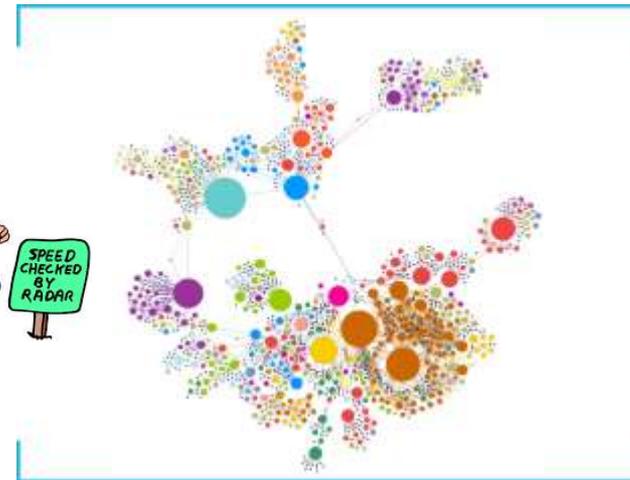




Consiglio Nazionale
delle Ricerche



SWIM: A NEW METHODOLOGY TOWARDS NETWORK MEDICINE



FEDERICA CONTE

Institute of Systems Analysis and Computer Science (IASI) "A. Ruberti"

CNR - Roma

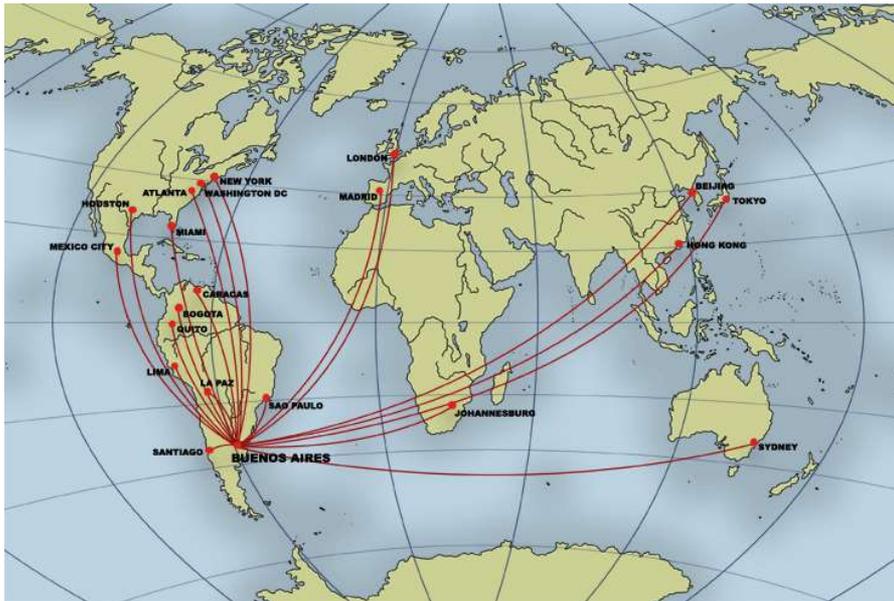
Social network



Computer network: internet



Network of airports

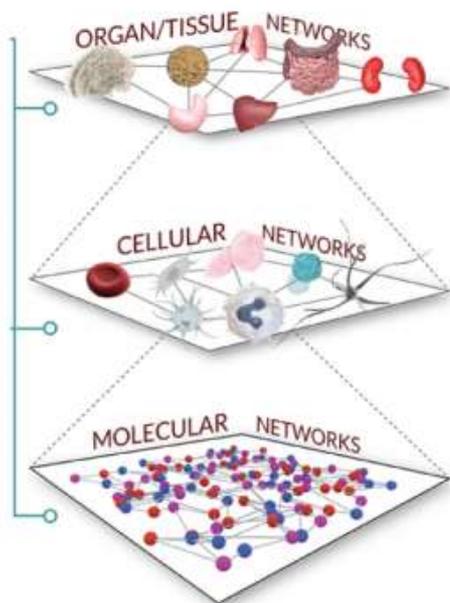


Networks of underground lines: London tube map



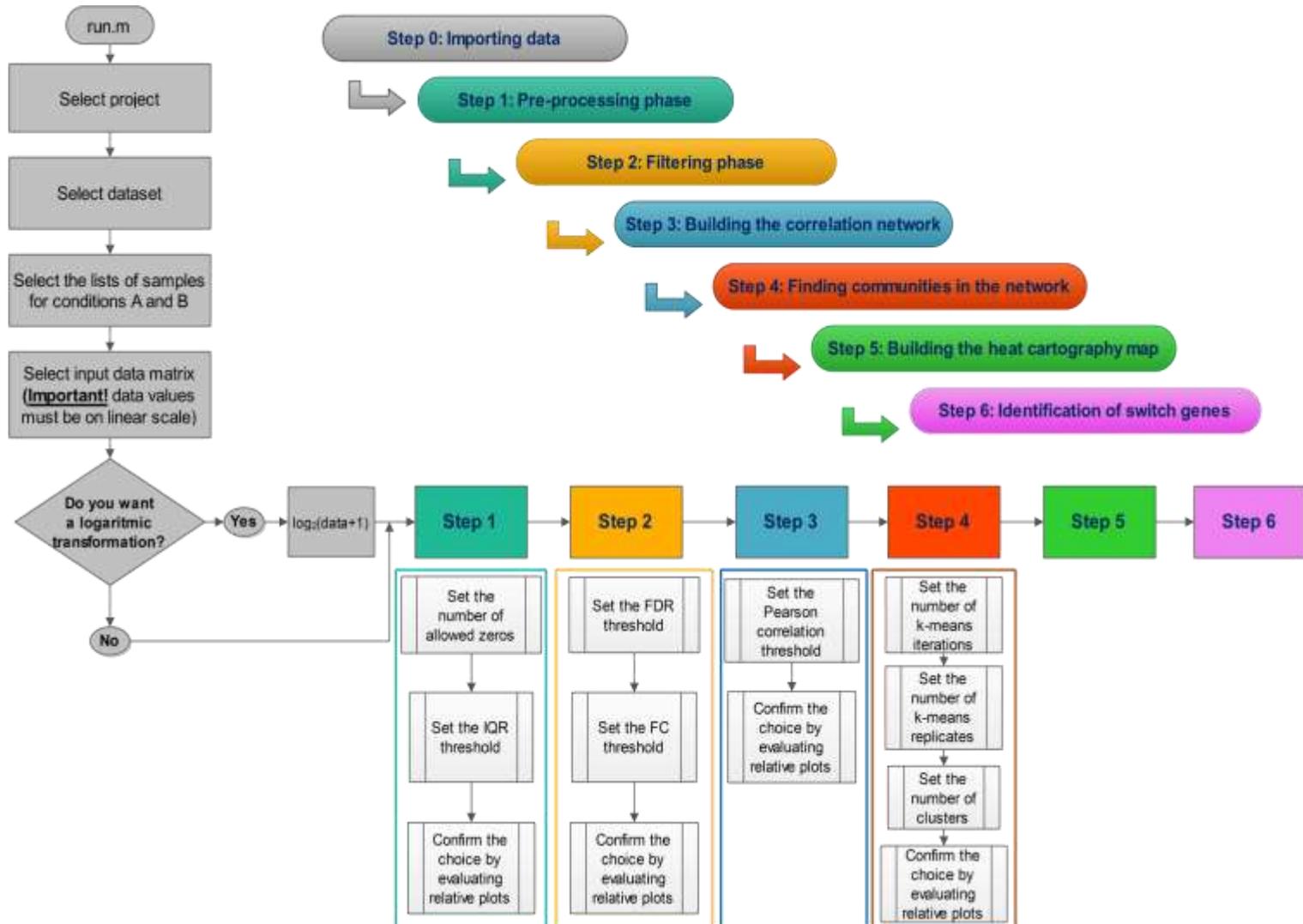
Biological Networks

Networks are successfully used to summarize and understand large data sets generated in biological and medical studies



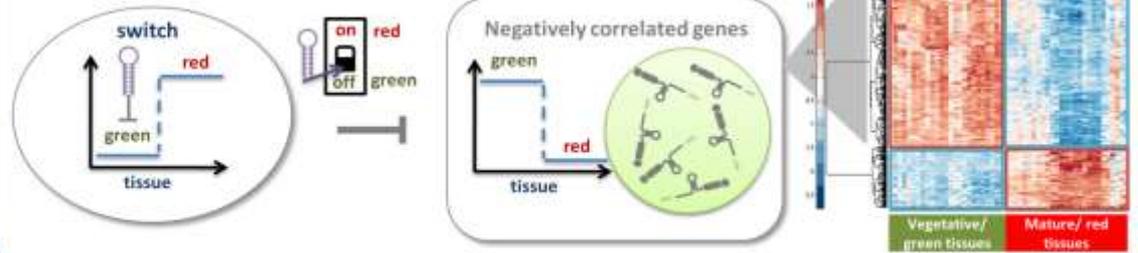
Interaction networks	Association networks
<p>Node A Node B</p> <p>Edge</p>	<p>Gene A Gene B</p> <p>Co-expression</p>
<p>Protein A Protein B</p> <p>Physical interaction</p>	<p>Protein A Protein B</p> <p>Targeting drug sharing</p>
<p>Protein Gene</p> <p>Transcriptional regulation</p>	<p>Drug A Drug B</p> <p>Protein target sharing</p>
<p>Substrate Product</p> <p>Biochemical reaction</p>	<p>Gene A Gene B</p> <p>Genetic disorder sharing</p>
<p>Protein Ligand/ small molecule</p> <p>Physical binding</p>	<p>Disorder A Disorder B</p> <p>Disease gene sharing</p>

Algorithm steps

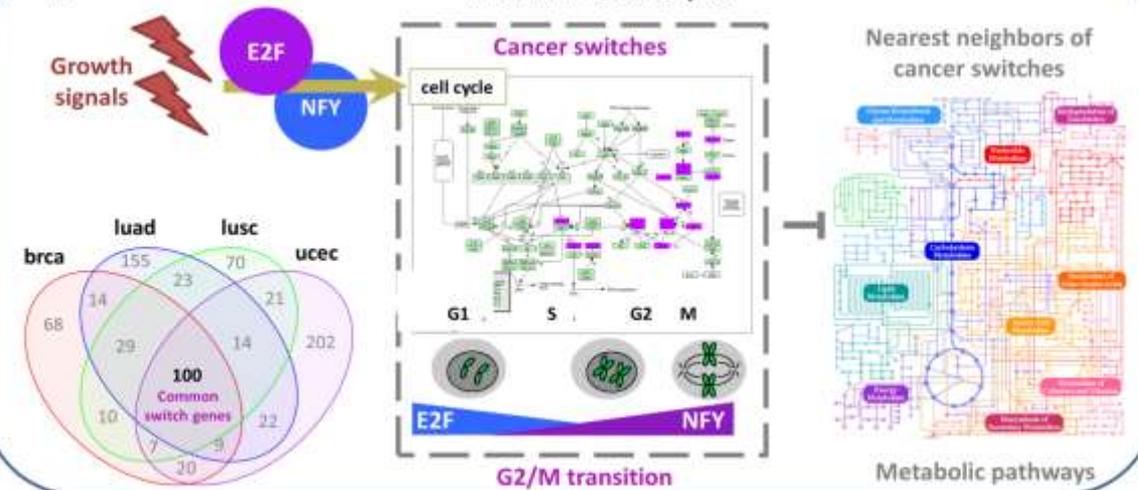


VITICULTURE

A

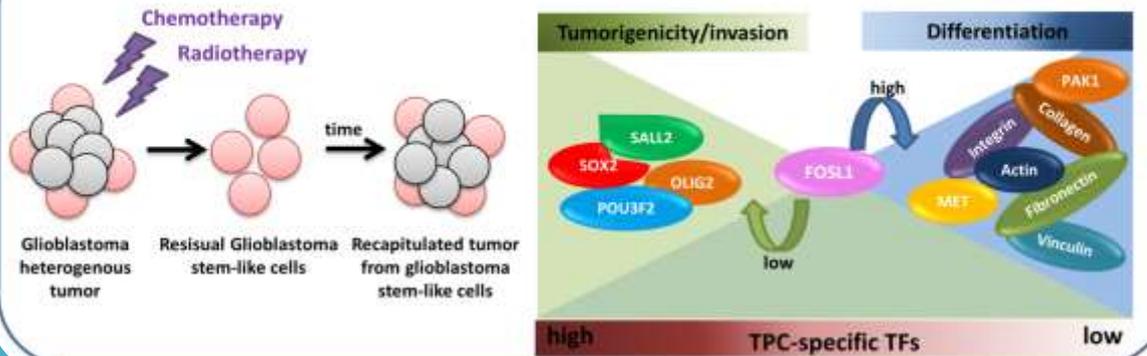


B



HUMAN CANCERS

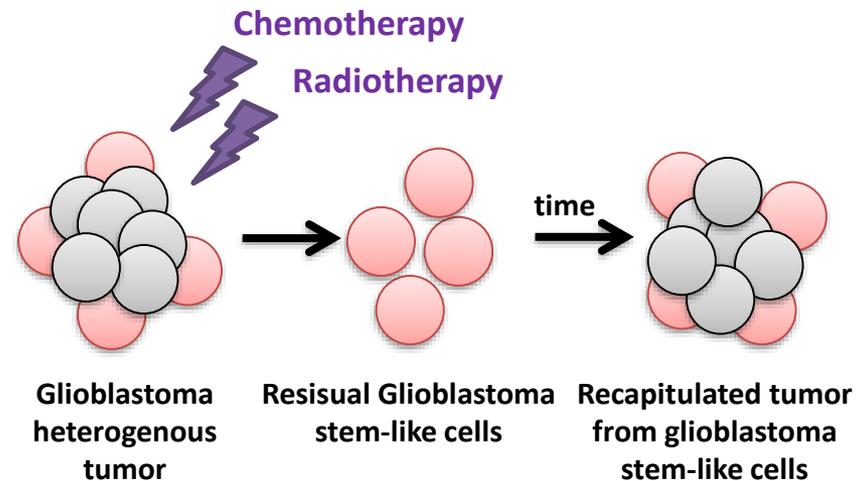
C



GLIOBLASTOMA

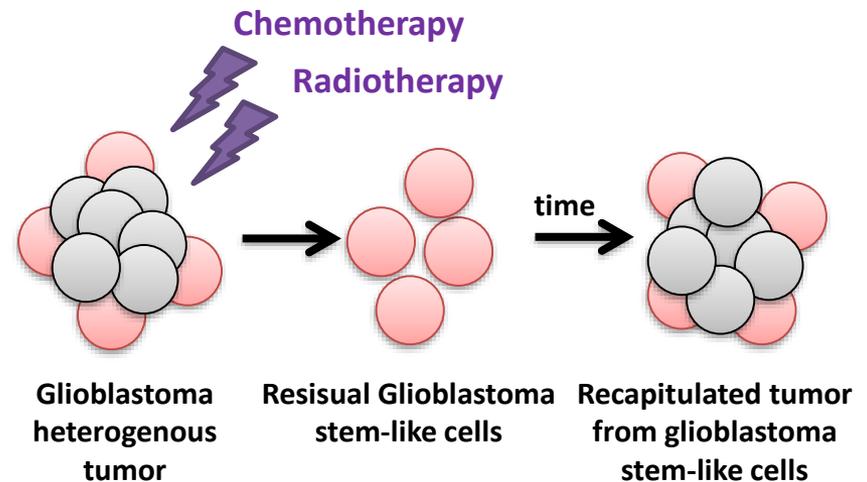
Glioblastoma

- ✓ Glioblastoma is the most aggressive and frequent brain tumor, with a median survival time of only 12–15 months from diagnosis
- ✓ The mortality rate is extremely high with respect to other cancers such as breast and lung cancer, with the 5-years survival rate achieved for only 5% of patients
- ✓ Glioblastoma is resistant to the standard therapies like radio and chemotherapy
- ✓ Its aggressiveness is due to the presence of **cancer stem-like cells** that sustain tumor growth (named “tumor fuel”)



Cancer stem-like cells

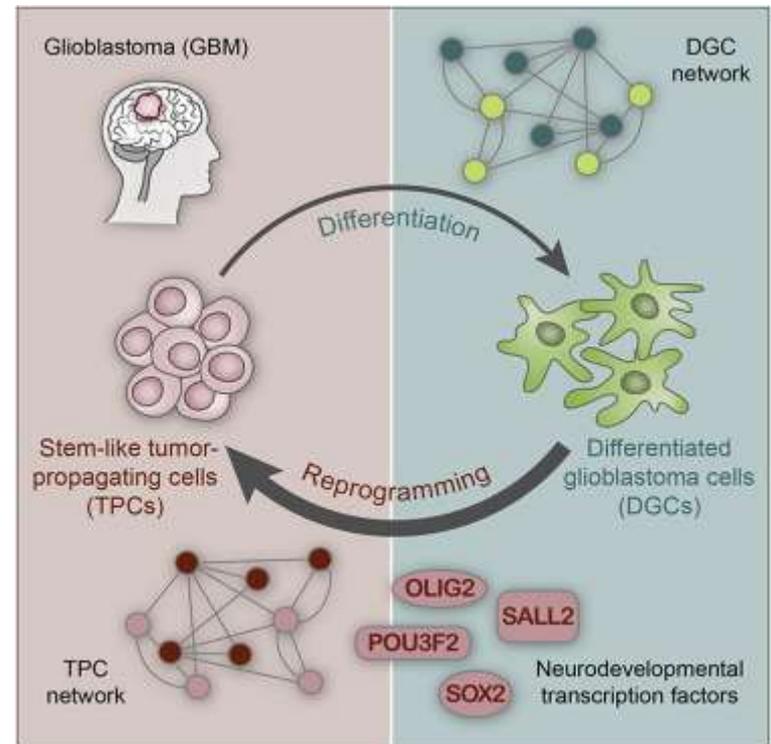
- ✓ **Cancer stem-like cells** are cancer cells that possess characteristics associated with normal stem cells:
 - ✓ **self-renewal** that is the ability to go maintaining the undifferentiated state
 - ✓ **potency** that is the ability to differentiate into specialized cell types
- ✓ **Cancer stem-like cells** are resistant to many conventional cancer therapies and cause relapse and metastasis by giving rise to new tumors
- ✓ Targeting **cancer stem-like cells** could pave the way for the development of novel therapeutic strategies



Glioblastoma dataset

Suva et. al dataset (GSE54792)

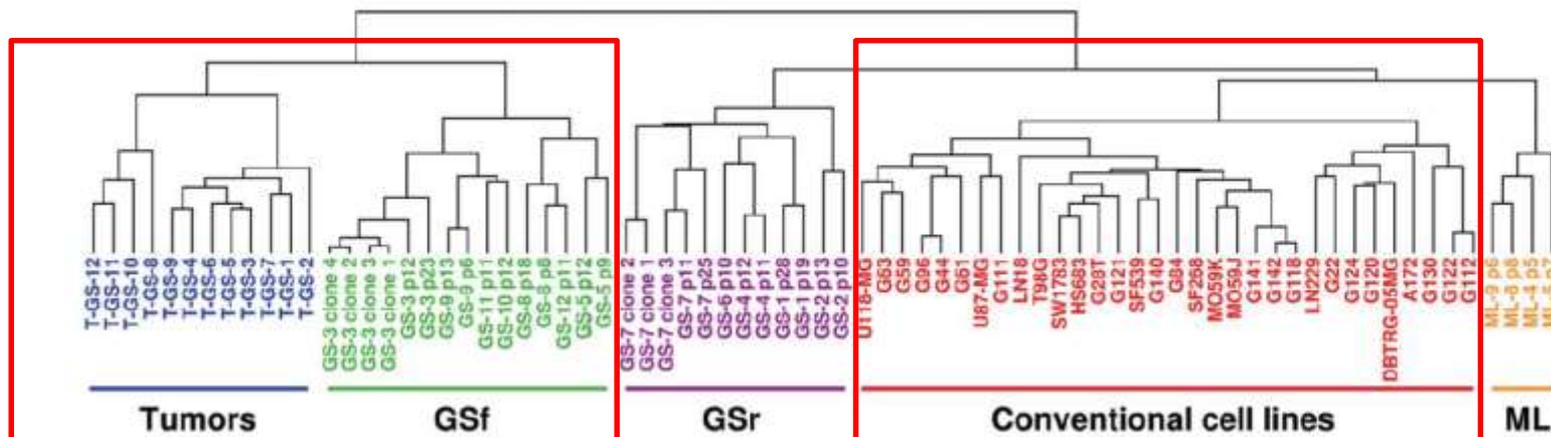
- Data include expression profiles - obtained by RNA sequencing (Illumina HiSeq. 2000–2500) - of:
 - 9 stem-like Tumor-Propagating Cells (**TPC**) grown in serum free medium, spherogenic culture
 - 9 matched Differentiated Glioblastoma Cells (**DGC**) grown as adherent monolayers in serum



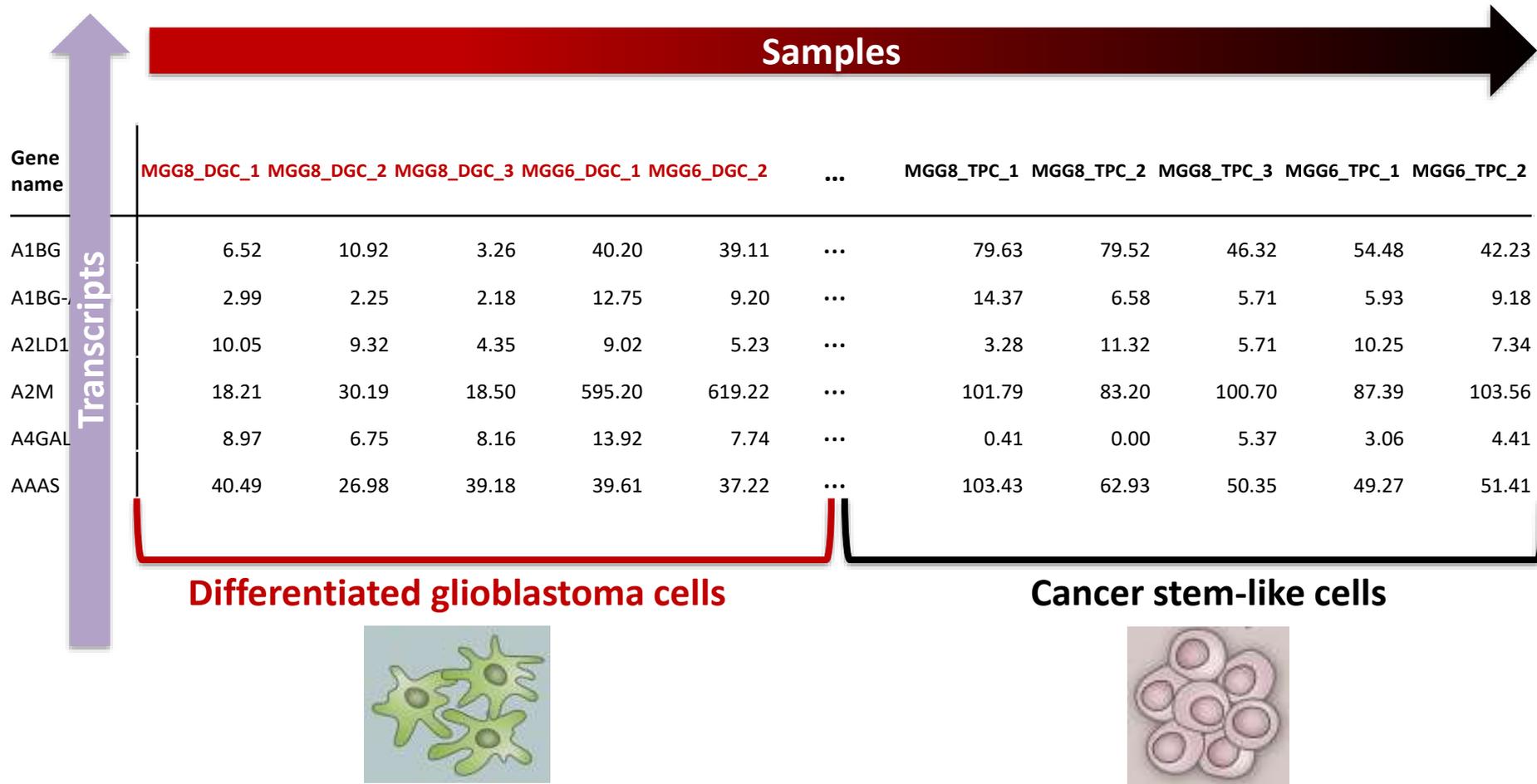
Glioblastoma dataset

Schulte et. al dataset (GSE23806)

- Data include expression profiles - obtained by microarray (Affymetrix HG U133 Plus 2.0 Array) – of:
 - 32 conventional glioblastoma cell lines
 - 12 glioblastoma stem-like cell lines (GS), among which 7 clonal sublines derived from two GS lines (GS-3, GS-7)
 - 12 original tumors from which GS-lines were derived
 - 4 monolayer cultures established from the same tumors as GS-lines using standard serum conditions
- Only one subgroup of GS cell lines, called **full stem-like phenotype** (GSf), fulfilled all criteria for glioma stem cells and mirrored the transcriptome of human glioblastomas more closely than other cell lines
- For this reason, in our analysis we compared the expression profiles of genes in 15 GSf cell lines and 12 corresponding primary tumors with respect to 32 conventional glioblastoma cell lines



Gene expression data of glioblastoma



Building correlation network

	G8_DGC_1	G8_DGC_2	G8_DGC_3	G6_DGC_1	G6_DGC_2	...	G8_TPC_1	G8_TPC_2	G8_TPC_3	G6_TPC_1	G6_TPC_2
	Differentiated glioblastoma cells						Cancer stem-like cells				
X	6.52	10.92	3.26	40.20	39.11	...	79.63	79.52	46.32	54.48	42.23
Y	2.99	2.25	2.18	12.75	9.20	...	14.37	6.58	5.71	5.93	9.18
...
...

X_i

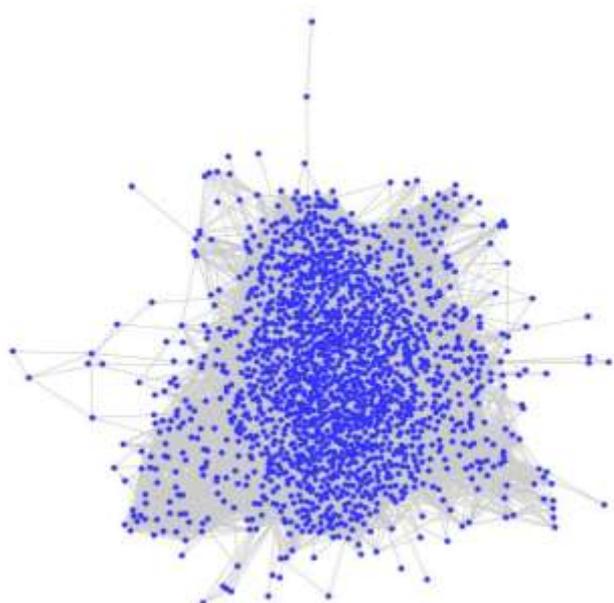
Y_i

$$\rho_{xy} = \frac{\sum_{i=1}^{col} (x_i - \bar{x})(y_i - \bar{y})}{\sqrt{\sum_{i=1}^{col} (x_i - \bar{x})^2 \sum_{i=1}^{col} (y_i - \bar{y})^2}}$$

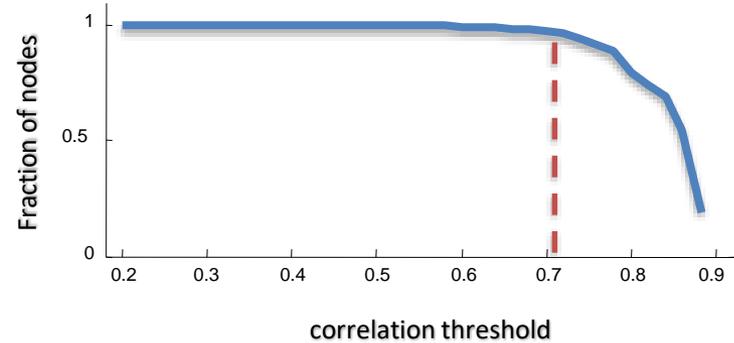
Building correlation network

A

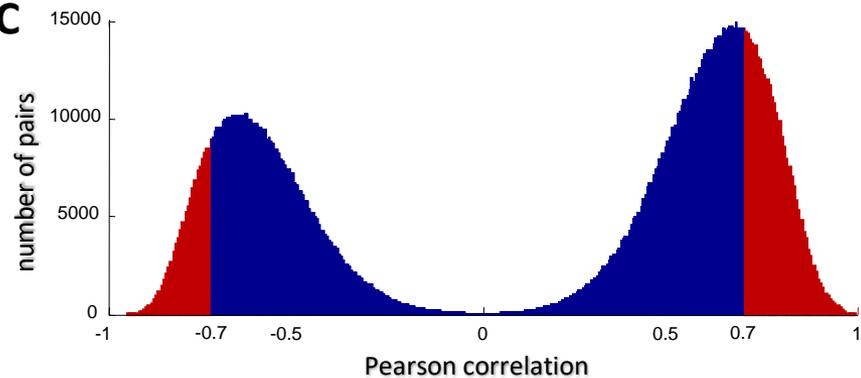
correlation network



B



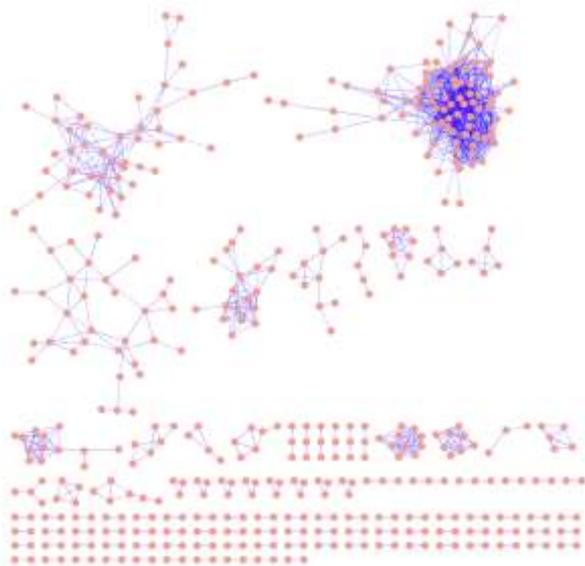
C



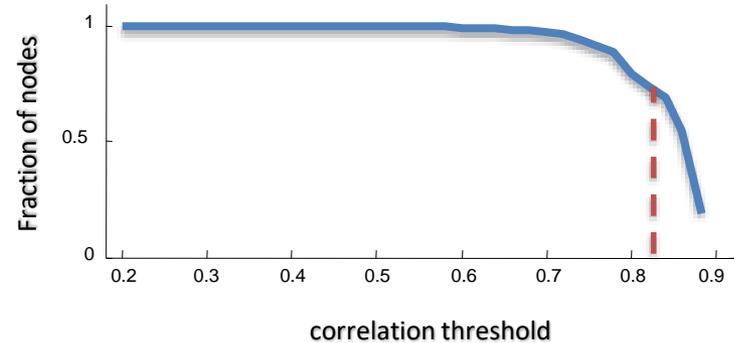
Building correlation network

A

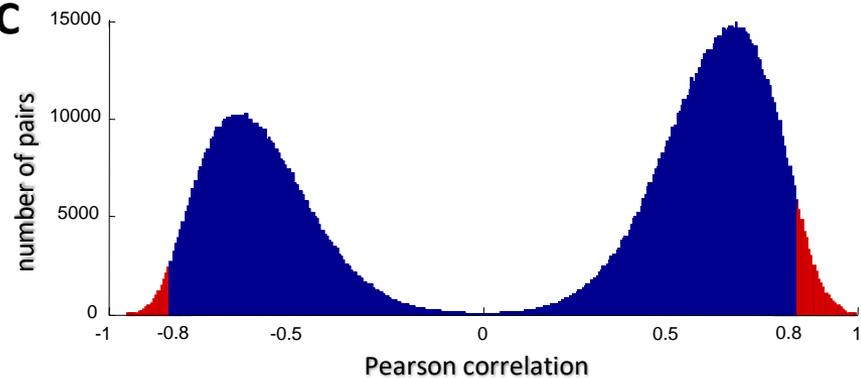
correlation network



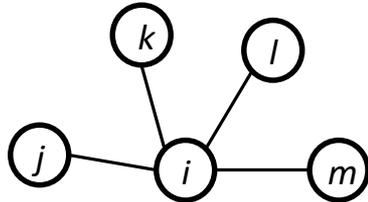
B



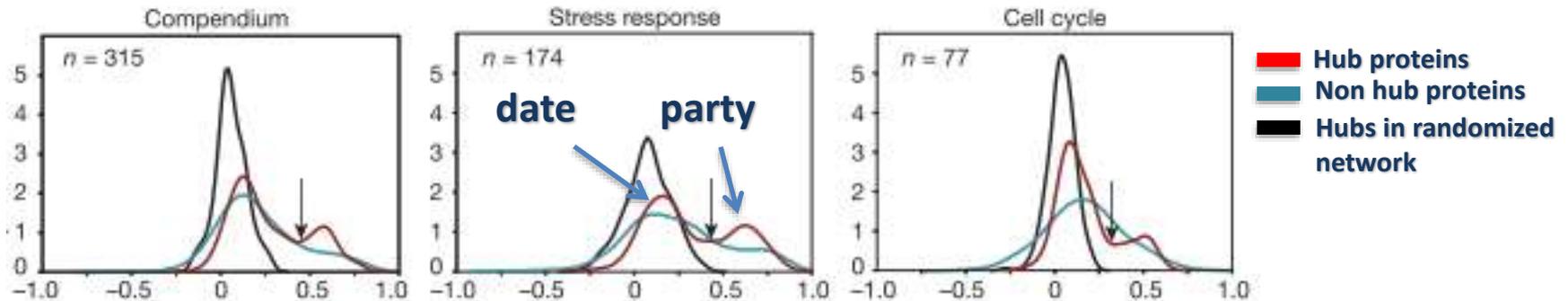
C



The Average Pearson Correlation Coefficient (APCC)

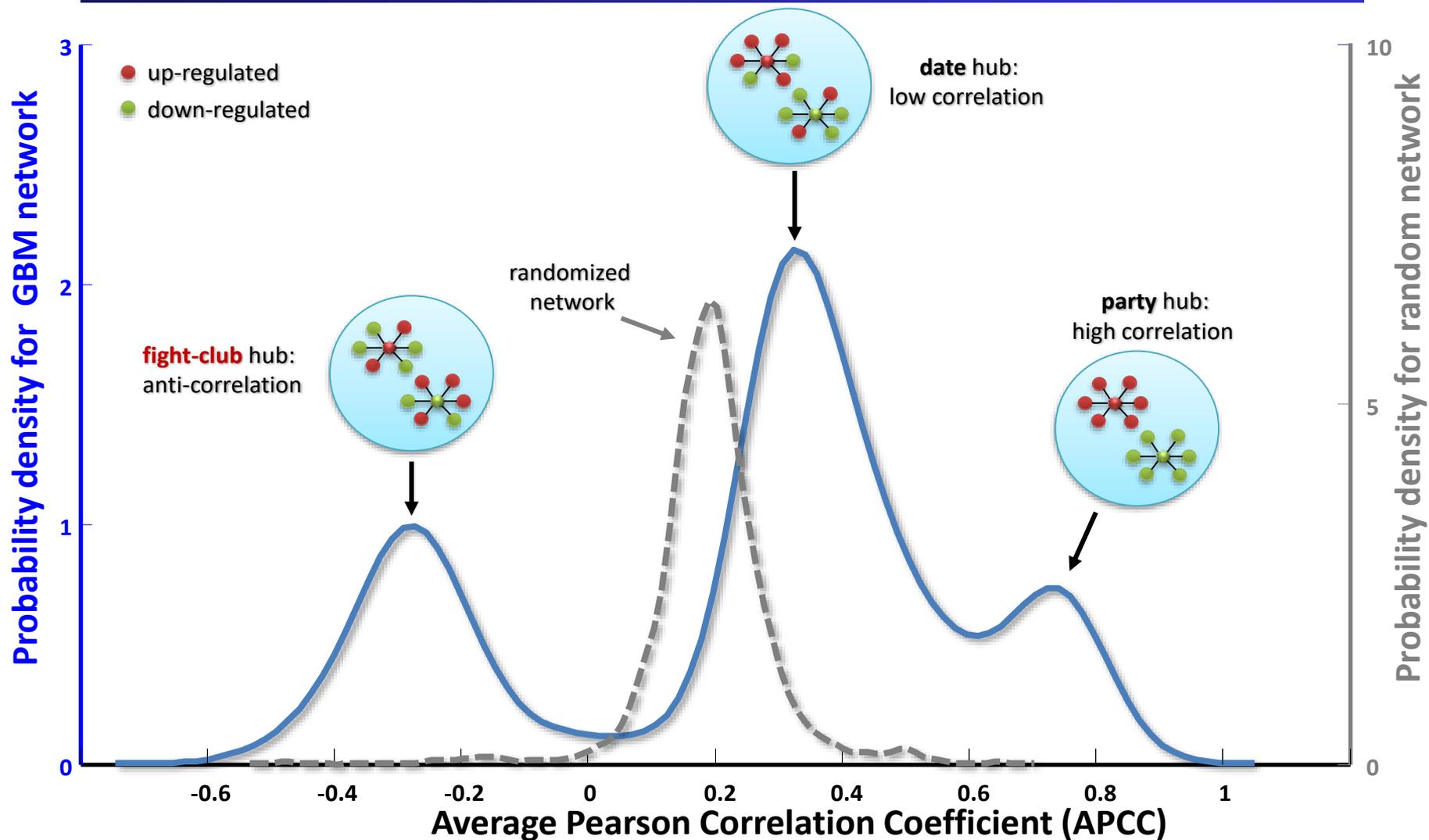


APCC measures how the nodes are co-expressed with their nearest neighbors
An APCC value is assigned to each node



Party hubs are highly correlated in expression with their partners, and presumably interact with them at similar times. **Date hubs** are much less correlated in expression with their partners, and presumably the corresponding physical interactions occur at different times and/or different locations.

The Average Pearson Correlation Coefficient (APCC)



Finding communities: k-means

Step 1

- Select the numbers of clusters k

Step 2

- Select k points as initial centroids (center points)

Step 3

- Form k clusters by assigning all points to the closest centroid

Step 4

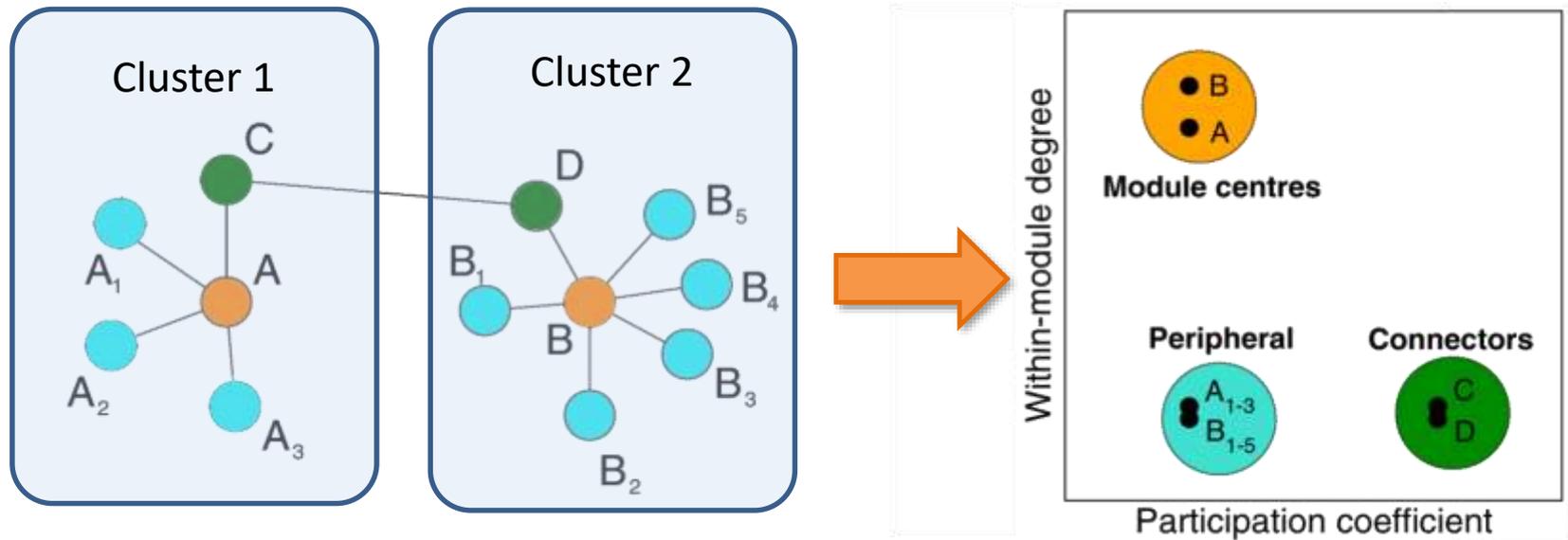
- Recompute the centroid of each cluster

repeat

until

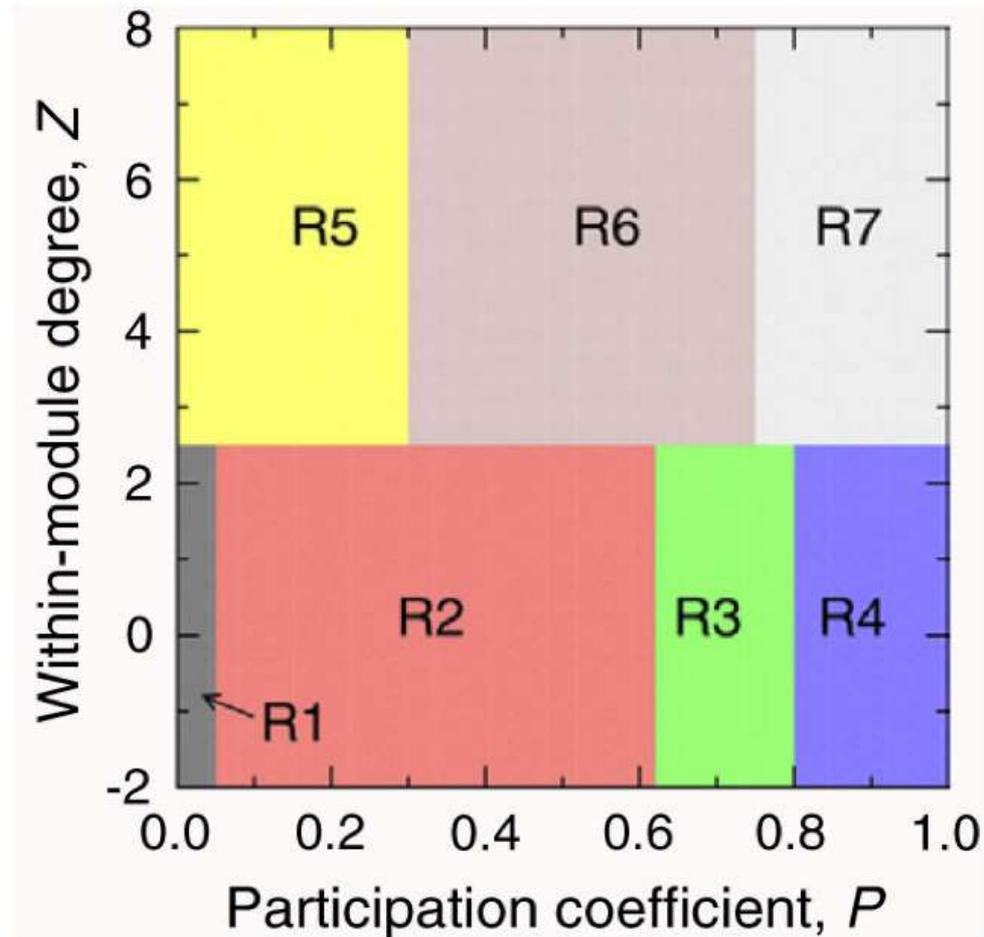
the centroids
don't change

Node roles in complex networks

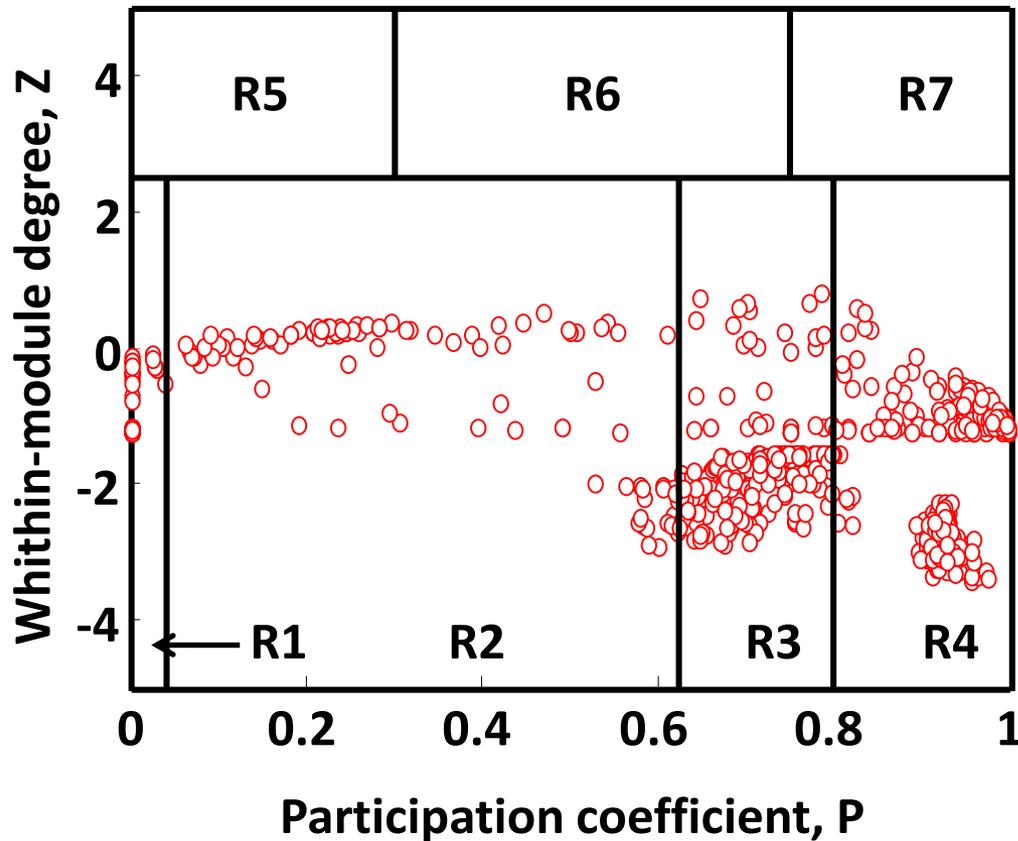


Guimerà-Amara (GA)

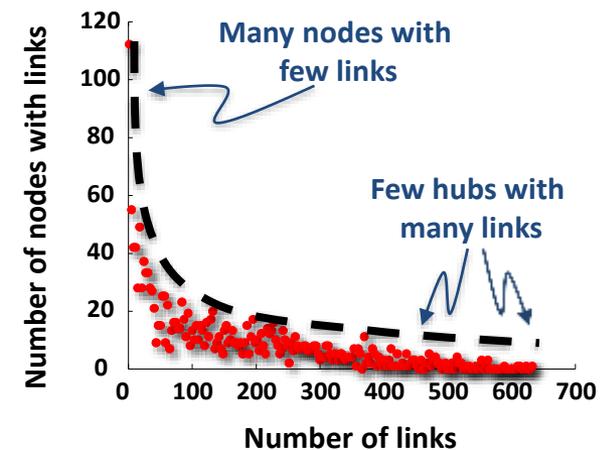
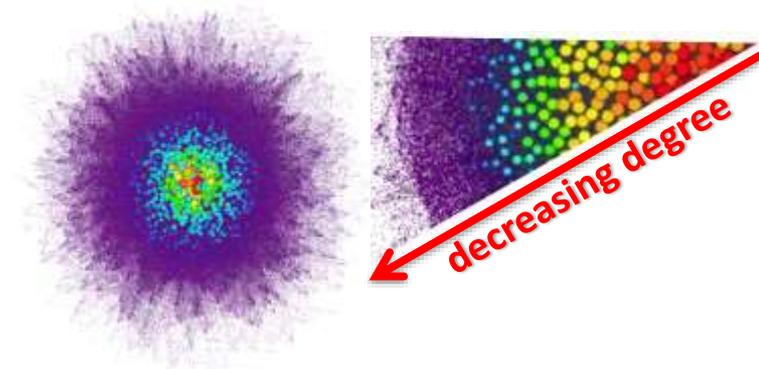
Guimerà-Amaraal (GA) cartography



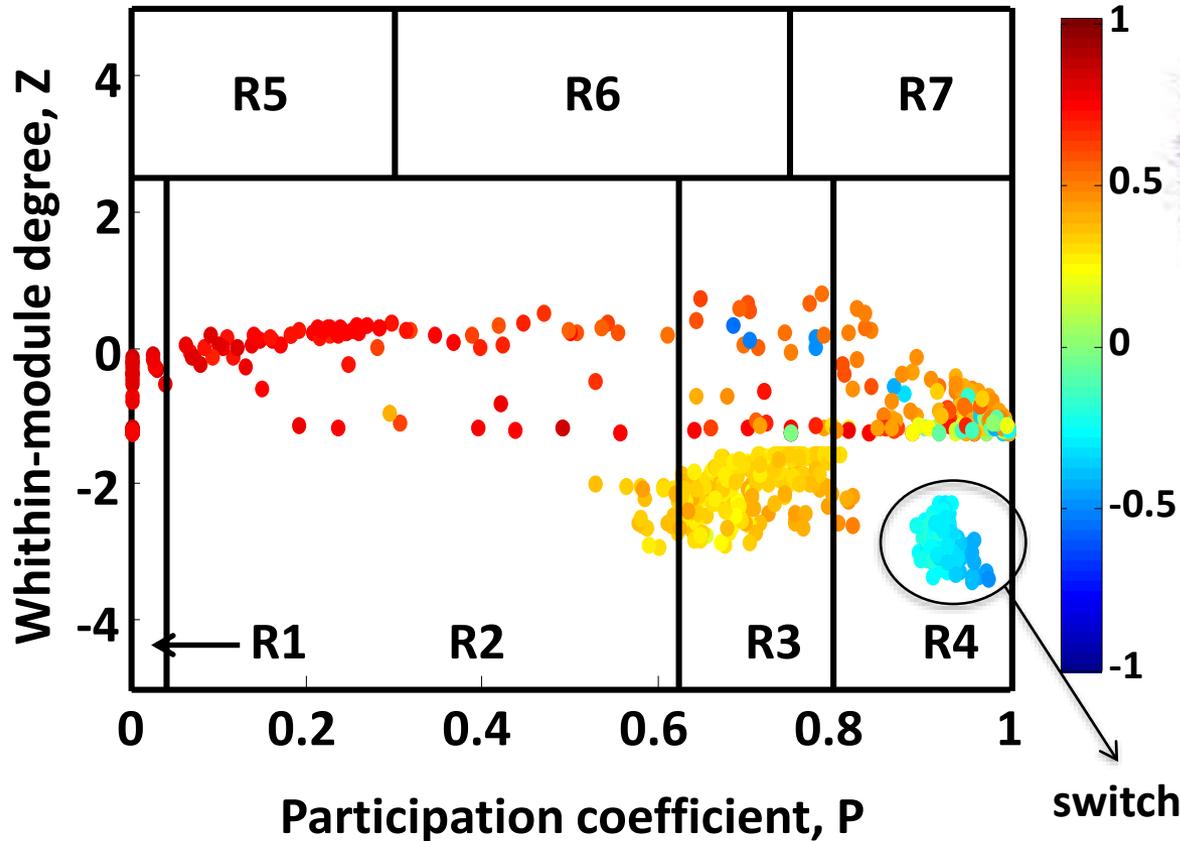
GA cartography: glioblastoma



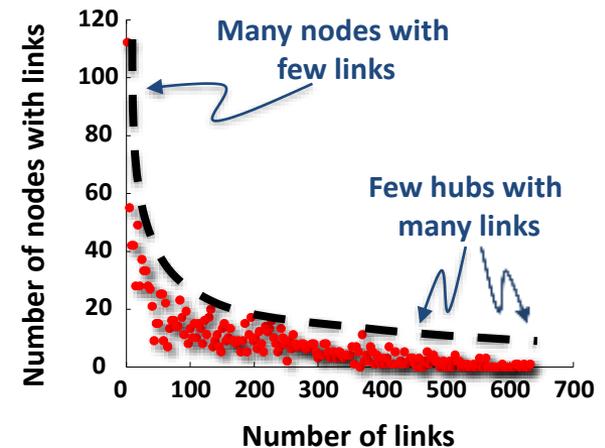
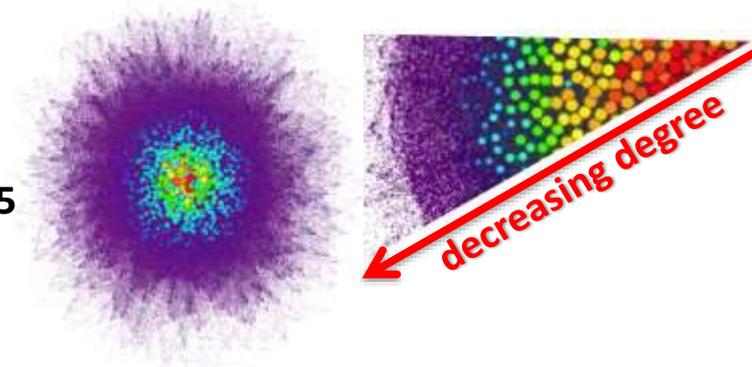
Scale-free



Heat cartography: glioblastoma



Scale-free



Switch features

High participation coefficient P



The switches highly interacts with genes outside their own cluster

Low within-module degree
z-score



The switches poorly interacts with genes inside their own cluster

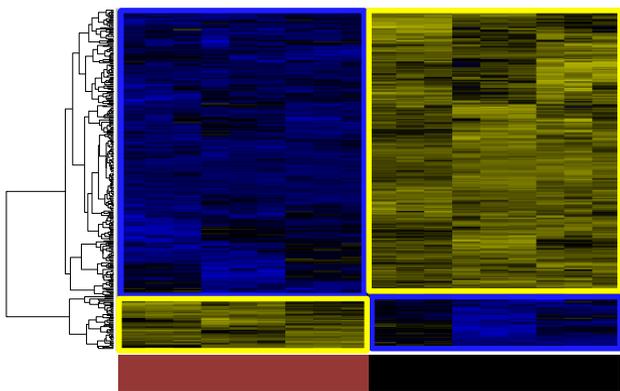
Negative APCCs values



The switches are mainly anti-correlated with their partners

a**Suva et al. dataset**

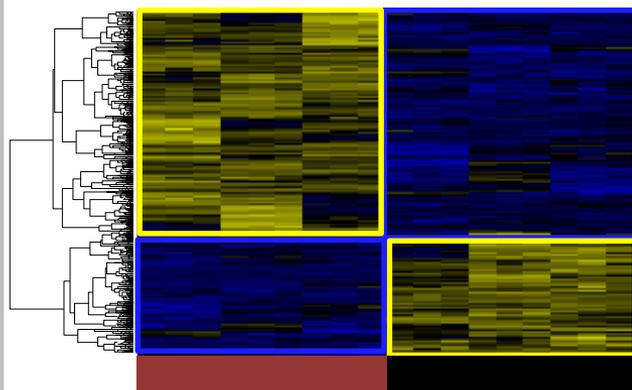
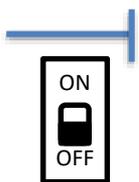
switch genes = 336



Differentiated Glioblastoma Cells Tumor-Propagating Cells

Focal adhesion
ECM-receptor interaction

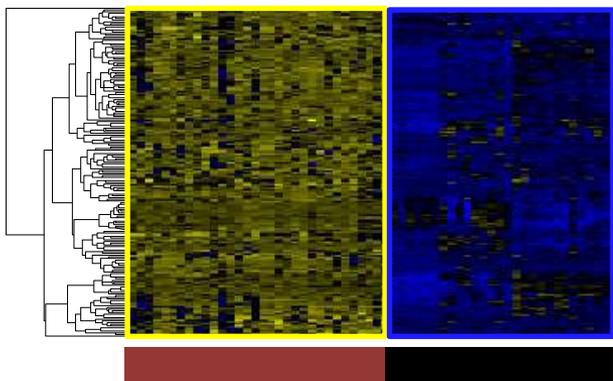
Negative nearest neighbors = 1355



Differentiated Glioblastoma Cells Tumor-Propagating Cells

Focal adhesion
ECM-receptor interactionPOU3F2
SALL2
SOX2
OLIG2**b****Schulte et al. dataset**

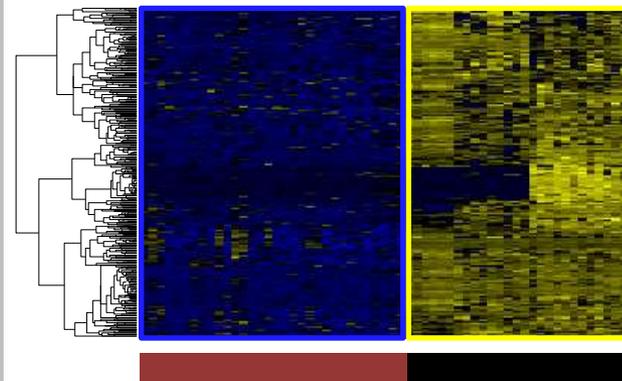
switch genes = 171



Conventional cell lines Tumors + full stem-like cell phenotype

Focal adhesion
ECM-receptor interaction

Negative nearest neighbors = 449



Conventional cell lines Tumors + full stem-like cell phenotype

POU3F2
SALL2
SOX2
OLIG2

Suva et al. dataset

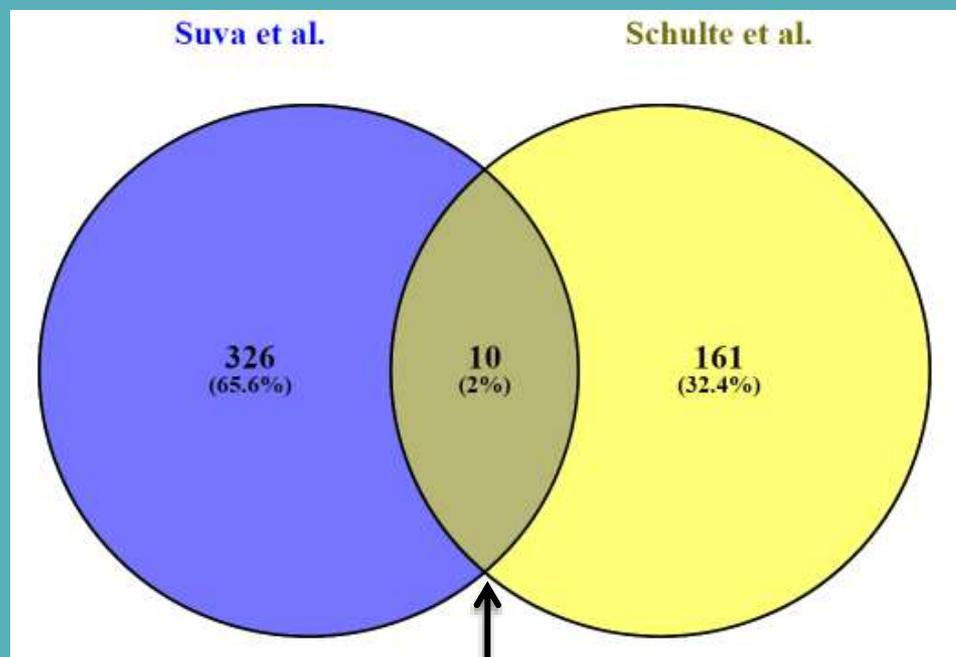
a

switch genes = 336



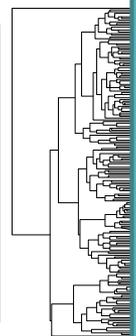
Focal adhesion
ECM-receptor
interaction

POU3F2
SALL2
SOX2
OLIG2



b

switch genes = 171



- CD109
- CDC42EP3
- CNN2
- CTGF
- EDIL3
- FBN1
- FLNB
- FOSL1**
- FXYS5
- IL1R1

POU3F2
SALL2
SOX2
OLIG2

Conventional cell lines

Tumors + full stem-like cell phenotype

Conventional cell lines

Tumors + full stem-like cell phenotype

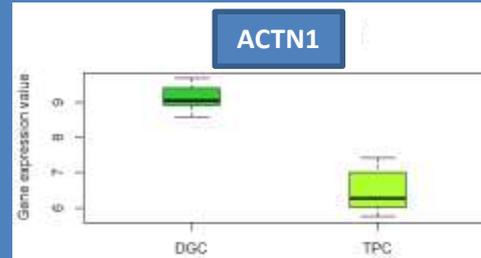


FOSL1 expression

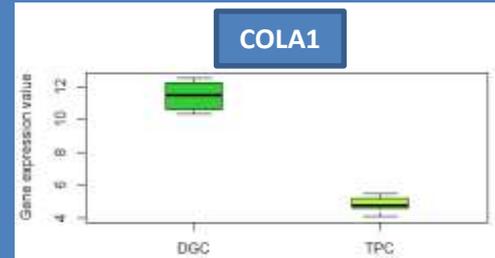
Suva et al. dataset

Cell-cell communications genes

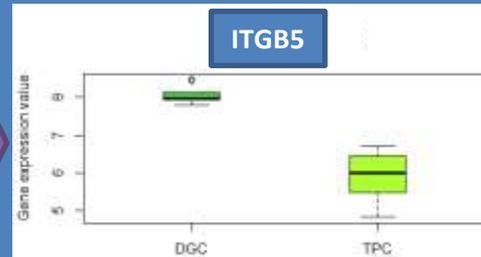
FOSL1



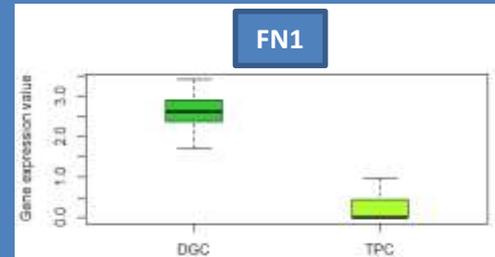
Actin



Collagen



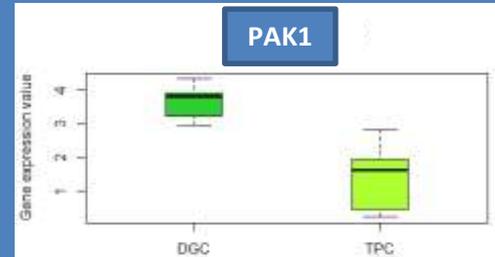
Integrin



Fibronectin



MET



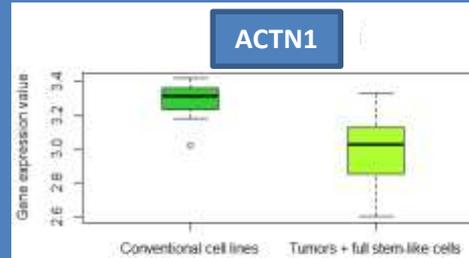
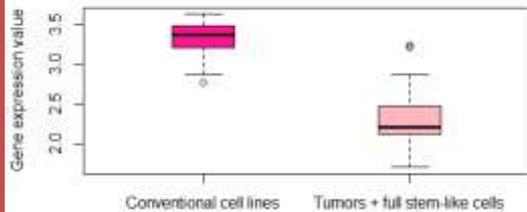
PAK1

FOSL1 expression

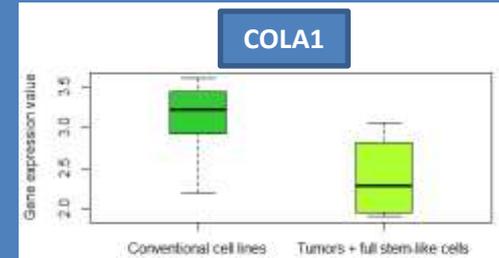
Schulte et al. dataset

Cell-cell communications genes

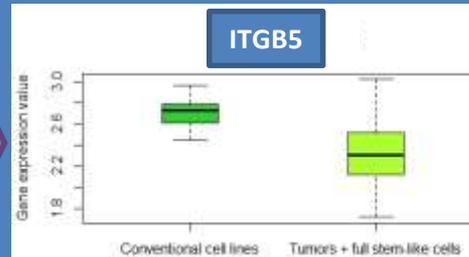
FOSL1



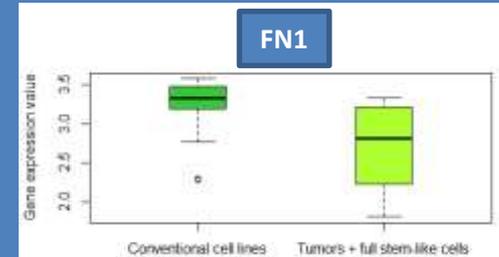
Actin



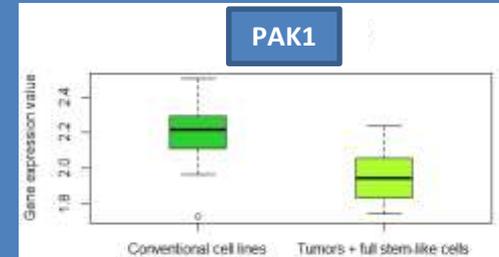
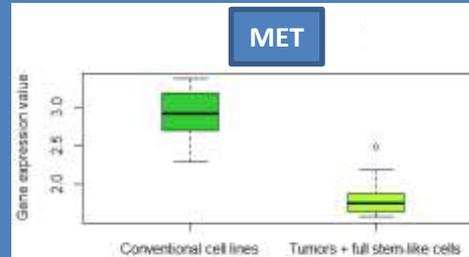
Collagen



Integrin

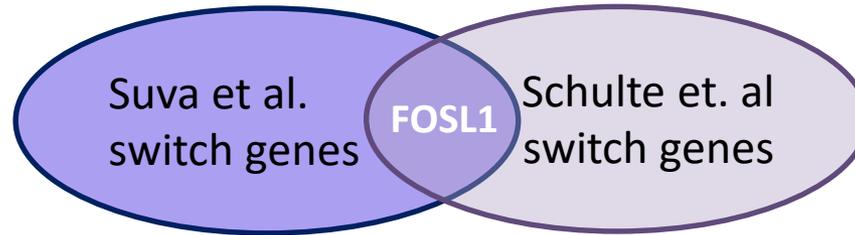


Fibronectin



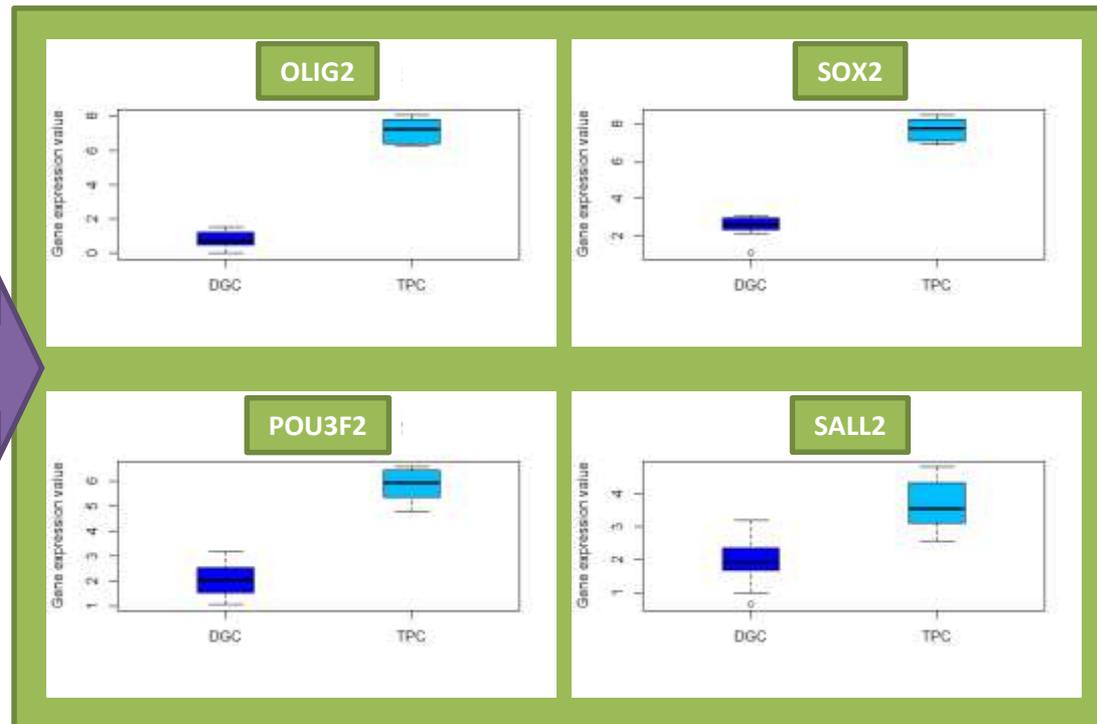
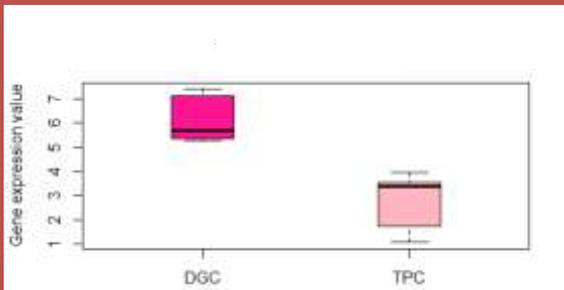
FOSL1 expression

Suva et al. dataset



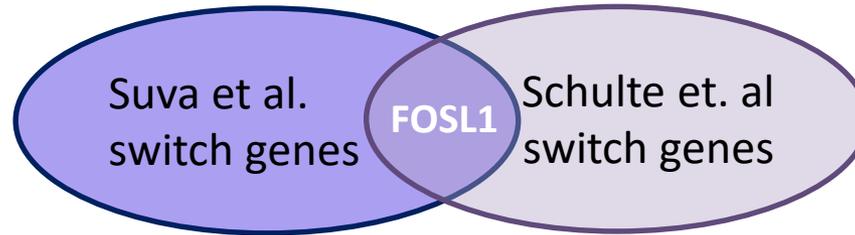
4-core TFs

FOSL1



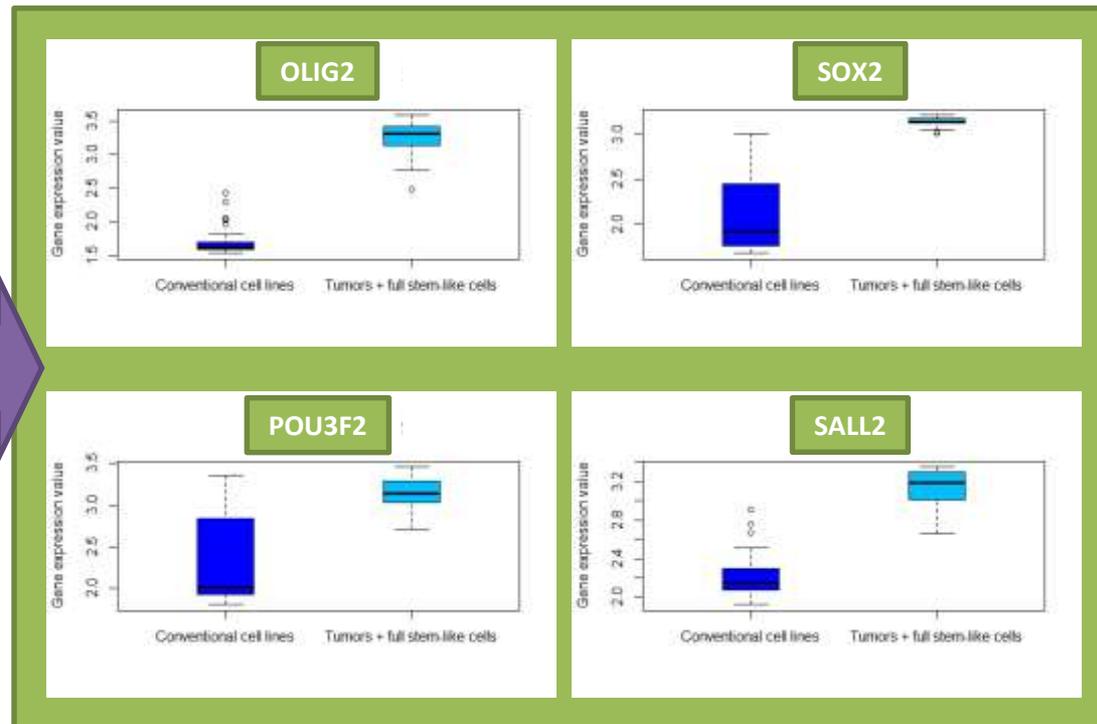
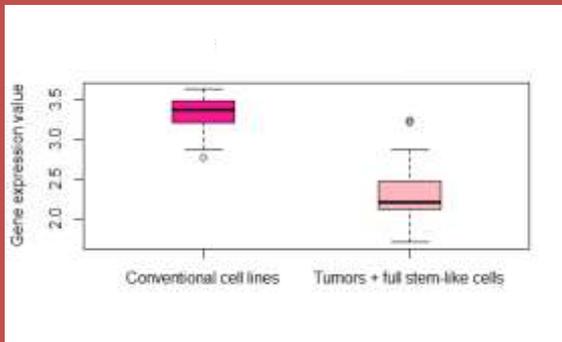
FOSL1 expression

Schulte et al. dataset

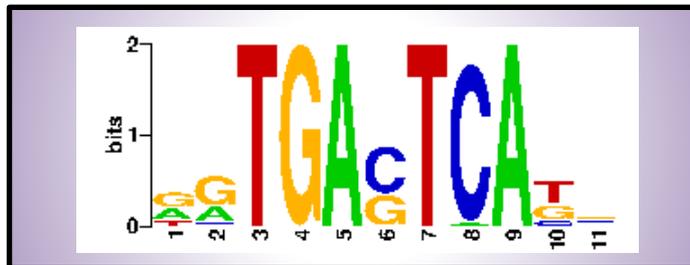
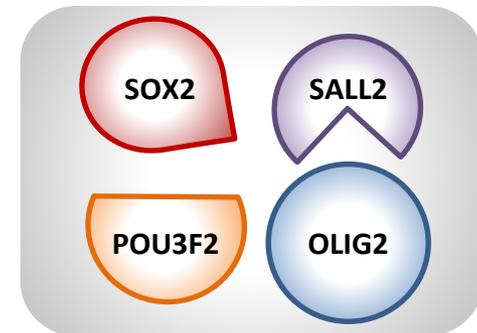
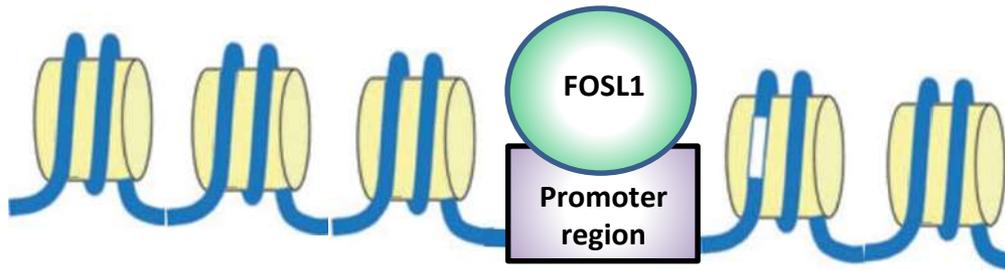
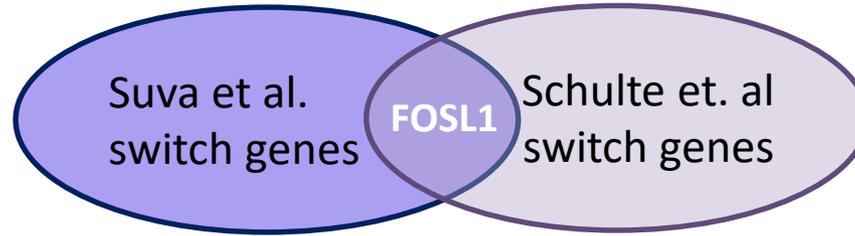


4-core TFs

FOSL1

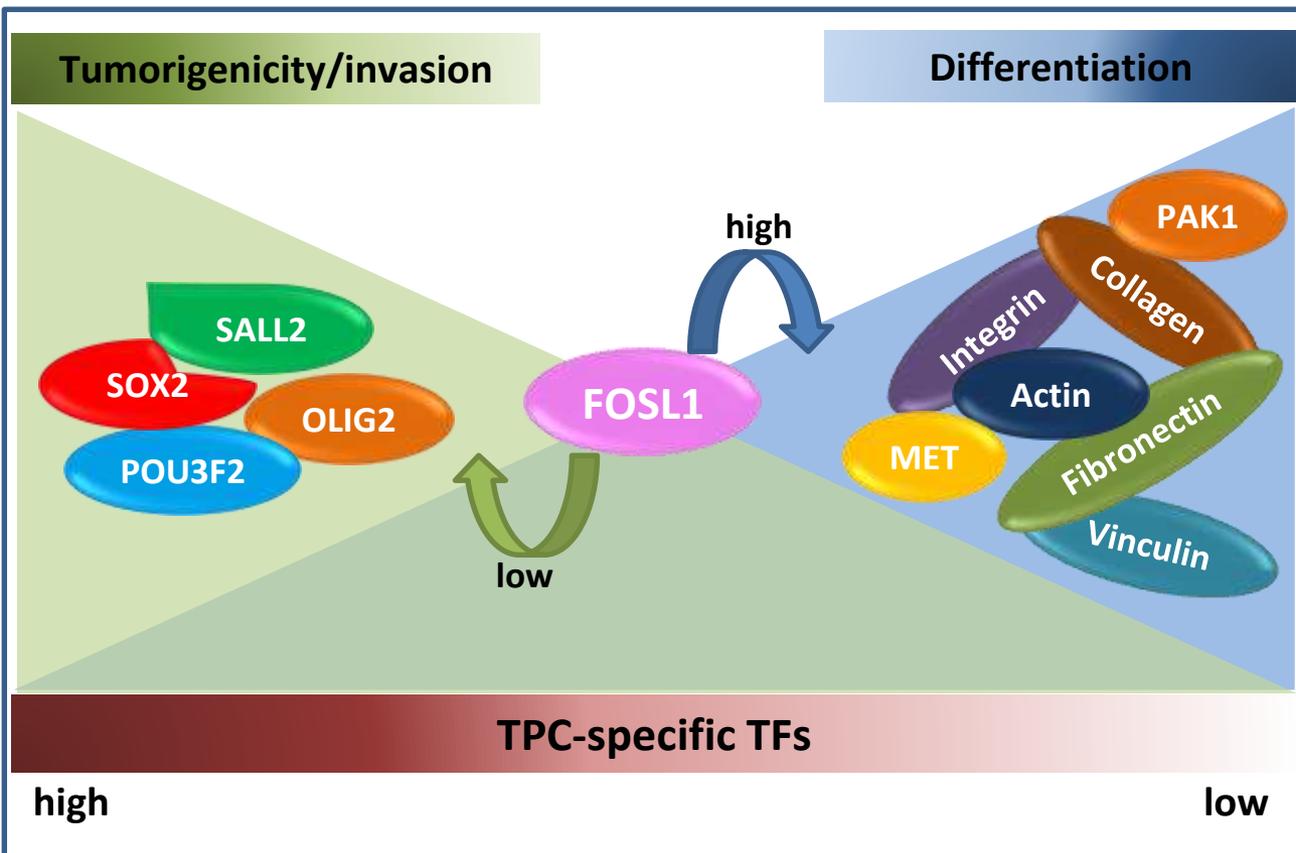


FOSL1 consensus binding motif



Name	Score	Position	Sequence	Strand
SOX2	0.88	-414	GGTGGCTCAGG	-
SALL2	0.87	-377	AGGGACTCAGC	+
OLIG2	0.82	-371	ACAGAGTCAGG	-
POU3F2	0.78	-382	GGTGAGGAAGA	+

FOSL1 switch gene



- ❖ It positively correlates with genes related to cell-cell communications pathways
- ❖ It resulted down-regulated in stem-like cells and negatively correlated with the 4-core TFs
- ❖ The promoter regions of the 4-core TFs were found harboring a consensus binding motif for FOSL1
- ❖ FOSL1 could be a novel and prognostic therapeutic biomarker, which could induce the differentiation of cancer stem-like cells by repressing the 4-core gene expression



THANK
YOU