidine kina
CDC21 homolo
RAD54
Dihydrofolate reductase
CD38
Genetic profile of functionally related genes for a specific tumor
related genes
FAK=focal adhesion kinase
WIP=WASP interacting protein
Germinal Center B
FMR2
CD10
BCL-7A
A-myb
BCL-6
PI 3-kinase p110 γ
cluster
RGS13
CD105
CD14
FGF-7
MMP9
fms=CSF-1 receptor
Cathepsin B
Fc ε receptor γ chain
Lymph Node
TIMP-3
Integrin beta 5
NK4=NK cell protein-4
SDF-1 chemokine

K-means clustering: Explanation by example



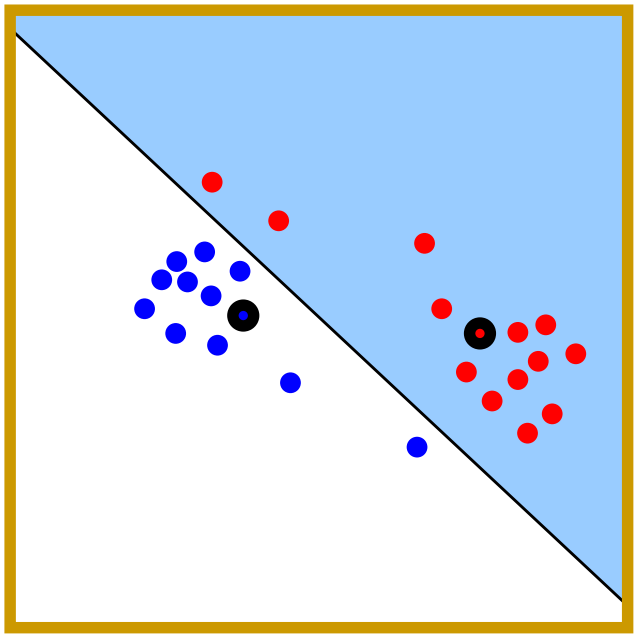
Choose randomly 2 prototypes

K-means clustering: Explanation by example



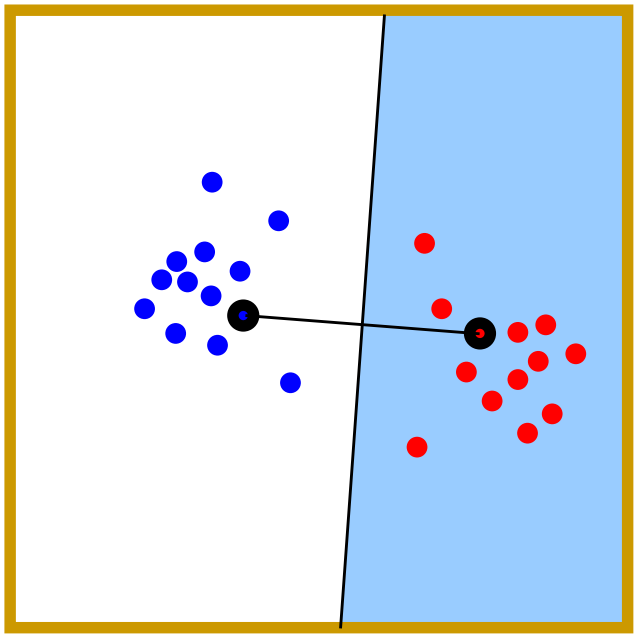
Assign objects to closest prototype
Blue area: cluster 1
White area: cluster 2

K-means clustering: Explanation by example



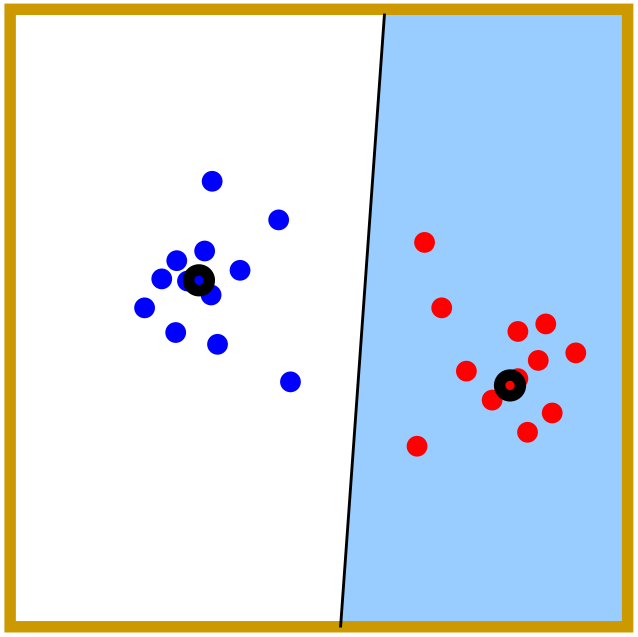
Calculate new cluster prototypes
By averaging objects

K-means clustering: Explanation by example



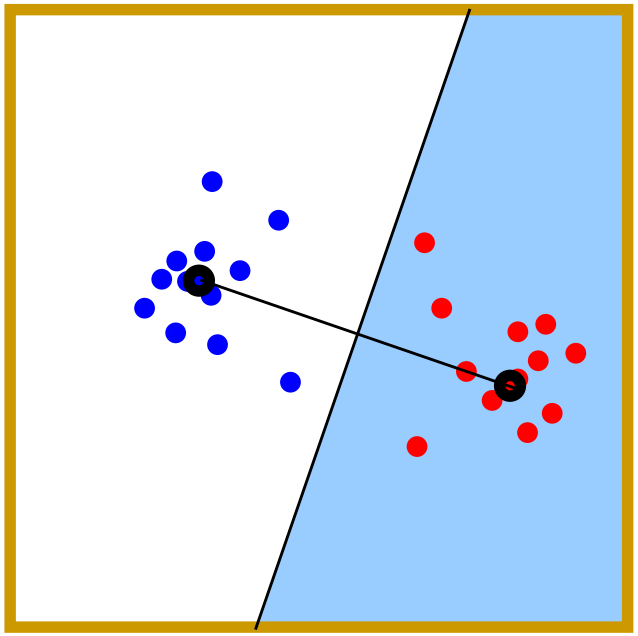
Re-assign objects to closest prototype
Blue area: cluster 1
White area: cluster 2

K-means clustering: Explanation by example



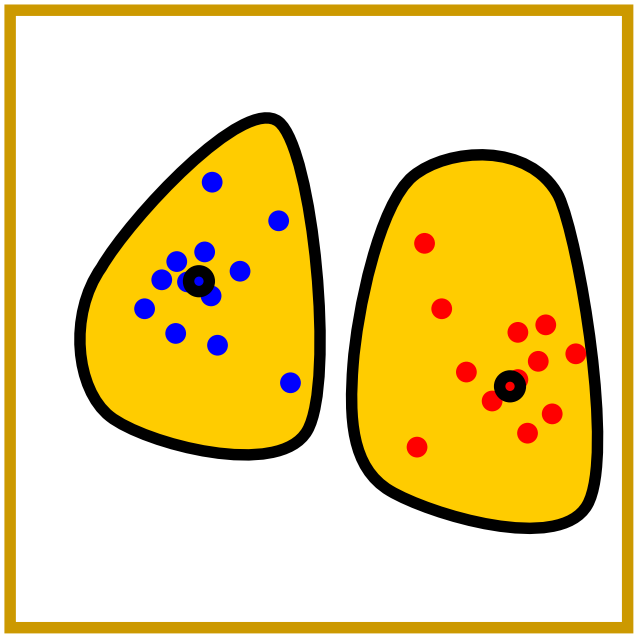
Re-calculate new cluster prototypes

K-means clustering: Explanation by example



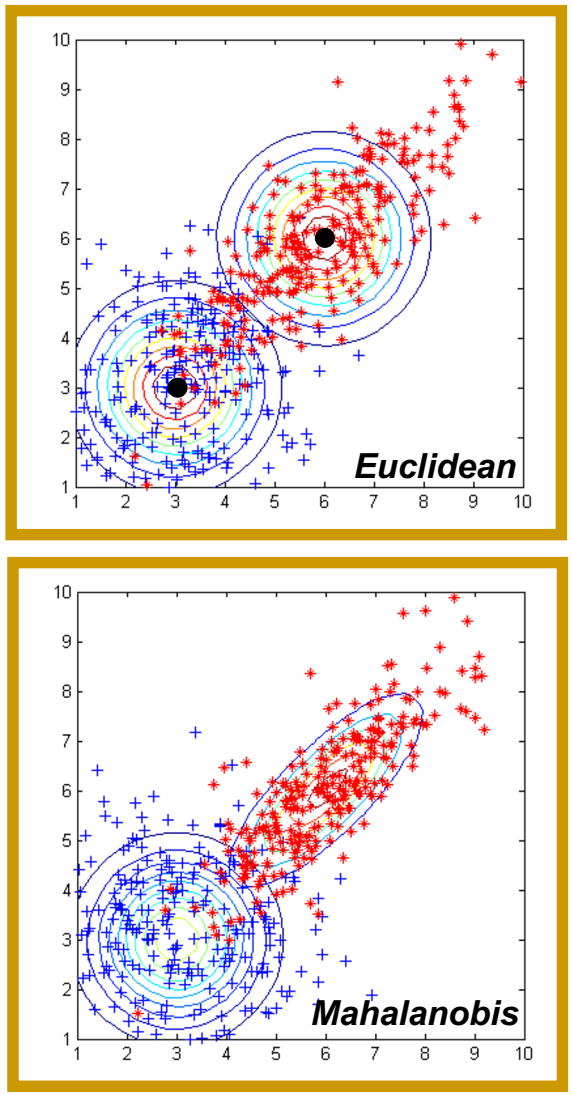
Re-assign objects to closest prototype
If no objects change cluster then finished

K-means clustering: Explanation by example



Establish clusters

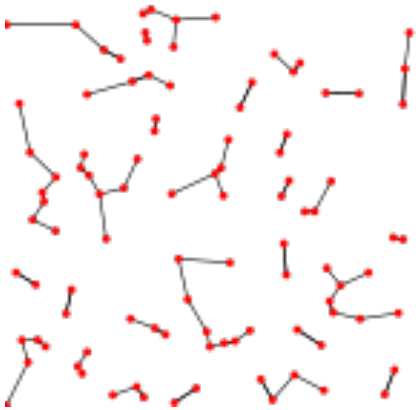
K-means clustering: Parameters



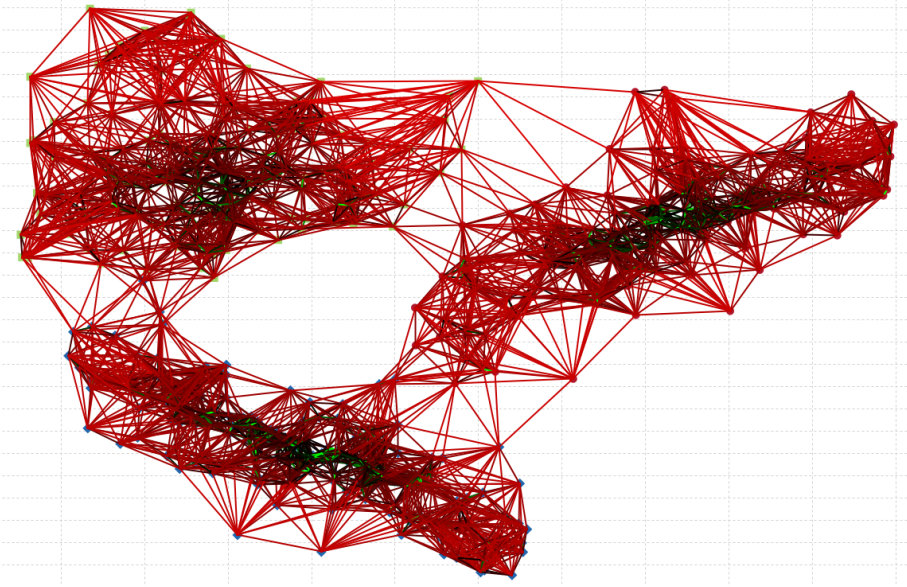
- **K-means**
  - Fixed number of clusters (need to know a priori)
  - Choice of distance measure
  - Prototype choice
- **Distance measure**
  - Euclidean: Round clusters
  - Mahalanobis: Elongated clusters
- **Prototype choice**
  - Point
  - Line etc.
- **Number of clusters**
  - Validate clustering!

Graph-based Clustering

- **K-NN graph:** Connect every node to its k-nearest nodes
- Find densely connected components



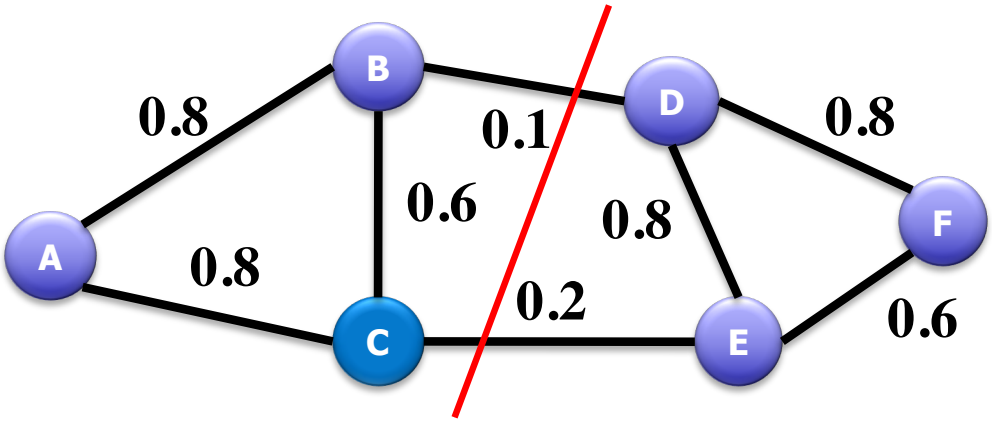
$k=1$



$k=20$

Spectral clustering (1)

- Minimise normalised cut
- Normalised cut between two clusters C_1 and C_2:

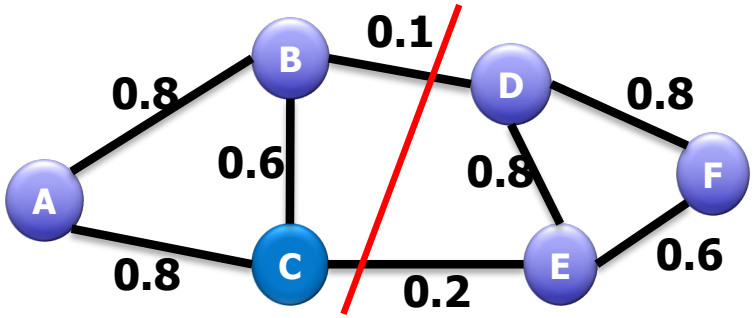


$$NC(C_1,C_2) = \frac{\text{cut}(C_1,C_2)}{assoc(C_1,V)} + \frac{\text{cut}(C_2,C_1)}{assoc(C_2,V)} = 2 - \left(\frac{assoc(C_1,C_1)}{assoc(C_1,V)} + \frac{assoc(C_2,C_2)}{assoc(C_2,V)}\right)$$

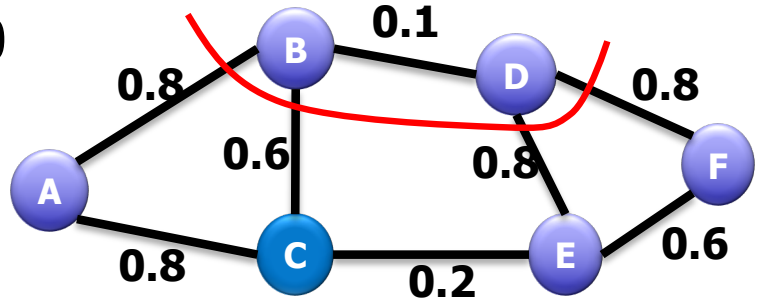
- cut(C_1, C_2) = weight of links between C_1 and C_2
- cut(C_2, C_1) = same
- assoc(C_1, V) = total weight of links from nodes in C_1 to entire graph
- assoc(C_2, V) = total weight of links from nodes in C_2 to entire graph

Normalized cut (example)

- cut(S,T) = 0.1 + 0.2 = 0.3
- vol(S)= 0.3 + 0.6 + 0.8 + 0.8 = 2.5
- vol(T)= 0.3 + 0.8 + 0.8 + 0.6 = 2.5
- Ncut(S,T) = 0.3/2.5 + 0.3/2.5 = 0.24



- cut(S,T) = 0.8 + 0.6 + 0.8 + 0.8 = 3.0
- vol(S) = 3.0 + 0.1 = 3.1
- vol(T) = 3.0 + 0.8 + 0.2 + 0.6 = 4.6
- Ncut(S,T) = 3.0/3.1 + 3.0/4.6 = 1.62



Spectral clustering (2) *(sum weights on diagonal – W)*

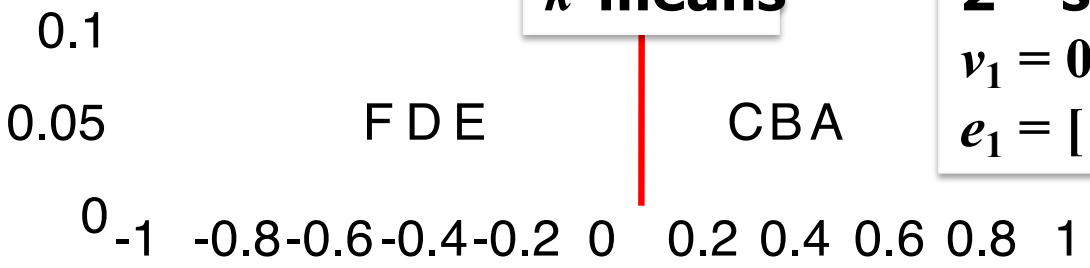
$$W = \begin{array}{c} \\ A \\ B \\ C \\ D \\ E \\ F \end{array} \begin{array}{c} \begin{array}{cccccc} A & B & C & D & E & F \end{array} \\ \begin{pmatrix} 0 & 0.8 & 0.8 & 0 & 0 & 0 \\ 0.8 & 0 & 0.6 & 0.1 & 0 & 0 \\ 0.8 & 0.6 & 0 & 0 & 0.2 & 0 \\ 0 & 0.1 & 0 & 0 & 0.8 & 0.8 \\ 0 & 0 & 0.2 & 0.8 & 0 & 0.6 \\ 0 & 0 & 0 & 0.8 & 0.6 & 0 \end{pmatrix} \end{array} \xrightarrow[L=\mathrm{diag}(1^T W)-W]{\text{Laplacian}} L = \begin{array}{c} \\ A \\ B \\ C \\ D \\ E \\ F \end{array} \begin{array}{c} \begin{array}{cccccc} A & B & C & D & E & F \end{array} \\ \begin{pmatrix} 1.6 & -0.8 & -0.8 & 0 & 0 & 0 \\ -0.8 & 1.5 & -0.6 & -0.1 & 0 & 0 \\ -0.8 & -0.6 & 1.6 & 0 & -0.2 & 0 \\ 0 & -0.1 & 0 & 1.7 & -0.8 & -0.8 \\ 0 & 0 & -0.2 & -0.8 & 1.6 & -0.6 \\ 0 & 0 & 0 & -0.8 & -0.6 & 1.4 \end{pmatrix} \end{array}$$

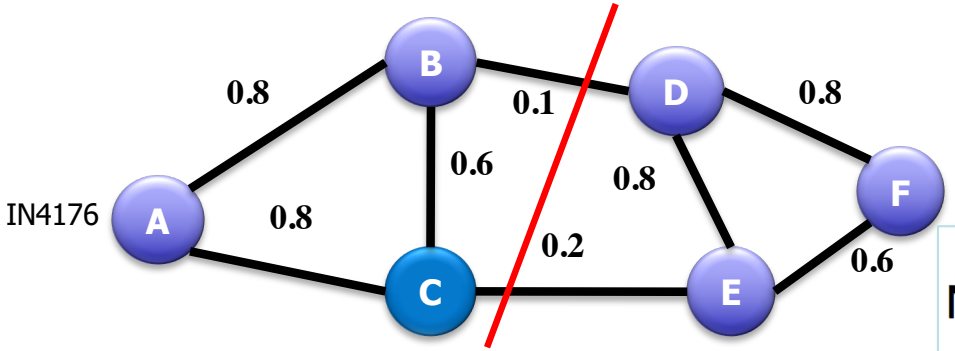
2nd smallest eigenvalue:

$v_1 = 0.19$

$e_1 = [\ 0.44\ 0.41\ 0.37\ -0.40\ -0.37\ -0.45\ ]^T$

***k*-means**





IN4176

IEEE TRANSACTIONS ON PATTERN ANALYSIS AND MACHINE INTELLIGENCE, VOL. 22, NO. 8, AUGUST 2000

Normalized Cuts and Image Segmentation

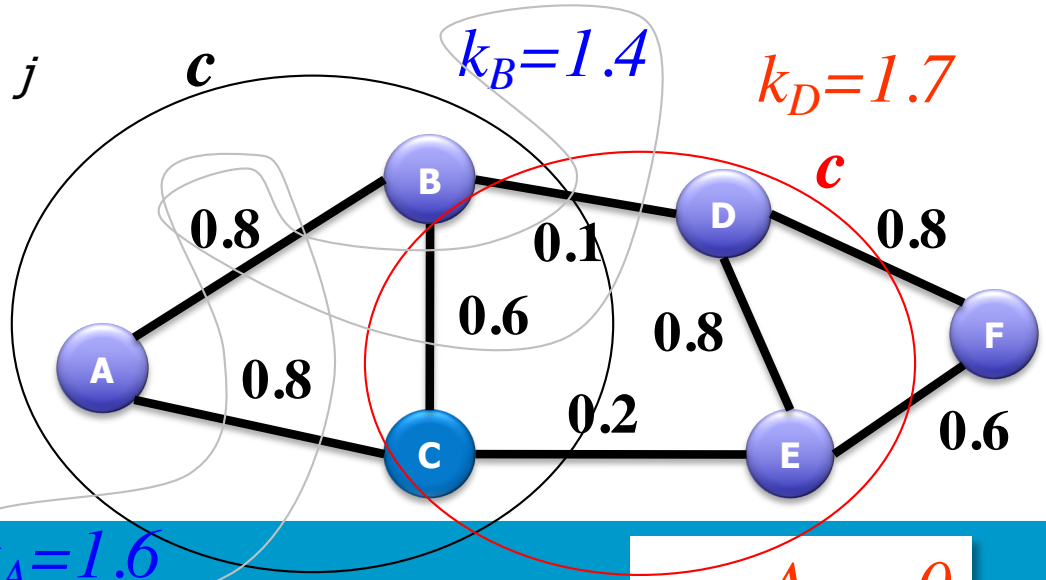
Jianbo Shi and Jitendra Malik, *Member, IEEE*

Louvain method for community detection

Maximize modularity

$$Q = \frac{1}{2m} \sum_{ij} \underbrace{\left[A_{ij} - \frac{k_i k_j}{2m} \right]}_{Q_{ij}} \delta(c_i, c_j) \qquad (Q^*=2mQ)$$

i , j	nodes
c_i , c_j	community of node i and j
A_{ij}	weight edge node i and j
k_i , k_j	total weight of edges of nodes i and j
$\delta(c_i,c_j)$	1 if $c_i=c_j$, zero otherwise
m	total weight of edges



$A_{AB}=0.8$

$\delta(c_A,c_B)=1$

$Q_{AB}=0.8-1.6*1.4/2m$

$Q_{CD}=0-1.6*1.7/2m$

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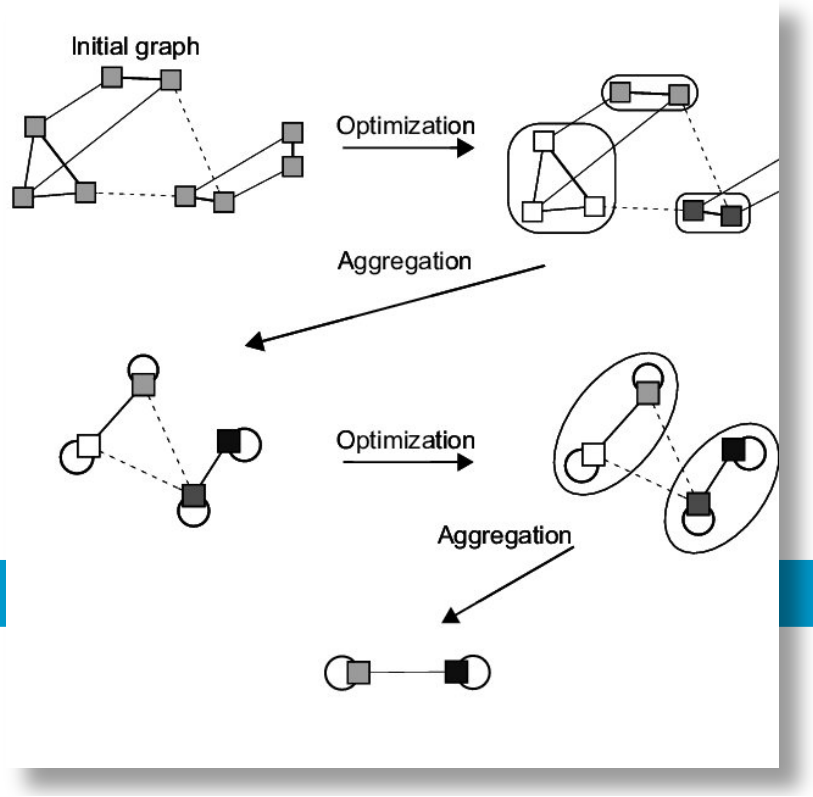
Louvain method for community detection

Modularity optimized in two phases, applied iteratively

Phase 1: Optimization (communities); moving nodes from own community to community of neighboring node (*improve Q*)

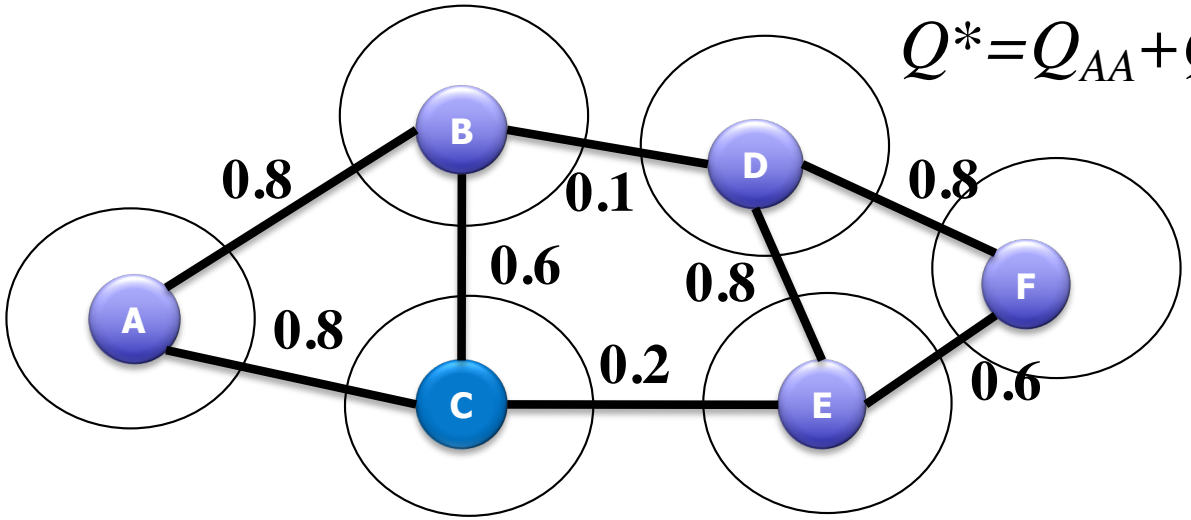
Phase 2: Aggregation; building new network by aggregating nodes in detected communities



Louvain method, running example
(start: every node in separate community)

$M=0.8+0.8+0.6+0.1+0.2+0.8+0.8+0.6=4.7$

$Q^*=Q_{AA}+Q_{BB}+Q_{CC}+Q_{DD}+Q_{EE}+Q_{FF}$



$Q_{AA} = 0 - 1.6*1.6/9.4$
$Q_{BB} = 0 - 1.5*1.5/9.4$
$Q_{CC} = 0 - 1.6*1.6/9.4$
$Q_{DD} = 0 - 1.7*1.7/9.4$
$Q_{EE} = 0 - 1.6*1.6/9.4$
$Q_{FF} = 0 - 1.4*1.4/9.4$

$$Q = \frac{1}{2m} \sum_{ij} \left[A_{ij} - \frac{k_i k_j}{2m} \right] \delta(c_i, c_j)$$

Only 1 for AA,BB,CC,DD,EE,FF

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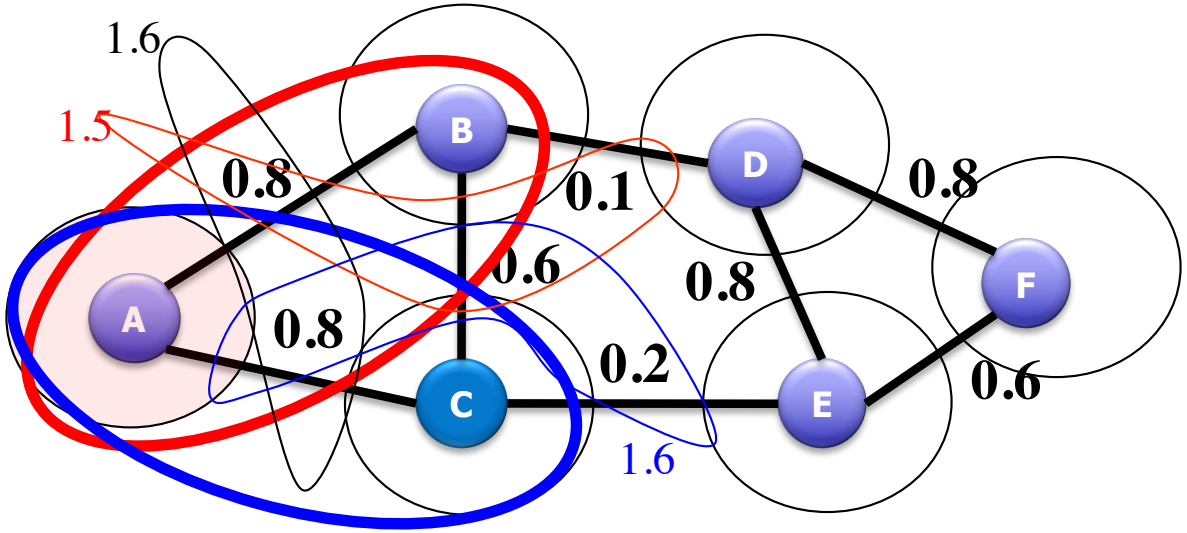
1: Optimize (node A)

$$Q^*=Q_{AA}+Q_{BB}+Q_{CC}+Q_{DD}+Q_{EE}+Q_{FF}+Q_{AB}$$
$$Q^*=Q_{AA}+Q_{BB}+Q_{CC}+Q_{DD}+Q_{EE}+Q_{FF}+Q_{AC}$$



Q_{AB}=0.8-1.6*1.5/9.4=0.54

Q_{AC}=0.8-1.6*1.6/9.4=0.53

$$Q = \frac{1}{2m} \sum_{ij} \left[A_{ij} - \frac{k_i k_j}{2m} \right] \delta(c_i, c_j)$$

Now 1 for AA,BB,CC,DD,EE,FF AND AB or AC

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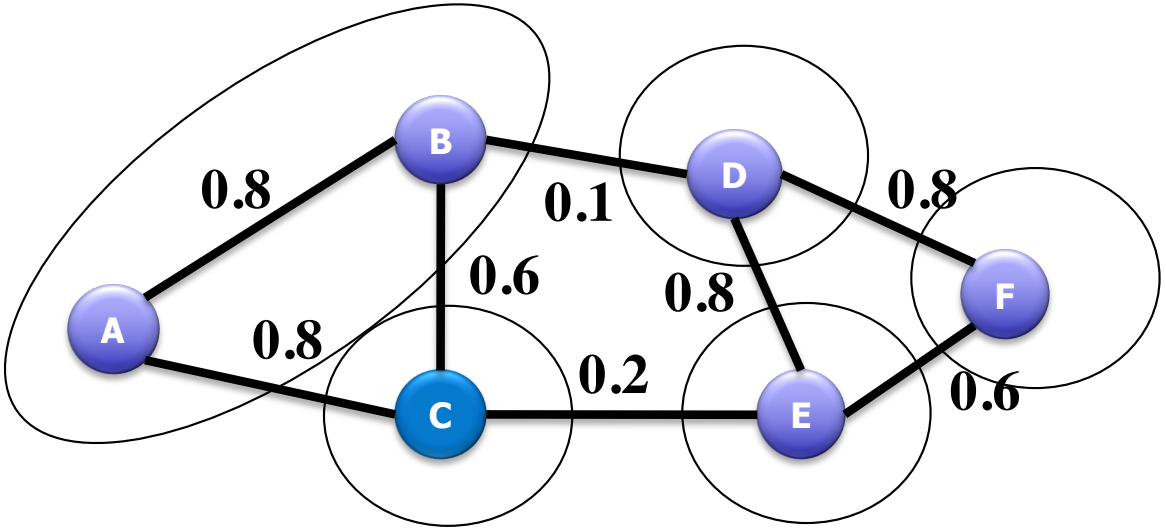
1: Optimize (node A)

$$Q^*=Q_{AA}+Q_{BB}+Q_{CC}+Q_{DD}+Q_{EE}+Q_{FF}+Q_{AB}$$
$$Q^*= Q_{AA}+Q_{BB}+Q_{CC}+Q_{DD}+Q_{EE}+Q_{FF}+Q_{AC}$$



Q_{AB}=0.8-1.6*1.5/9.4=0.54

Q_{AC}=0.8-1.6*1.6/9.4=0.53

$Q_{AB}>Q_{AC}$ and positive

Q_{AB} improves Q*

Move A with B

$$Q = \frac{1}{2m} \sum_{ij} \left[A_{ij} - \frac{k_i k_j}{2m} \right] \delta(c_i, c_j)$$

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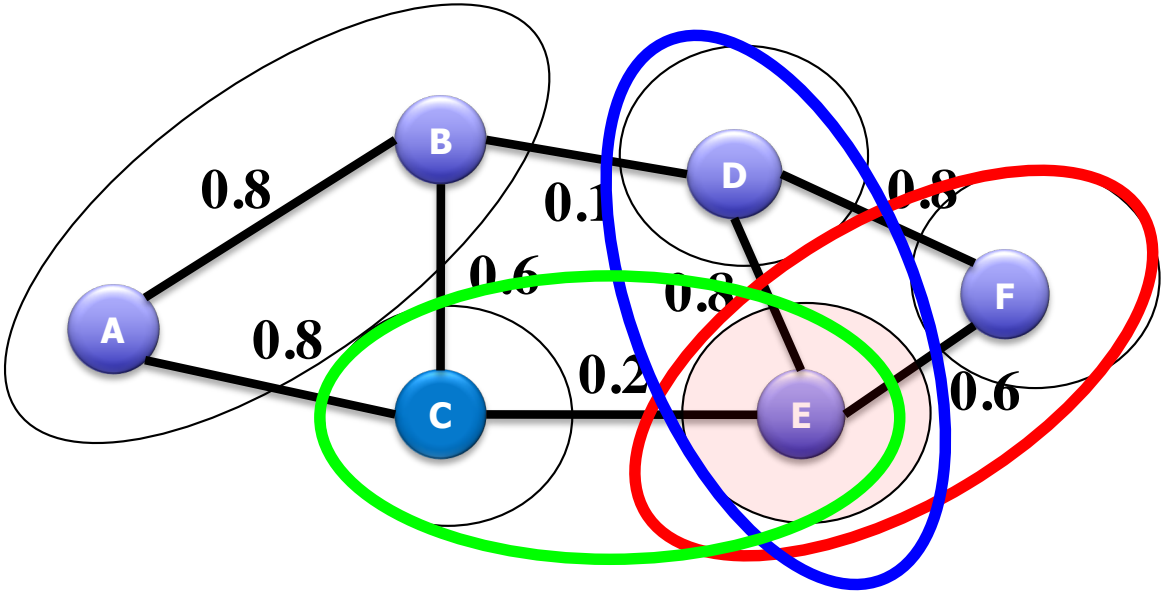
1: Optimize (node E)

$$Q^* = Q_{AA} + Q_{BB} + Q_{CC} + Q_{DD} + Q_{EE} + Q_{FF} + Q_{AB} + Q_{EC}$$
$$Q^* = Q_{AA} + Q_{BB} + Q_{CC} + Q_{DD} + Q_{EE} + Q_{FF} + Q_{AB} + Q_{ED}$$
$$Q^* = Q_{AA} + Q_{BB} + Q_{CC} + Q_{DD} + Q_{EE} + Q_{FF} + Q_{AB} + Q_{EF}$$



Q_{EC}=0.2-1.6*1.6/9.4=-0.07

Q_{ED}=0.8-1.6*1.7/9.4=0.51

Q_{EF}=0.6-1.6*1.4/9.4=0.36

$$Q = \frac{1}{2m} \sum_{ij} \left[A_{ij} - \frac{k_i k_j}{2m} \right] \delta(c_i, c_j)$$

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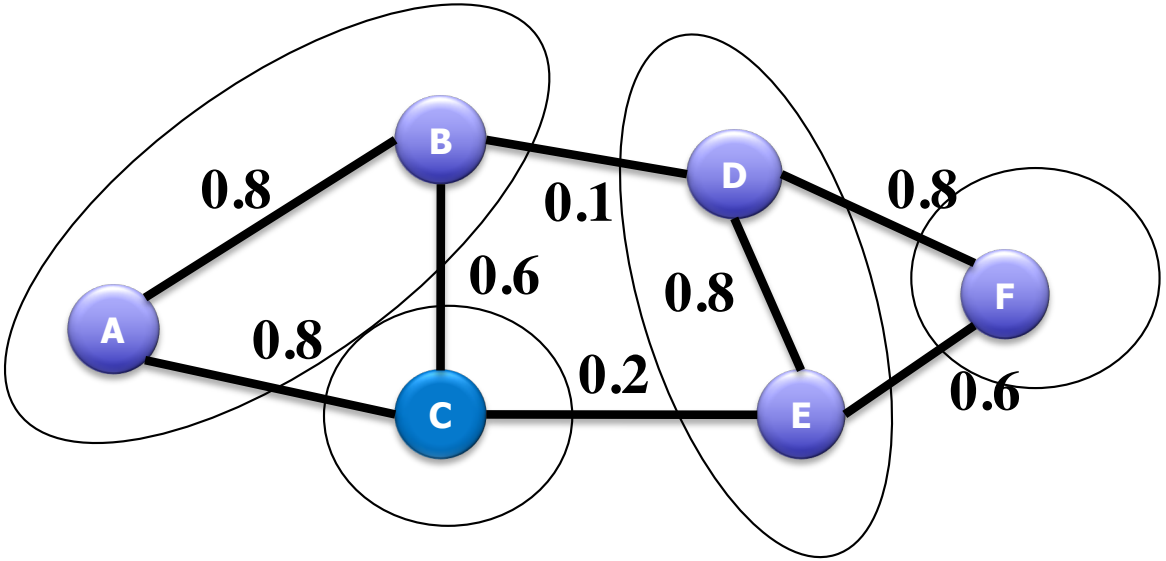
1: Optimize (node E)

$$Q^* = Q_{AA} + Q_{BB} + Q_{CC} + Q_{DD} + Q_{EE} + Q_{FF} + Q_{AB} + Q_{EC}$$
$$Q^* = Q_{AA} + Q_{BB} + Q_{CC} + Q_{DD} + Q_{EE} + Q_{FF} + Q_{AB} + Q_{ED}$$
$$Q^* = Q_{AA} + Q_{BB} + Q_{CC} + Q_{DD} + Q_{EE} + Q_{FF} + Q_{AB} + Q_{EF}$$



Q_{EC}=0.2-1.6*1.6/9.4=-0.07

Q_{ED}=0.8-1.6*1.7/9.4=0.51

Q_{EF}=0.6-1.6*1.4/9.4=0.36

Q_{ED} largest & positive

Move E with D

$$Q = \frac{1}{2m} \sum_{ij} \left[A_{ij} - \frac{k_i k_j}{2m} \right] \delta(c_i, c_j)$$

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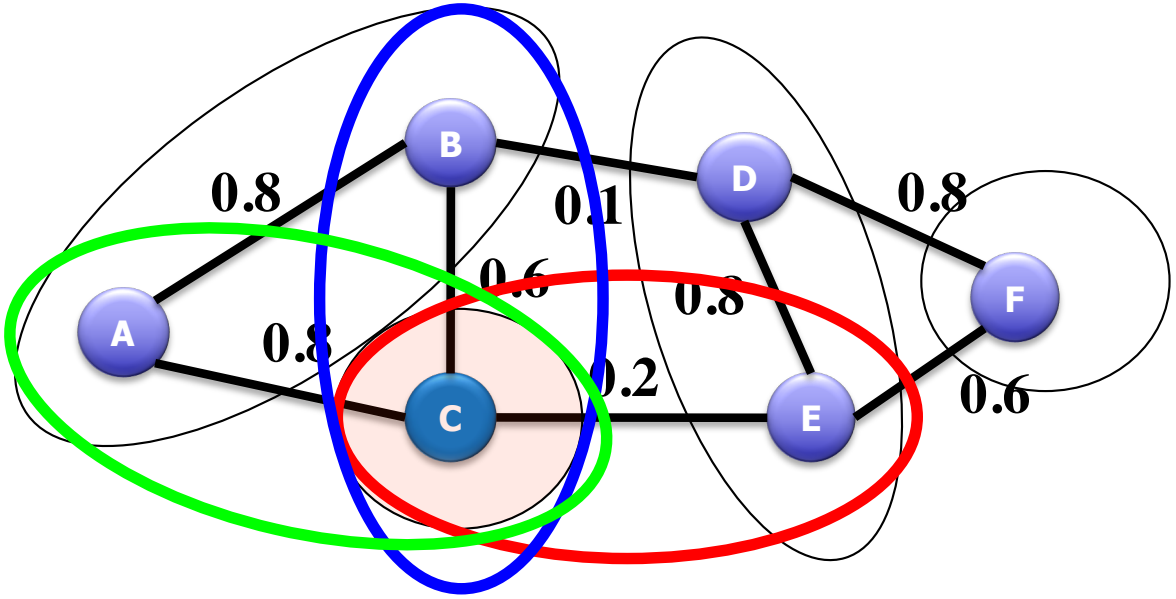
1: Optimize (node C)

$$Q^* = Q_{AA}+Q_{BB}+Q_{CC}+Q_{DD}+Q_{EE}+Q_{FF}+Q_{ED}+Q_{CA}$$
$$Q^* = Q_{AA}+Q_{BB}+Q_{CC}+Q_{DD}+Q_{EE}+Q_{FF}+Q_{ED}+Q_{CB}$$
$$Q^* = Q_{AA}+Q_{BB}+Q_{CC}+Q_{DD}+Q_{EE}+Q_{FF}+Q_{ED}+Q_{CE}$$



Q_{CA}=0.8-1.6*1.6/9.4=0.53
Q_{CB}=0.6-1.6*1.5/9.4=0.34
Q_{CE}=0.2-1.6*1.6/9.4=-0.07

$$Q = \frac{1}{2m}\sum_{ij}\left[A_{ij} - \frac{k_i k_j}{2m}\right]\delta(c_i, c_j)$$

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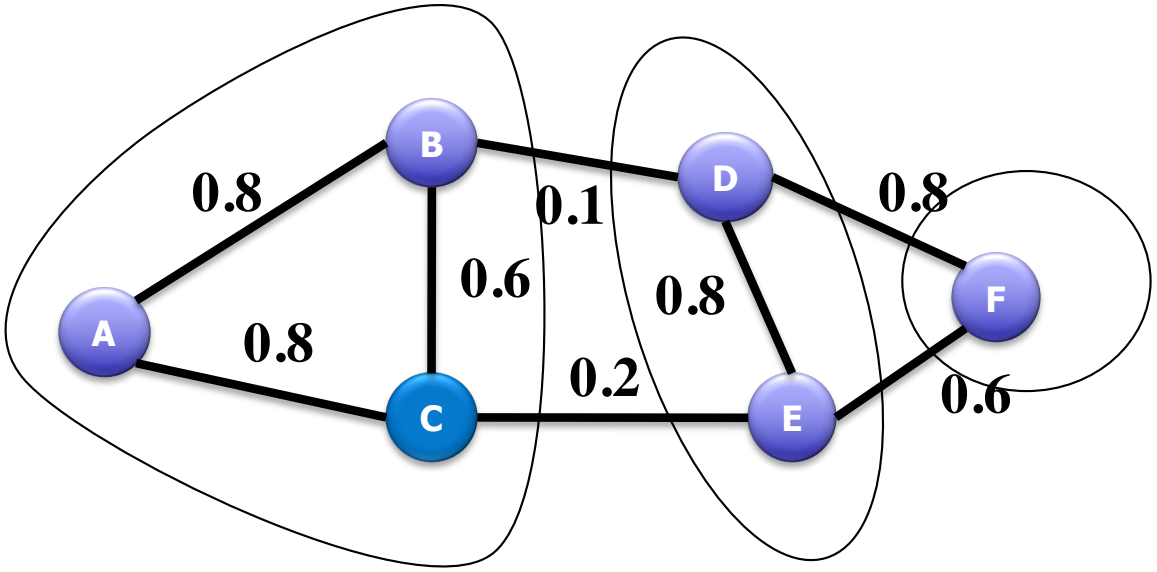
1: Optimize (node C)

$$Q^* = Q_{AA}+Q_{BB}+Q_{CC}+Q_{DD}+Q_{EE}+Q_{FF}+Q_{ED}+Q_{CA}$$
$$Q^* = Q_{AA}+Q_{BB}+Q_{CC}+Q_{DD}+Q_{EE}+Q_{FF}+Q_{ED}+Q_{CB}$$
$$Q^* = Q_{AA}+Q_{BB}+Q_{CC}+Q_{DD}+Q_{EE}+Q_{FF}+Q_{ED}+Q_{CE}$$



Q_{CA}=0.8-1.6*1.6/9.4=0.53
Q_{CB}=0.6-1.6*1.5/9.4=0.34
Q_{CE}=0.2-1.6*1.6/9.4=-0.07
Q_{CA} largest
Q_{CA} still postive
Move C with A (and B)

$$Q = \frac{1}{2m}\sum_{ij}\left[A_{ij} - \frac{k_i k_j}{2m}\right]\delta(c_i, c_j)$$

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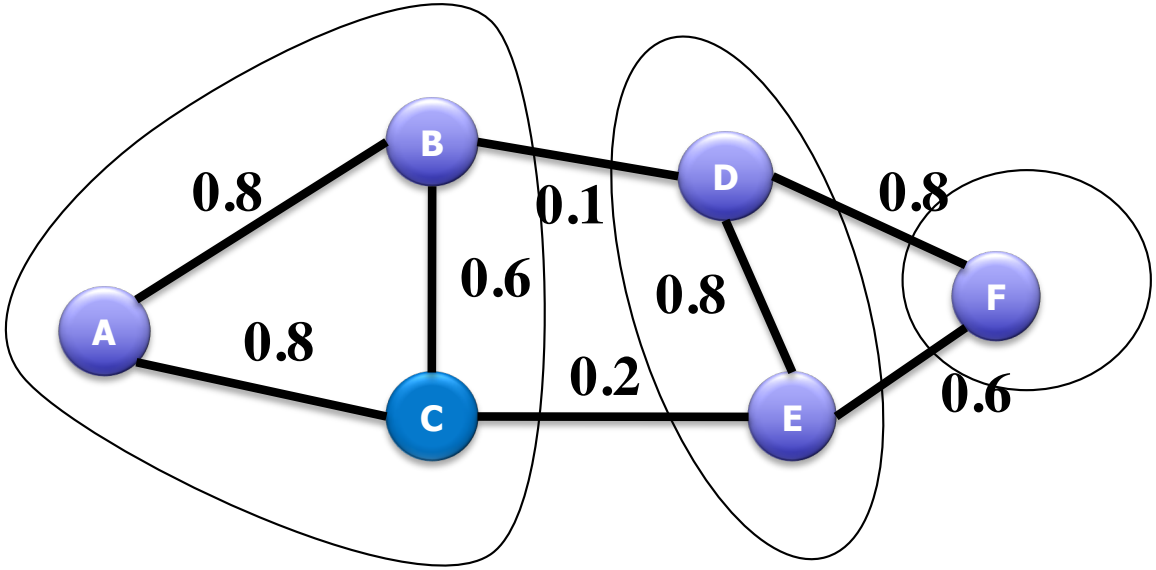
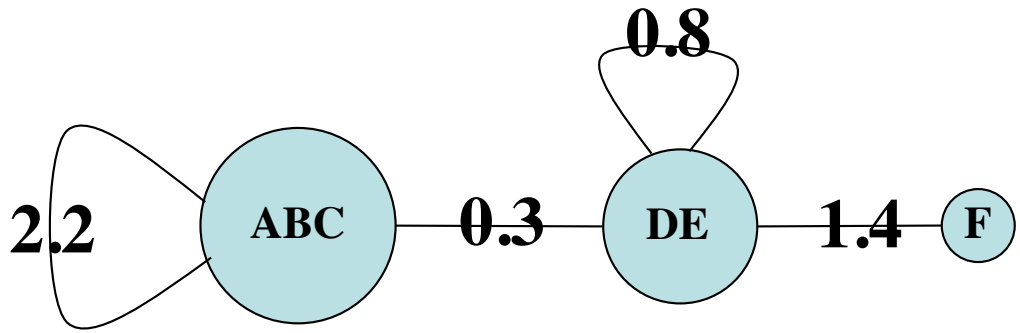
1: Aggregate





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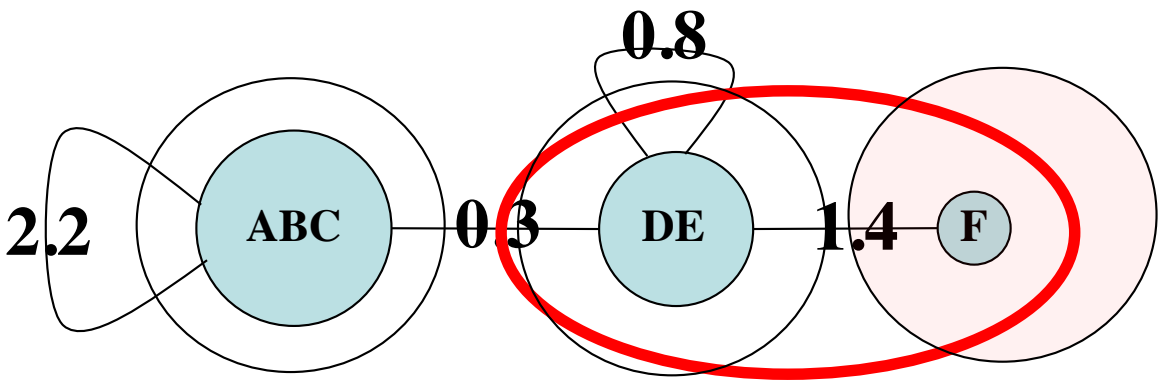
2: Optimize (Node F)

$$Q^* = Q_{ABC} + Q_{DE} + Q_F + Q_{F\text{-}DE}$$



$$Q_{F\text{-}DE} = 1.4 - 0 * 1.7/9.4 = 1.4$$

$$Q = \frac{1}{2m} \sum_{ij} \left[A_{ij} - \frac{k_i k_j}{2m} \right] \delta(c_i, c_j)$$

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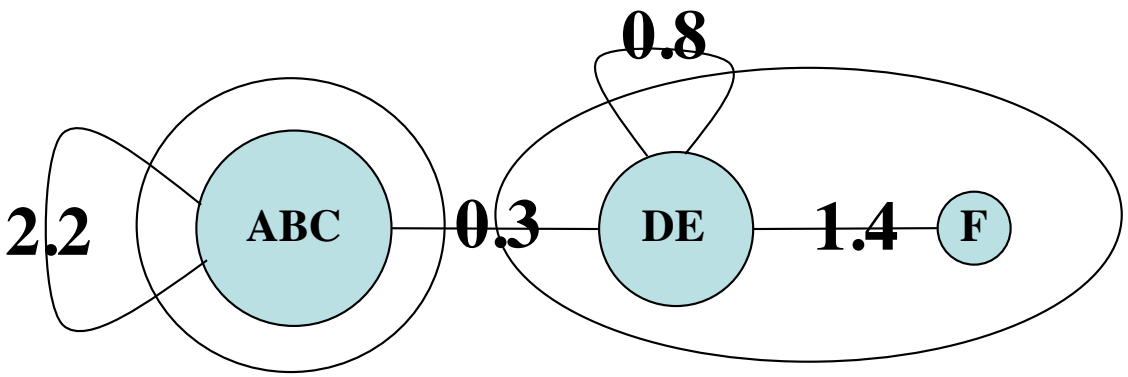
2: Optimize (Node F)

$$Q^* = Q_{ABC} + Q_{DE} + Q_F + Q_{F\text{-}DE}$$



$Q_{F\text{-}DE}$=1.4-0*1.7/9.4=1.4

$Q_{F\text{-}DE}$ postive

Move F with DE

$$Q = \frac{1}{2m} \sum_{ij} \left[A_{ij} - \frac{k_i k_j}{2m} \right] \delta(c_i, c_j)$$

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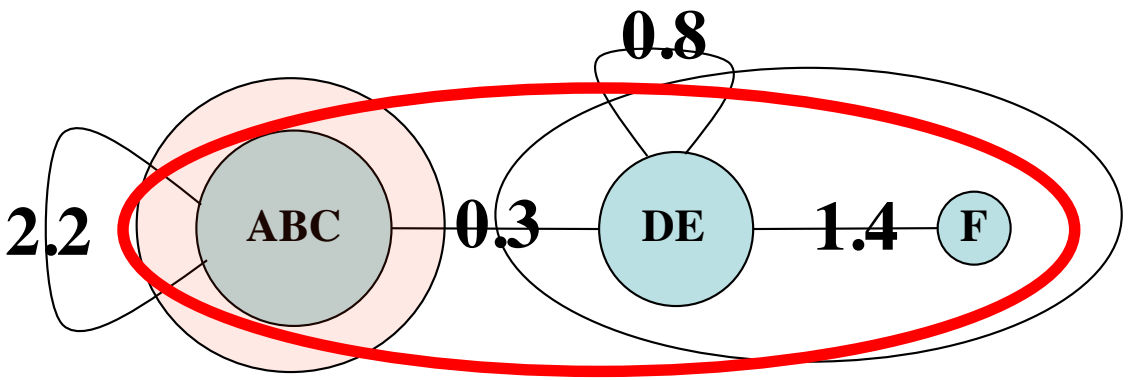
2: Optimize (Node ABC)

$$Q^* = Q_{ABC} + Q_{DE} + Q_F + Q_{F\text{-}DE} + Q_{ABC\text{-}DE}$$



$Q_{ABC\text{-}DE} = 0.3 - 2.2 * 1.8 / 9.4 = -0.12$

$Q_{ABC\text{-}DE} < 0$

STOP (no improvement of Q)

$$Q = \frac{1}{2m} \sum_{ij} \left[A_{ij} - \frac{k_i k_j}{2m} \right] \delta(c_i, c_j)$$

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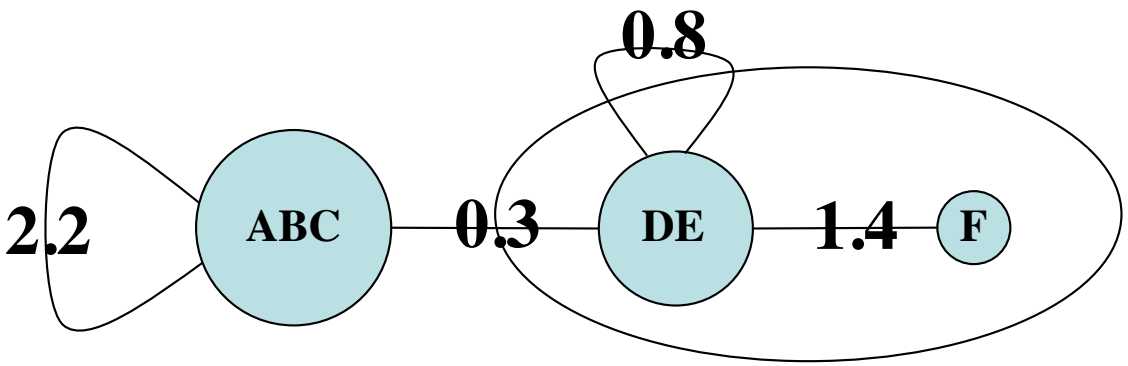
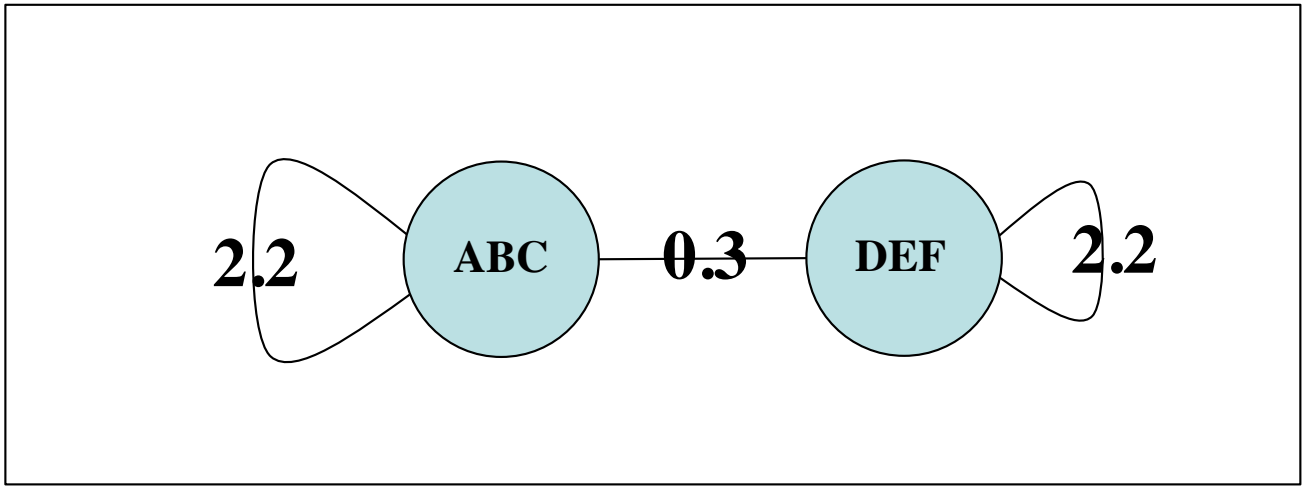
2: Agregate, finish





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Markov clustering (1)

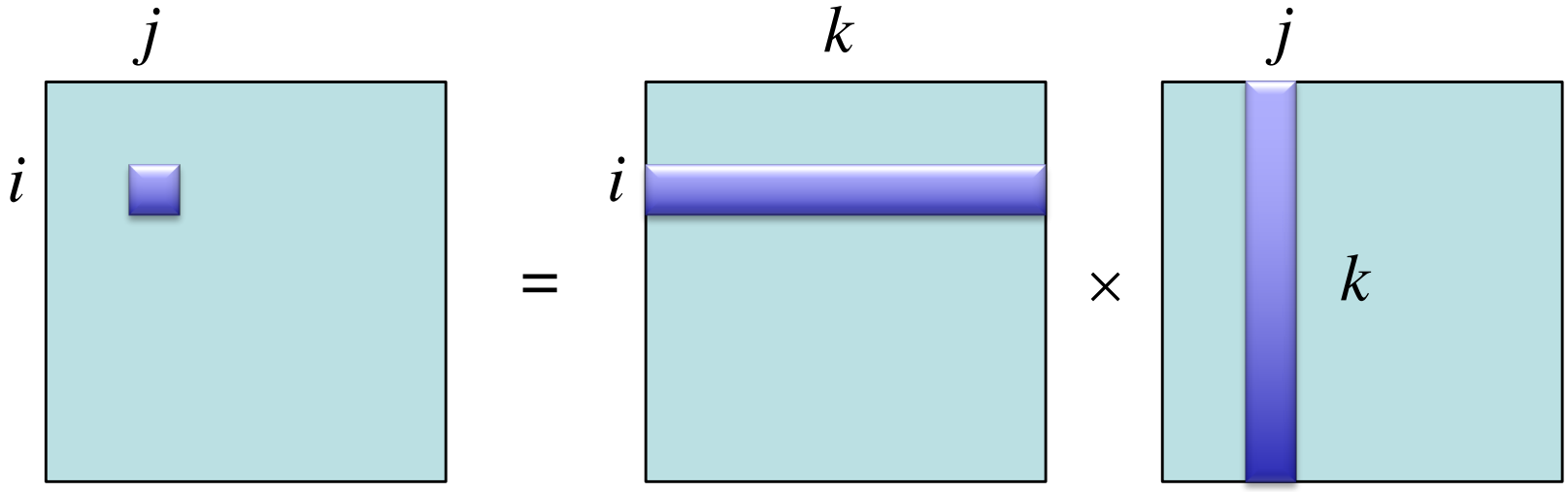
- **Markov clustering**
  - Random walks are Markov chains
  - Start with Markov matrix: $M_{ij} = p(j \rightarrow i)$
  - (optionally add loops (diagonal))

$$W = \begin{array}{c} \\ A \\ B \\ C \\ D \\ E \\ F \end{array} \begin{array}{c} \begin{array}{cccccc} A & B & C & D & E & F \end{array} \\ \begin{pmatrix} 0 & 0.8 & 0.8 & 0 & 0 & 0 \\ 0.8 & 0 & 0.6 & 0.1 & 0 & 0 \\ 0.8 & 0.6 & 0 & 0 & 0.2 & 0 \\ 0 & 0.1 & 0 & 0 & 0.8 & 0.8 \\ 0 & 0 & 0.2 & 0.8 & 0 & 0.6 \\ 0 & 0 & 0 & 0.8 & 0.6 & 0 \end{pmatrix} \end{array} \xrightarrow[\mathbf{M} = \mathbf{W}\mathrm{diag}(\mathbf{1}^T \mathbf{W})^{-1}]{\text{Markov}} M = \begin{array}{c} \\ A \\ B \\ C \\ D \\ E \\ F \end{array} \begin{array}{c} \begin{array}{cccccc} A & B & C & D & E & F \end{array} \\ \begin{pmatrix} 0 & 0.53 & 0.5 & 0 & 0 & 0 \\ 0.5 & 0 & 0.38 & 0.06 & 0 & 0 \\ 0.5 & 0.4 & 0 & 0 & 0.12 & 0 \\ 0 & 0.07 & 0 & 0 & 0.5 & 0.57 \\ 0 & 0 & 0.12 & 0.47 & 0 & 0.43 \\ 0 & 0 & 0 & 0.47 & 0.38 & 0 \end{pmatrix} \end{array}$$

$$(sum\ columns = 1)$$

Markov clustering (2)

- $M_{ij} = p(j \rightarrow i)$ probability of arriving in i from j in 1 step

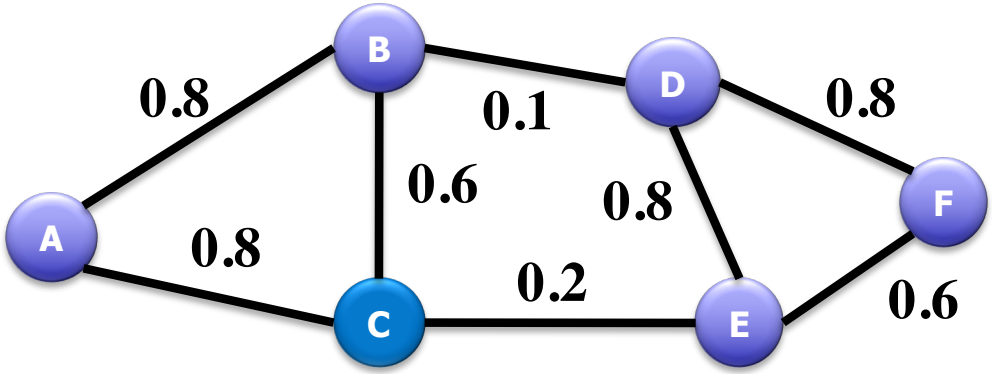


$$\left(M^2\right)_{ij} = \sum_k p(j \rightarrow k)p(k \rightarrow i)$$

probability of arriving in i from j in 2 steps (etc.)

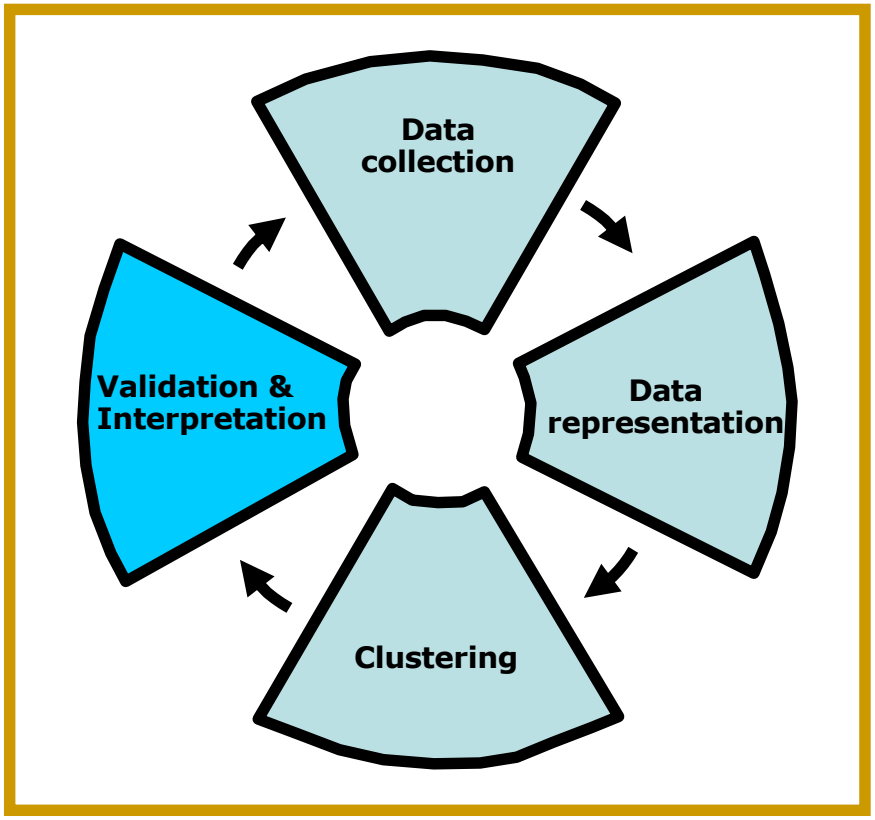
Markov clustering (3)

- **Markov clustering:**
  - Iterate
    1. $M = M^{\alpha}$
    2. $M_{ij} = M_{ij}^{\beta} \Big/ \sum_i M_{ij}^{\beta}$
- Step 1 : take walk of α steps
- Step 2 : increase difference between small probabilities (<0.5) and large probabilities (>0.5) ; converges to maximum value in column
- E.g. for $\alpha = \beta = 2$



$$M = \begin{array}{c} \\ A \\ B \\ C \\ D \\ E \\ F \end{array} \begin{array}{c} \begin{array}{cccccc} A & B & C & D & E & F \end{array} \\ \begin{pmatrix} 0.\blacksquare & 0.\blacksquare & 0.\blacksquare & 0.00 & 0.0\blacksquare & 0.00 \\ 0.\blacksquare & 0.\blacksquare & 0.\blacksquare & 0.0\blacksquare & 0.0\blacksquare & 0.00 \\ 0.\blacksquare & 0.\blacksquare & 0.\blacksquare & 0.0\blacksquare & 0.0\blacksquare & 0.0\blacksquare \\ 0.00 & 0.0\blacksquare & 0.0\blacksquare & 0.\blacksquare & 0.\blacksquare & 0.\blacksquare \\ 0.0\blacksquare & 0.0\blacksquare & 0.0\blacksquare & 0.\blacksquare & 0.\blacksquare & 0.\blacksquare \\ 0.00 & 0.00 & 0.0\blacksquare & 0.\blacksquare & 0.\blacksquare & 0.\blacksquare \end{pmatrix} \end{array}$$

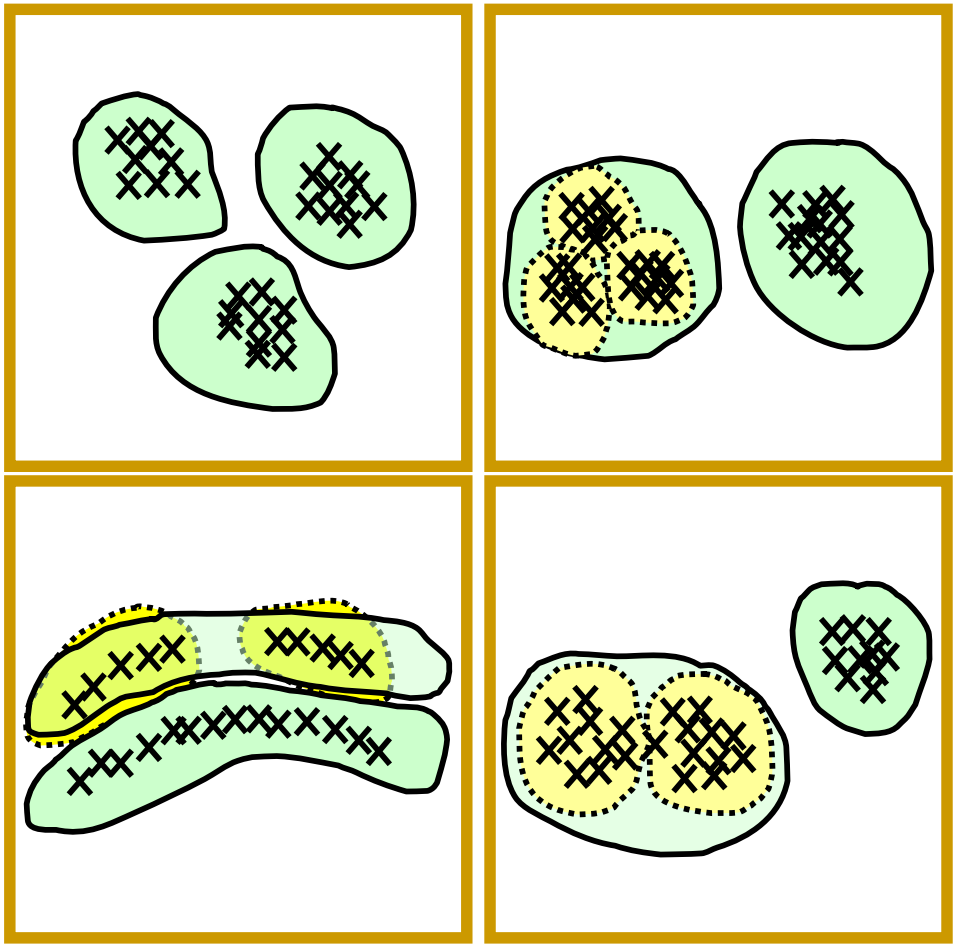
Validation



TOPICS

- **Cluster tendency**
- **Cluster validity**

Subjectivity

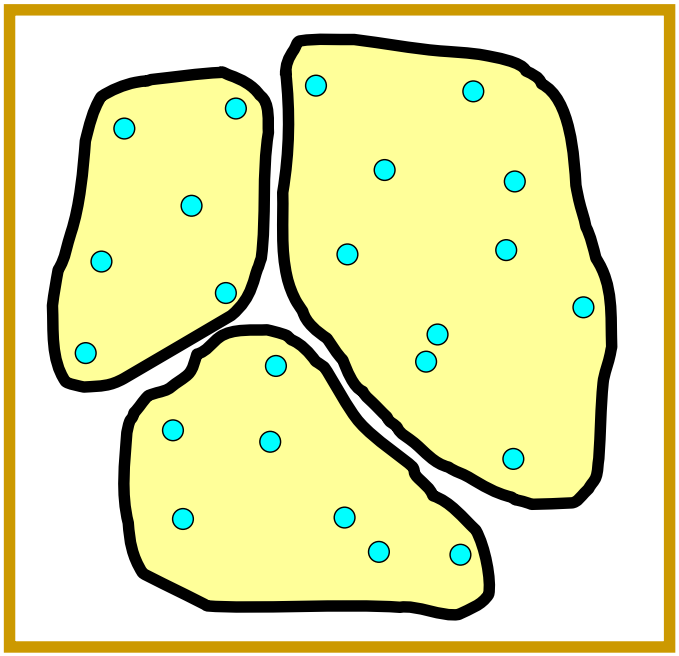


- **Principle choices:**
  - **similarity**
  - **algorithm**
- **Different choice leads to different results**

  Subjectivity becomes reality
- **Cluster process**

  Validate, interpret (generate hypothesis), repeat steps

Cluster Validation



- **Cluster tendency**

  Clustering **IMPOSES** structure even though data may not posses it

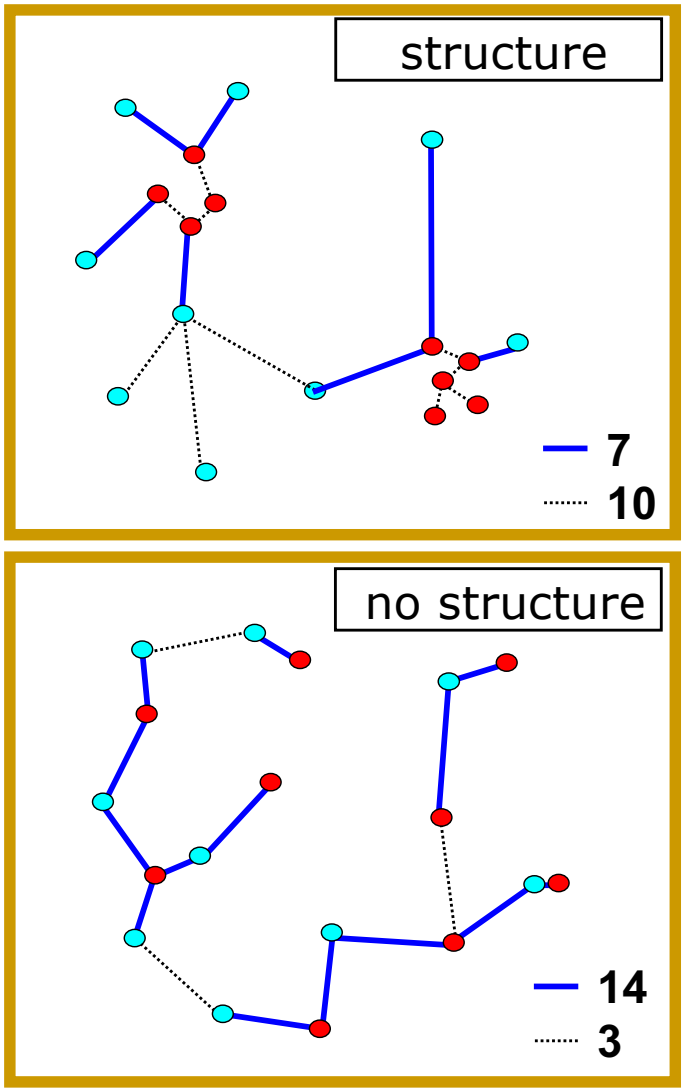
  Aim: Test whether data possesses structure

- **Cluster validity**

  Choices impose restrictions on for example shape

  Aim: Quantitative evaluation of the clustering results

Test for spatial randomness



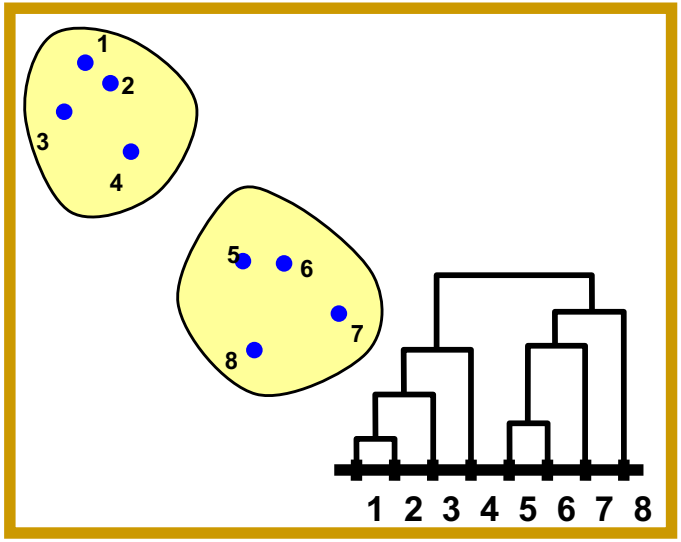
- **Test**

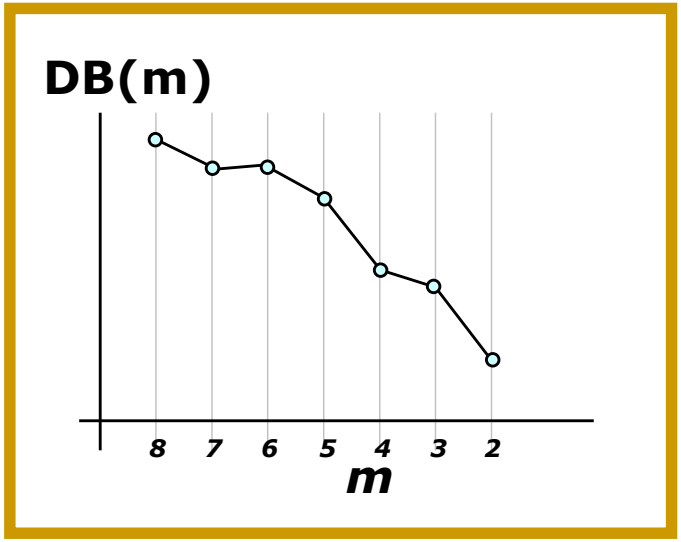
  If data (●) clusters frequently with random data (●) then data structureless

- **Approach**
  - Generate random vectors (**Y**) uniformly over observed region of data (**X**)
  - Find MST (single linkage HC) of **X** ∨ **Y**
  - Determine number of edges *q* that connect vectors of **X** with **Y**
  - If **X** contains clusters *q* should be small!

  (multiple random vs random measurements gives likelihood for *q*)

Davis-Bouldin index





- **Test**

  Select specific clustering according to a criteria

  For example: Davis-Bouldin index

- **DB index**

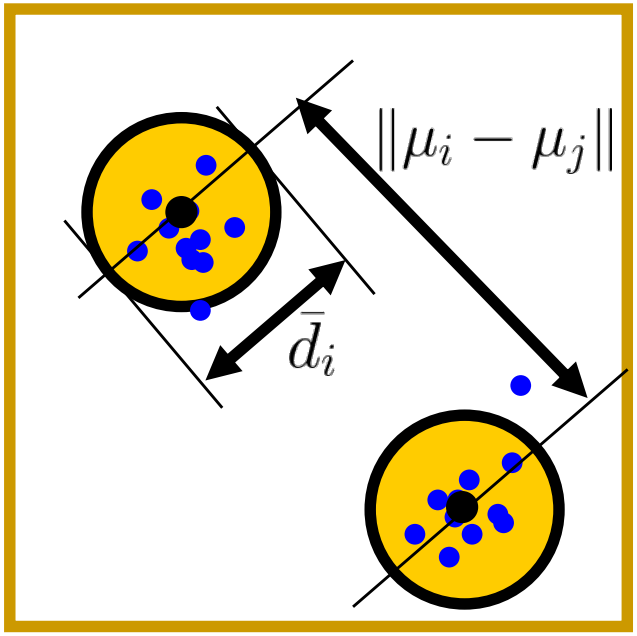
  For a specific clustering m, **DB(m)** : Average similarity of a cluster with its most similar cluster

- **Approach**

  Goal: Clusters to have minimal similarity

  Seek: Clustering that minimize *DB*(*m*) wrt *m*

Davis-Bouldin index



- **Similarity cluster C_i and C_j**

$$D_{i,j} = \frac{(\bar{d}_i + \bar{d}_j)}{\|\mu_i - \mu_j\|}$$

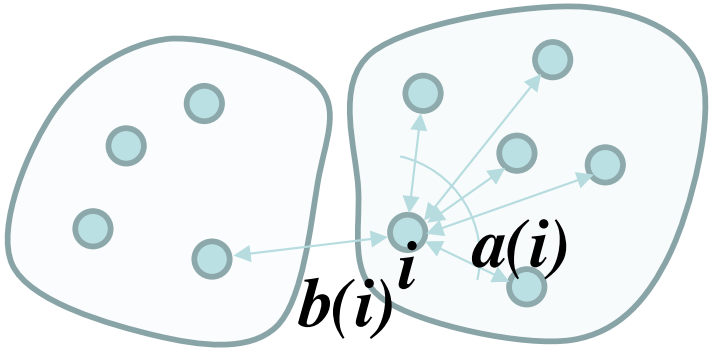
- $\bar{d}_i$:average distance within cluster *i*, μ_i:centroid of cluster *i*
- **Most similar cluster to C_i**

$$R_{i,j} = \max_{j \neq i} \{D_{i,j}\}$$

- **DB index**

$$DB = \frac{1}{k} \sum_{k=1}^{k} R_{i,j}$$

Silhouette score



- **Measure similarity of object to its own cluster**

$$s(i) = \frac{b(i) - a(i)}{max(a(i), b(i))}$$

with $a(i)$ being average distance to all objects in same cluster and $b(i)$ being closest object from all other clusters:

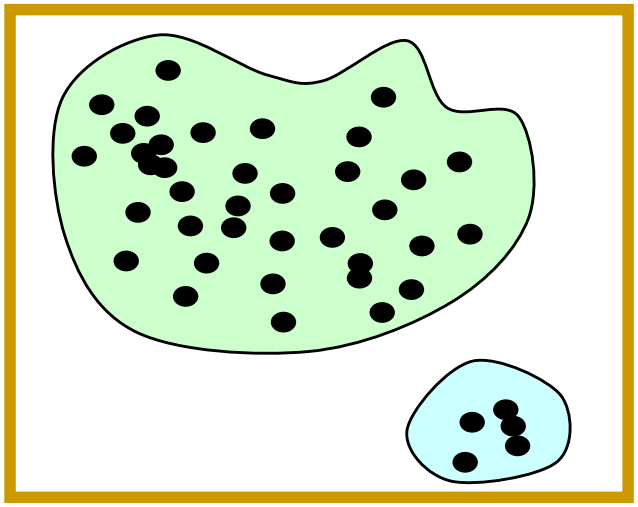
$$a(i) = \frac{1}{|C_i|} \sum_{\forall j} d(x_i, x_j) \qquad b(i) = min_{\forall j, j \notin C_i} d(x_i, x_j)$$

$-1 \leq s(i) \ll 1$; $s(i)$ is close to 1, if $a(i) \ll b(i)$; average distance within cluster much smaller than nearest objects

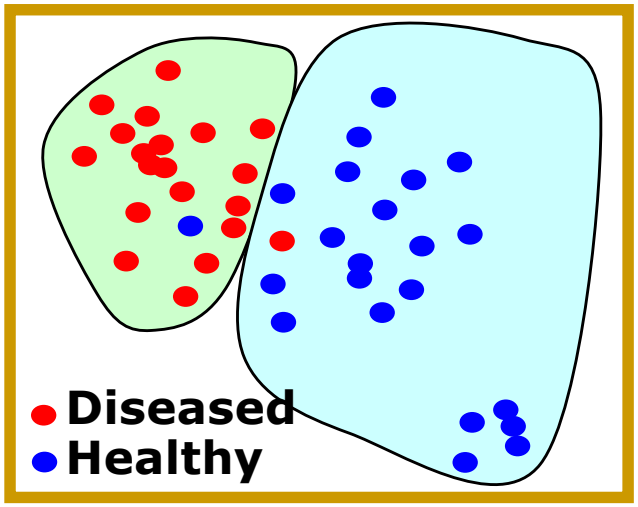
- **Silhouette score is average of all these similarities**

$$S = \frac{1}{N} \sum S(i)$$

Clustering vs classification

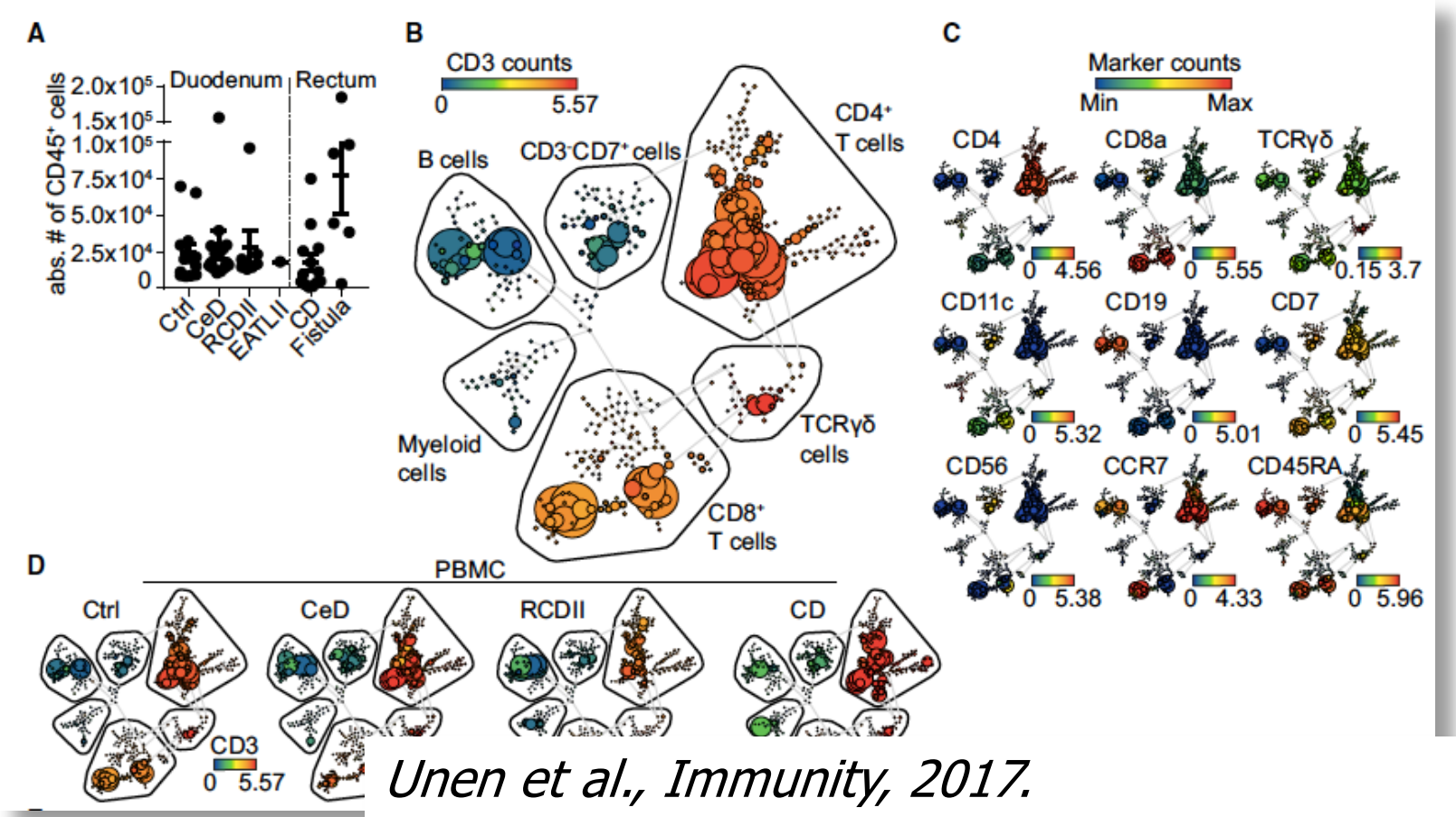


- **Machine learning**
- **Clustering**
  - **unsupervised** learning
  - discovering structure/relations



- **Classification**
  - **Supervised** learning
  - Learning certain behavior
  - Prior information available about different groups

Exploration, clustering



Unen et al., Immunity, 2017.

… mass cytometry to **dissect the human mucosal immune system** …

… **identify immune subsets** with tissue- and disease-specificity with implications for diagnostic procedures and individualized therapeutics….

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Clustering: Summary

- Clustering is an unsupervised, iterative process of interpreting data – not proof!
- Cluster results highly depend on the choice of cluster algorithm and dissimilarity measure
- Clustering and classification serve different purposes

Thank you!

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References/Reading material

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