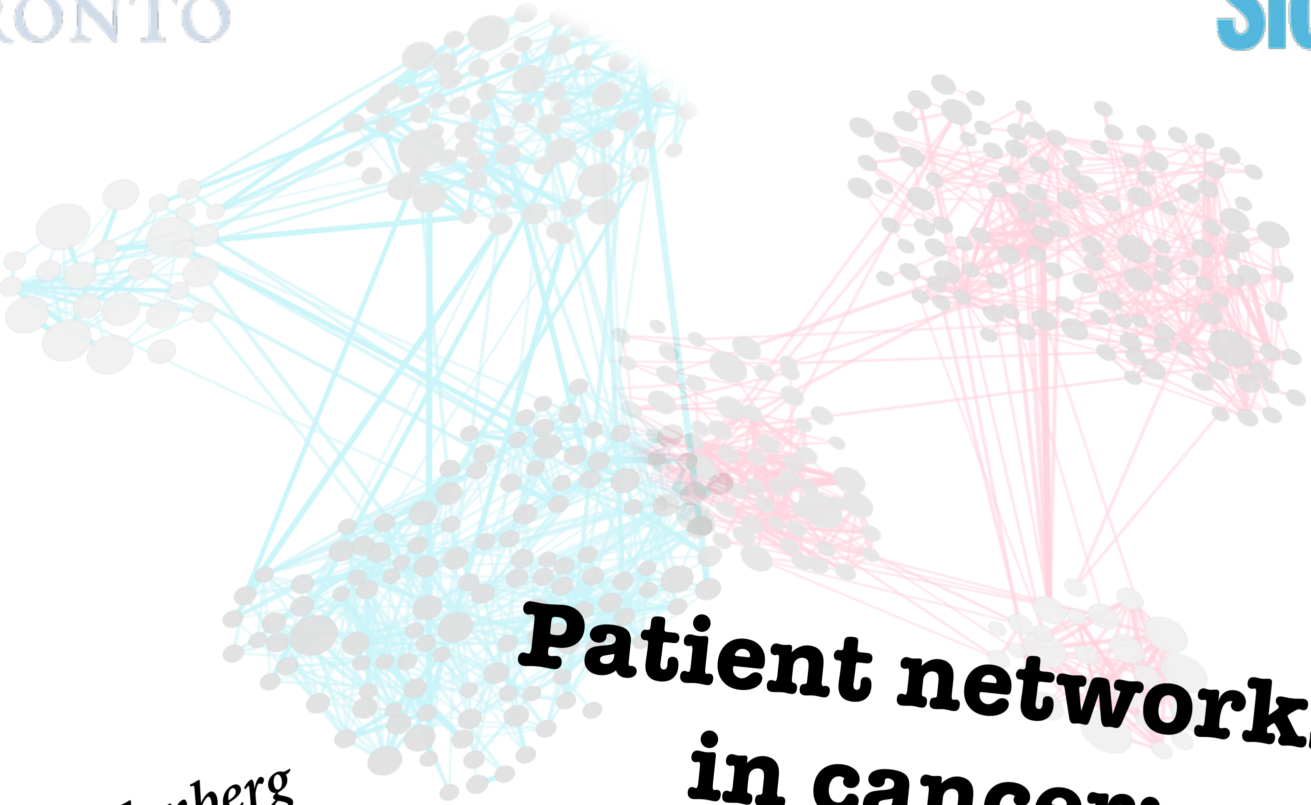
UNIVERSITY OF TORONTO

SickKids



Patient networks in cancer: a platform for data integration

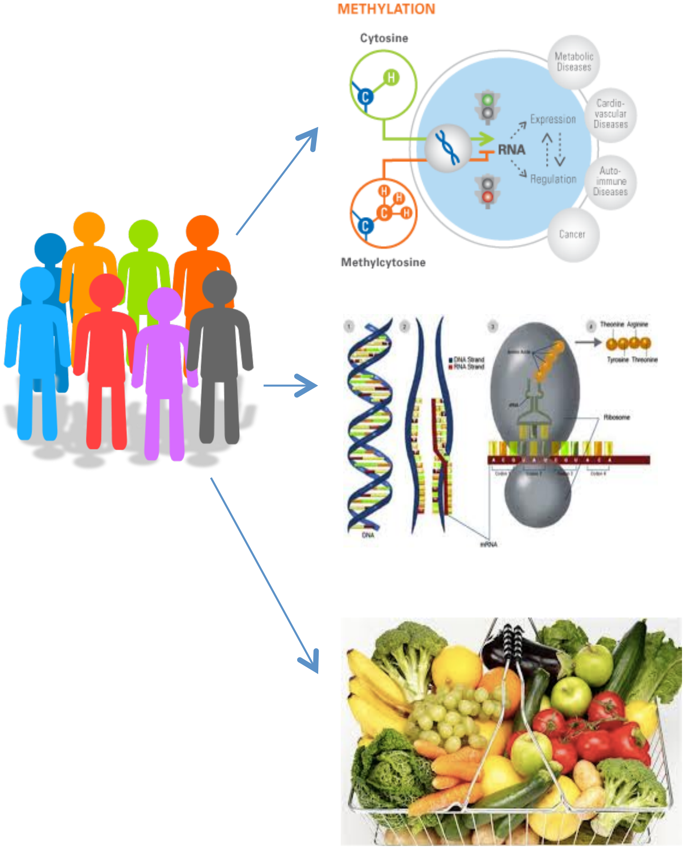
Anna Goldenberg and The Goldenberg Lab

Outline

- Data integration – problem setup
- Patient network representation – why and how
- Similarity Network Fusion – novel integration method
- Network driven analysis:
  - Cancer heterogeneity
  - Differential feature selection
- Missing data
  - Random entries
  - Patients
- Taking networks further:
  - Survival analysis (novel formulation)
  - Personalized medicine

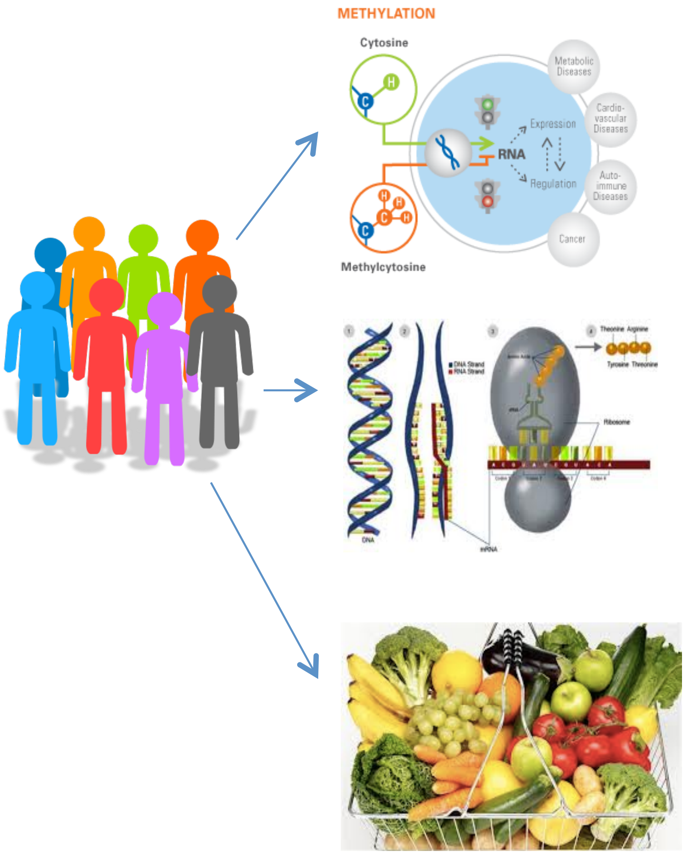
Problem setup

Problem setup



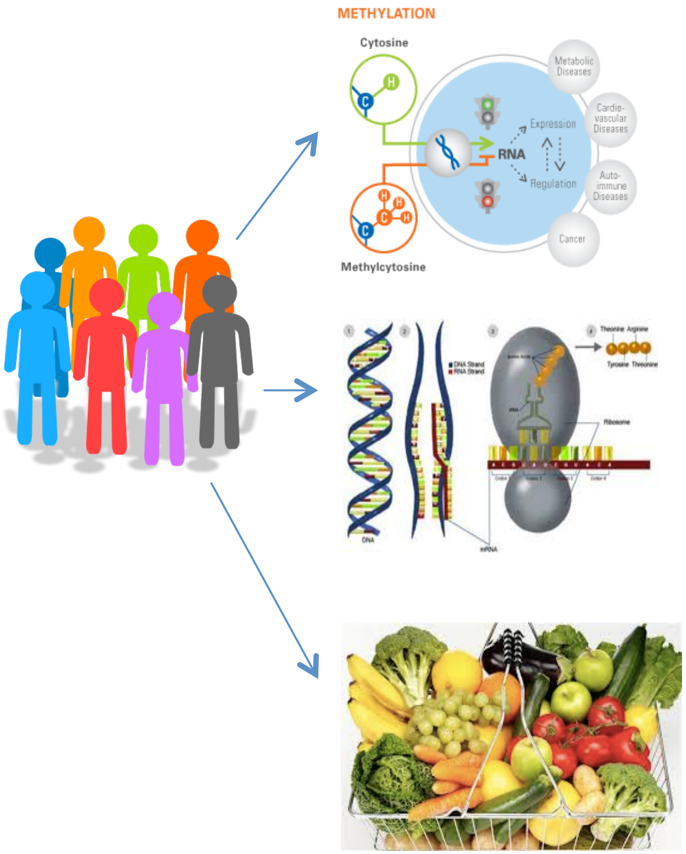
Problem setup

How to combine?



Problem setup

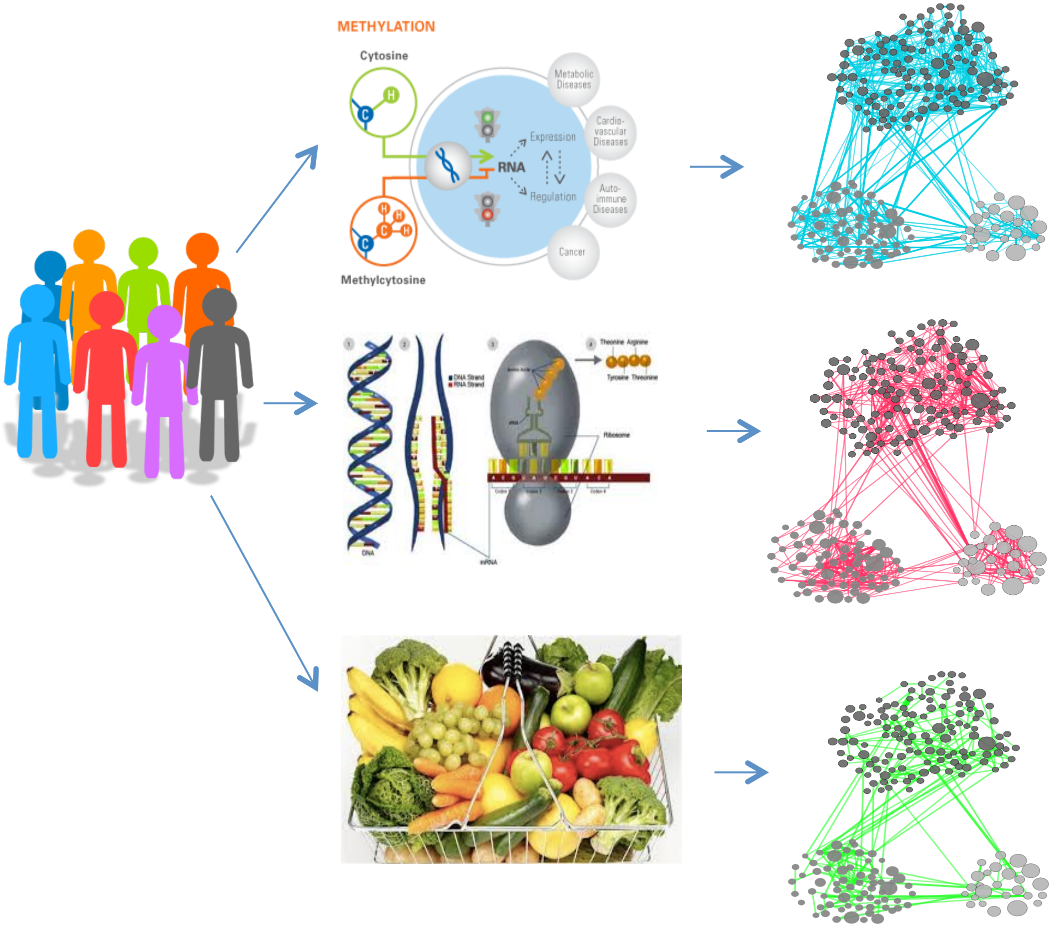
How to combine?



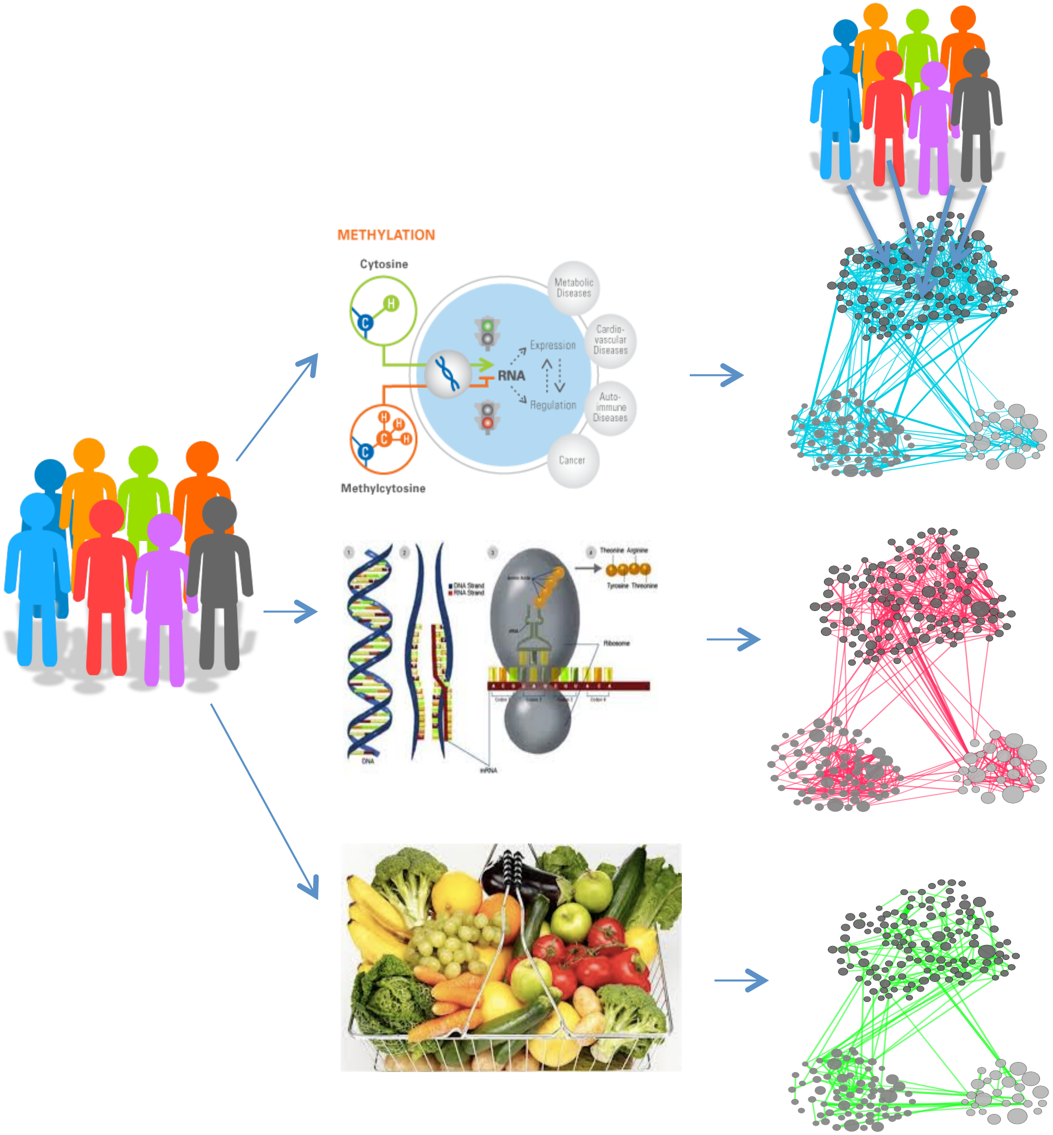
Issues

- Large number of measurements, small sample sizes (p>>n)
- Need to integrate common and complementary information
- Not all measurements can be mapped to the same unit (gene)

Goldenberg Lab: Similarity Network Fusion

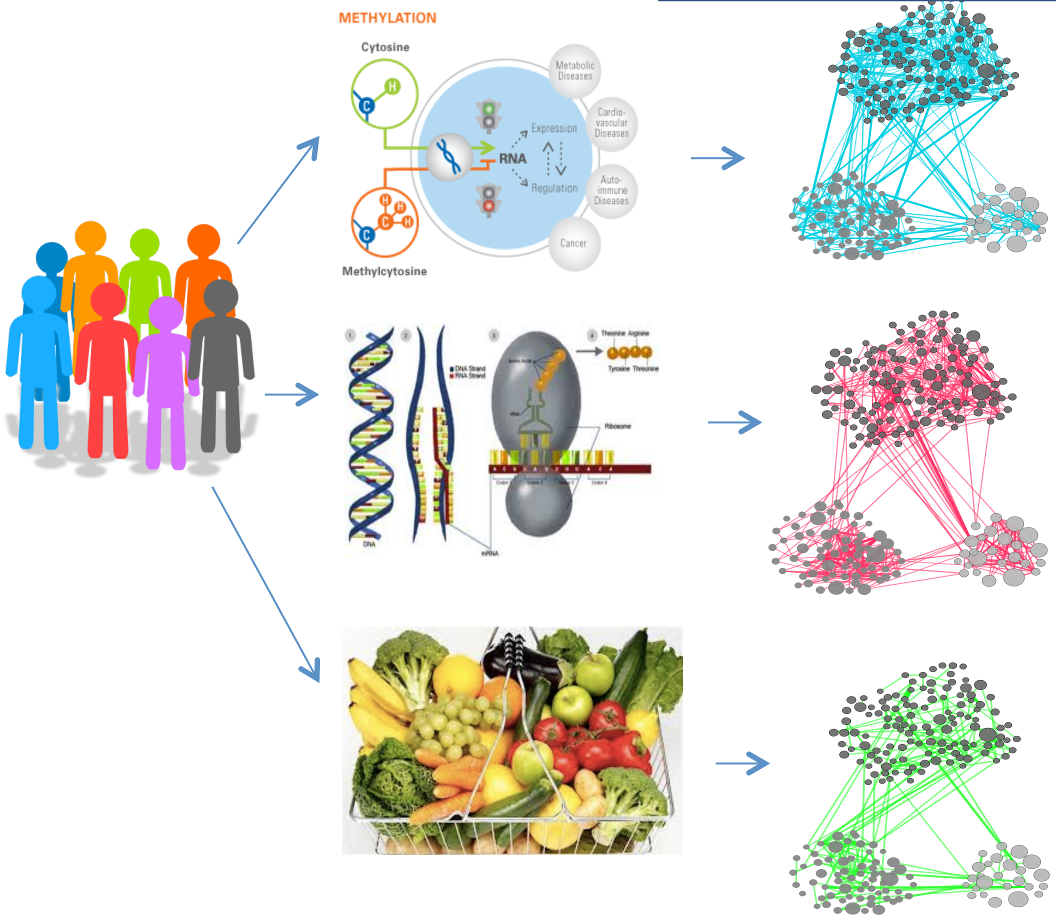


Goldenberg Lab: Similarity Network Fusion



Goldenberg Lab: Similarity Network Fusion

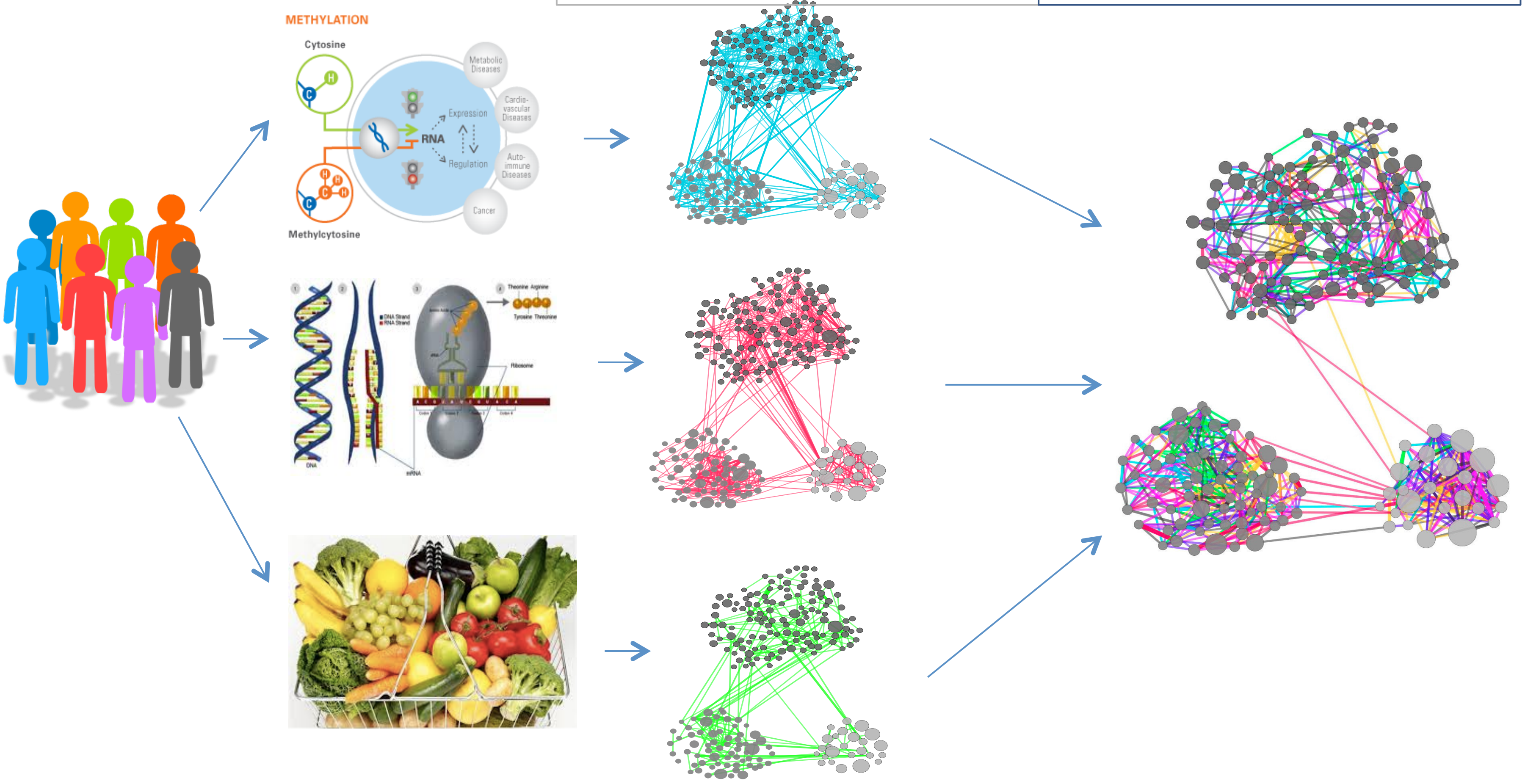
Step 1. Construct a similarity network for each data source



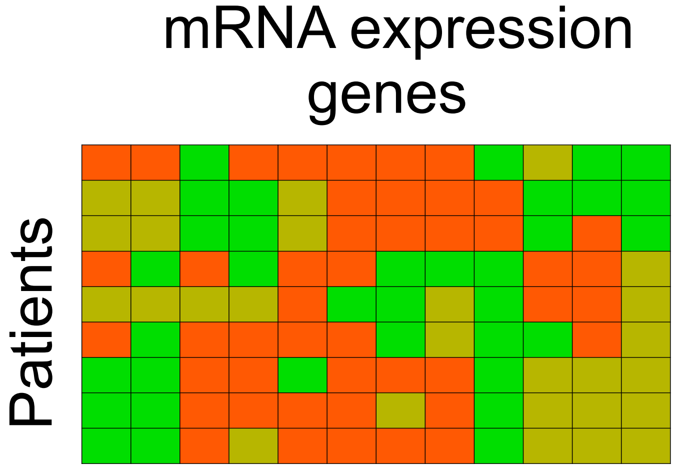
Goldenberg Lab: Similarity Network Fusion

Step 1. Construct a similarity network for each data source

Step 2. Integrate networks using non-linear fusion method



1. Construct similarity networks



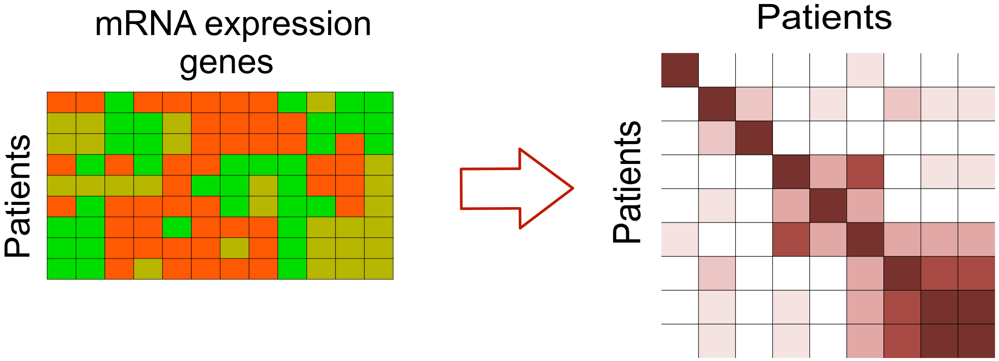
1. Construct similarity networks

Patient similarity:

$$W(i,j) = exp(\frac{\rho(x_i,x_j)^2}{\eta\xi_{ij}^2})$$

Adjacency matrix:

$$P(i,j) = \frac{W(i,j)}{\sum_{k\in V} W(i,k)}$$

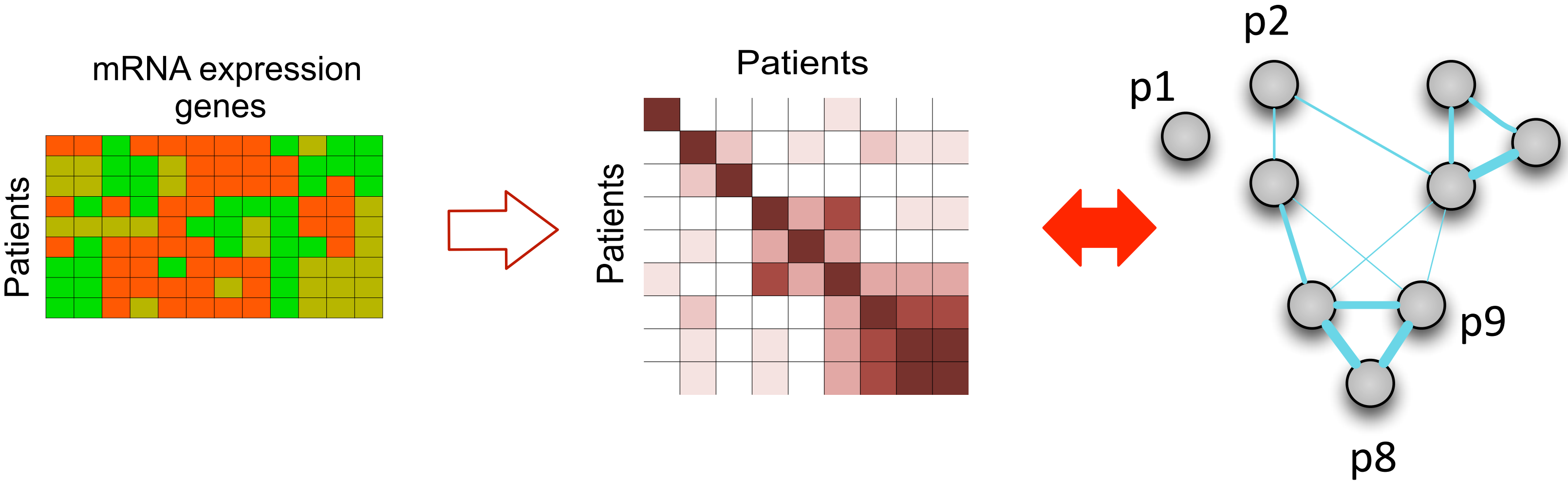


1. Construct similarity networks

Sparsification

1) $$\mathcal{W}(i,j) = \begin{cases} W(i,j) \text{ if } x_j \in KNN(x_i) \\ 0 \text{ otherwise} \end{cases}$$

2) $$\mathcal{P}(i,j) = \frac{\mathcal{W}(i,j)}{\sum_{x_k \in KNN(x_i)} \mathcal{W}(i,k)}$$



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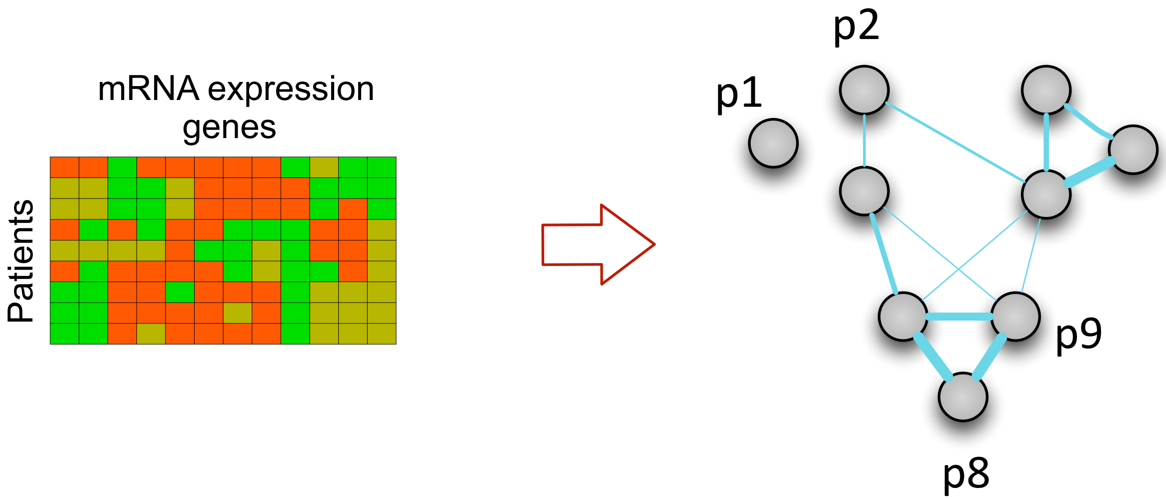

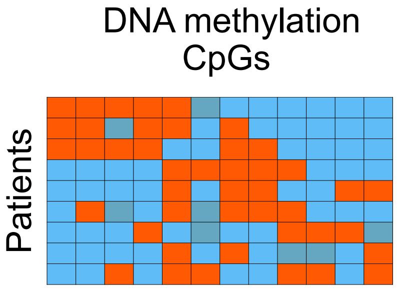

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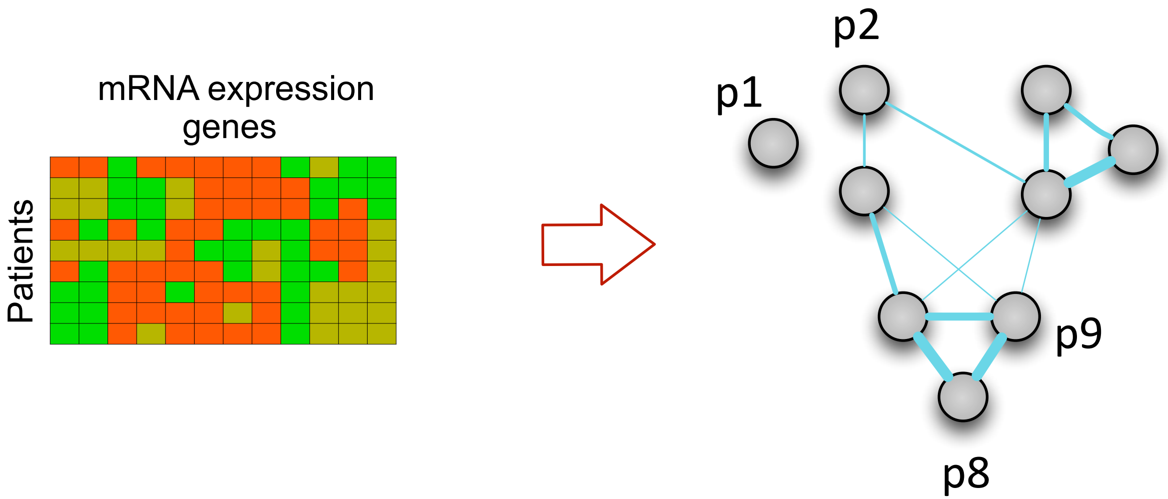
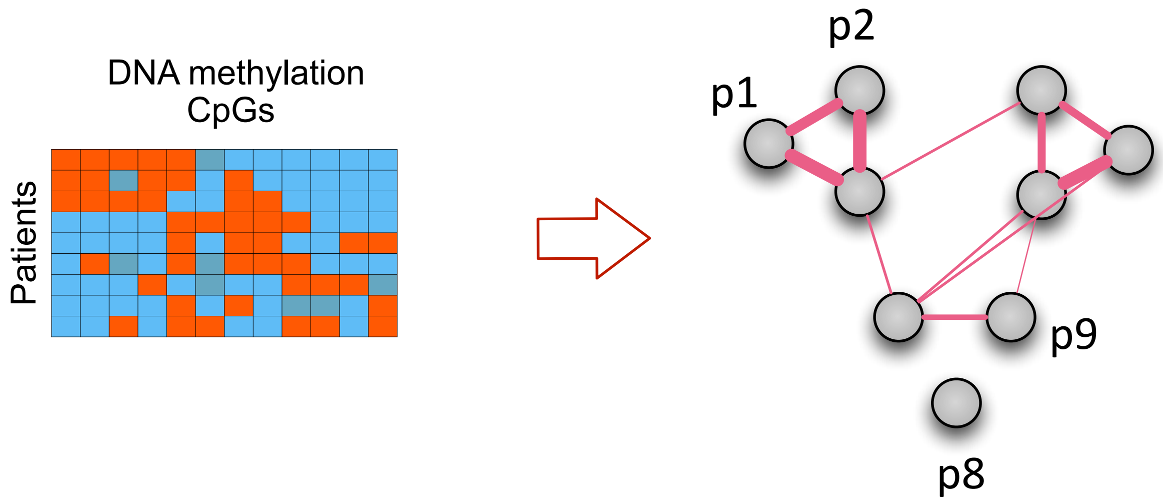
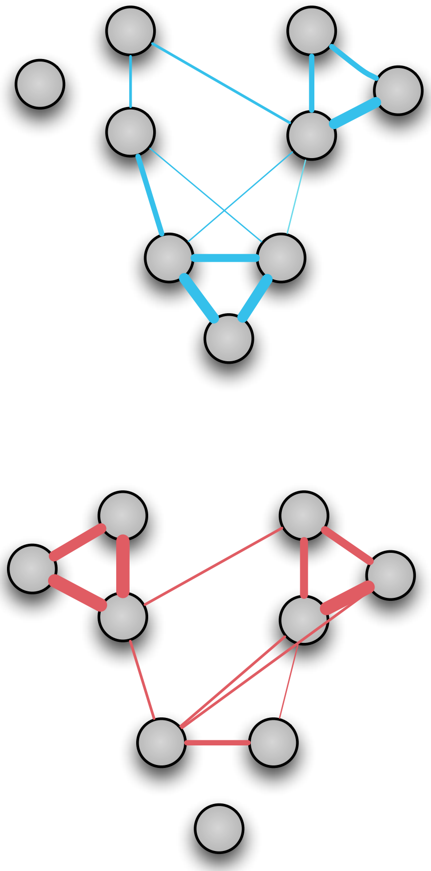




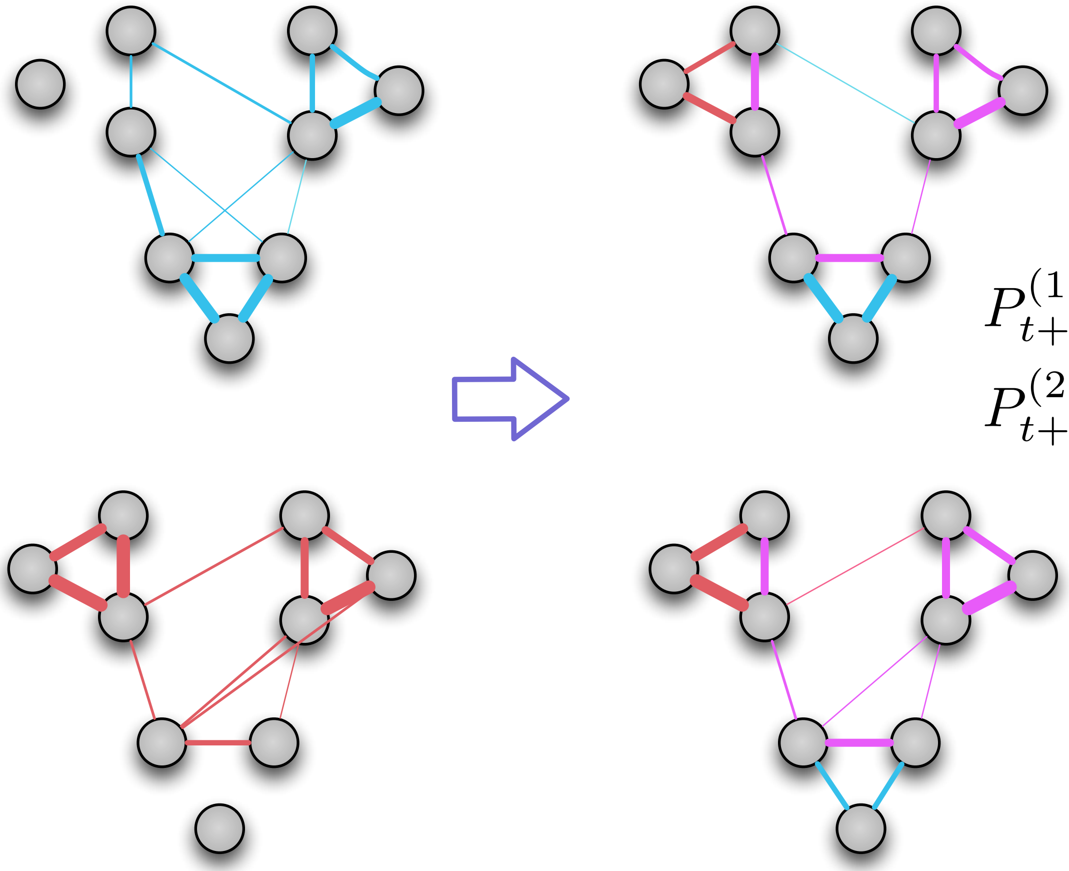
2. Combine networks

Sample Similarity Networks



● Patient   Patient similarity: ▬ mRNA-based ▬ DNA Methylation-based ▬ Supported by all data

2. Combine networks



Sample Similarity Networks

Fusion

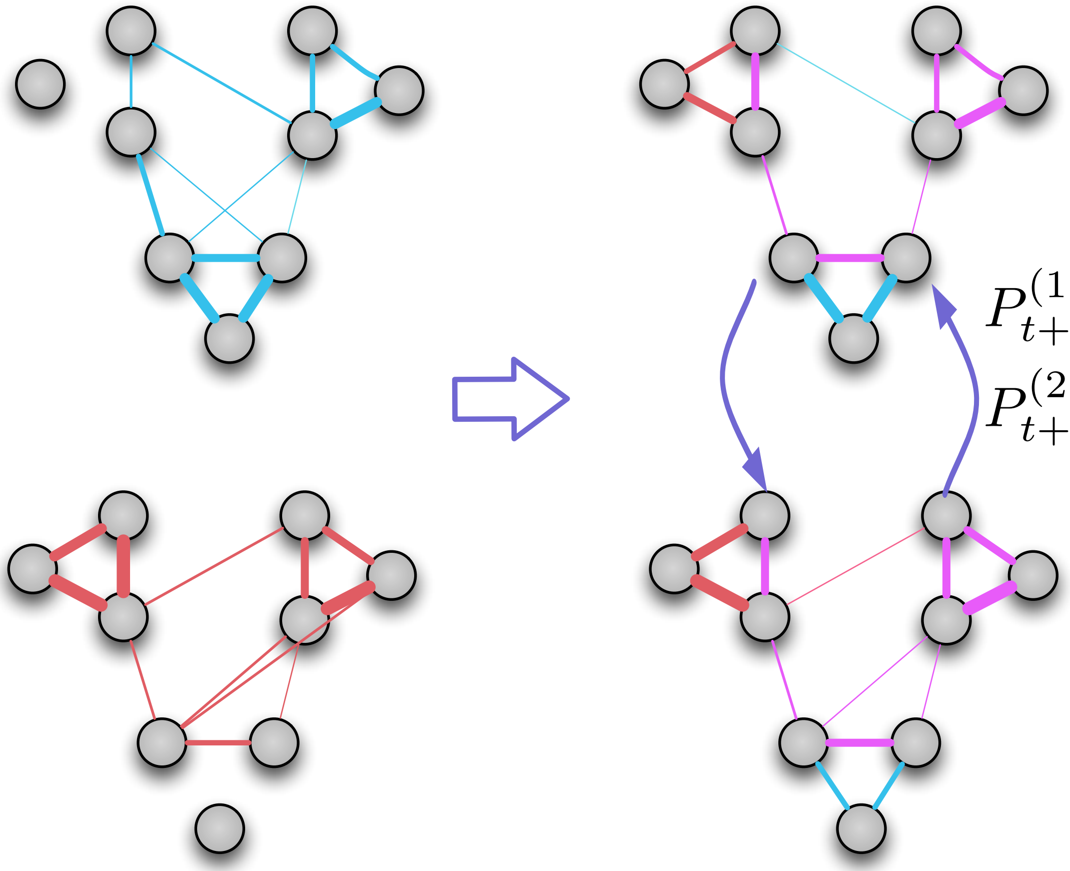
$$P_{t+1}^{(1)} = \mathcal{P}^{(1)} \times (P_t^{(2)}) \times (\mathcal{P}^{(1)})'$$
$$P_{t+1}^{(2)} = \mathcal{P}^{(2)} \times (P_t^{(1)}) \times (\mathcal{P}^{(2)})'$$

● Patient Patient similarity: ▬ mRNA-based ▬ DNA Methylation-based ▬ Supported by all data

2. Combine networks

Sample Similarity Networks

Fusion Iterations



$$P^{(1)}_{t+1} = \mathcal{P}^{(1)} \times (P^{(2)}_t) \times (\mathcal{P}^{(1)})'$$

$$P^{(2)}_{t+1} = \mathcal{P}^{(2)} \times (P^{(1)}_t) \times (\mathcal{P}^{(2)})'$$

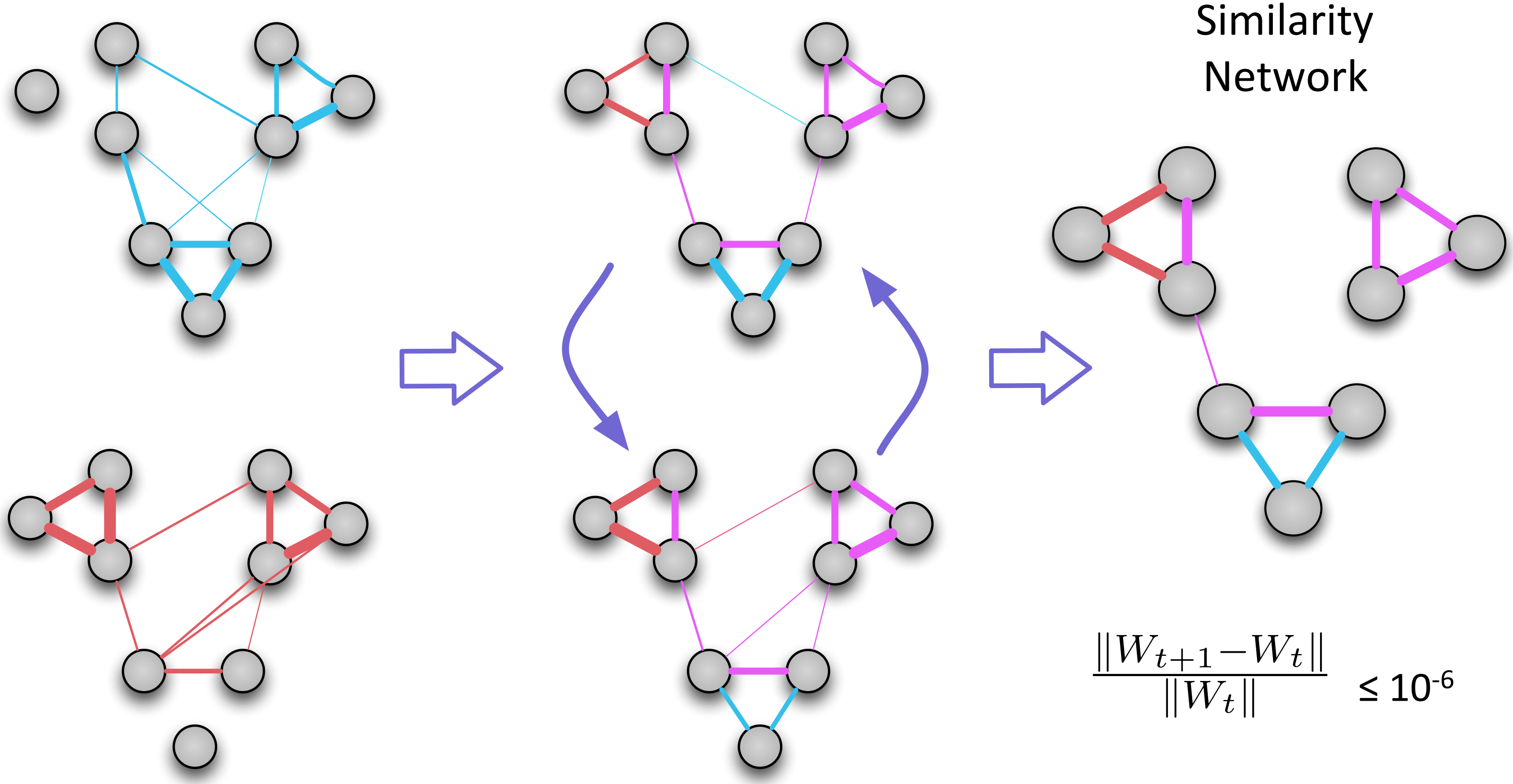
● Patient Patient similarity: 🟦 mRNA-based 🟥 DNA Methylation-based 🟪 Supported by all data

2. Combine networks

Sample Similarity Networks

Fusion Iterations

Fused Similarity Network



$$\frac{||W_{t+1} - W_t||}{||W_t||} \leq 10^{-6}$$

● Patient   Patient similarity: 🟦 mRNA-based   🟥 DNA Methylation-based   🟪 Supported by all data

Network Fusion

Fusing 2 networks:

$$P_{t+1}^{(1)} = \mathcal{P}^{(1)} \times (P_t^{(2)}) \times (\mathcal{P}^{(1)})'$$
$$P_{t+1}^{(2)} = \mathcal{P}^{(2)} \times (P_t^{(1)}) \times (\mathcal{P}^{(2)})'$$

Fusing m networks:

$$P_{t+1}^{(i)} \quad = \quad \mathcal{P}^{(i)} \times (\frac{1}{m-1} \sum_{j \neq i} P_t^{(j)}) \times (\mathcal{P}^{(i)})' + \eta I$$

Experiments

Data:

5 TCGA cancers

METABRIC (Large Breast Cancer db)

Comparative Methods:

Concatenation

iCluster

PDSB

Multiple kernel learning

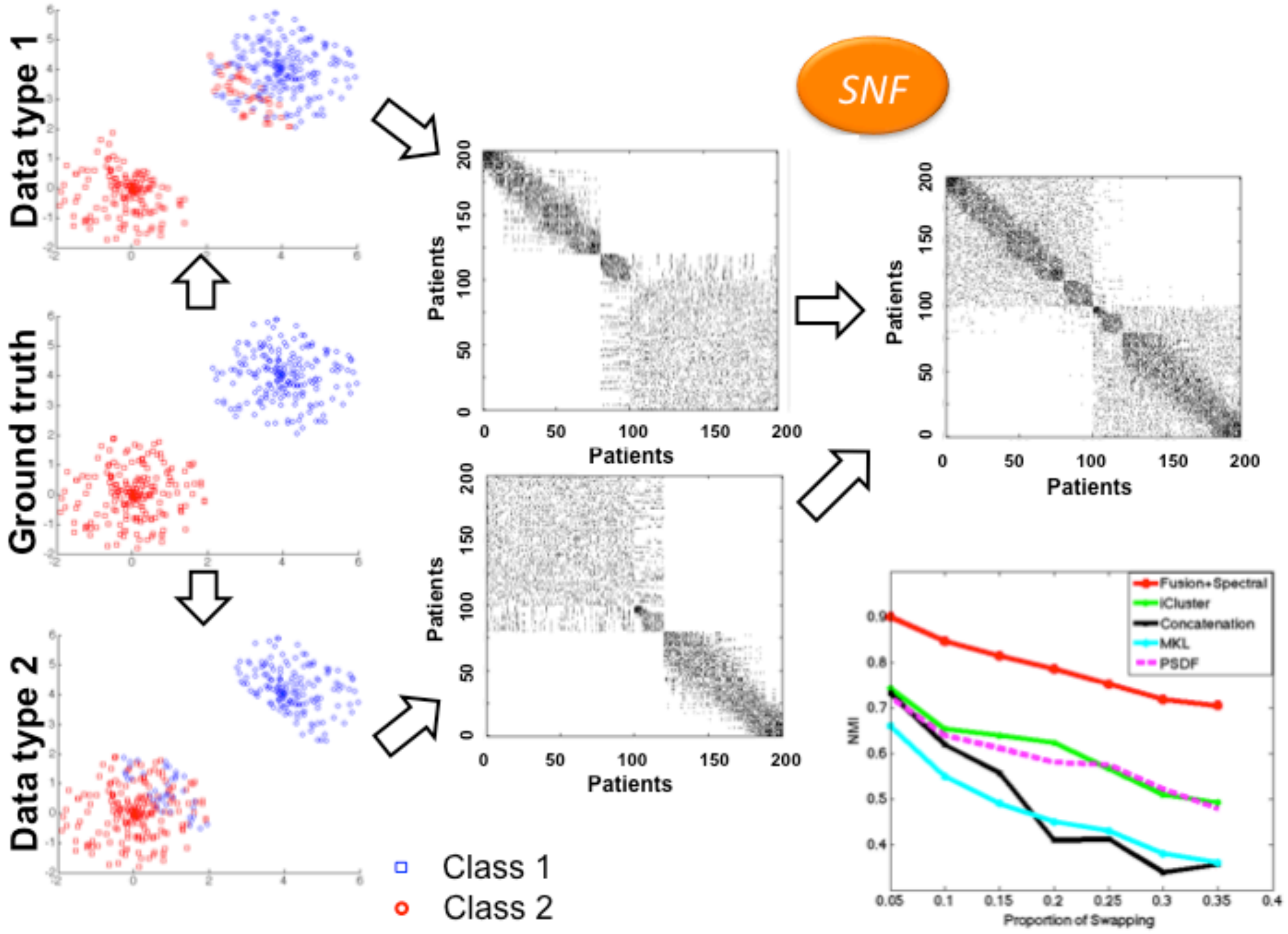
Criteria:

-$\log_{10}$(log rank pvalue)

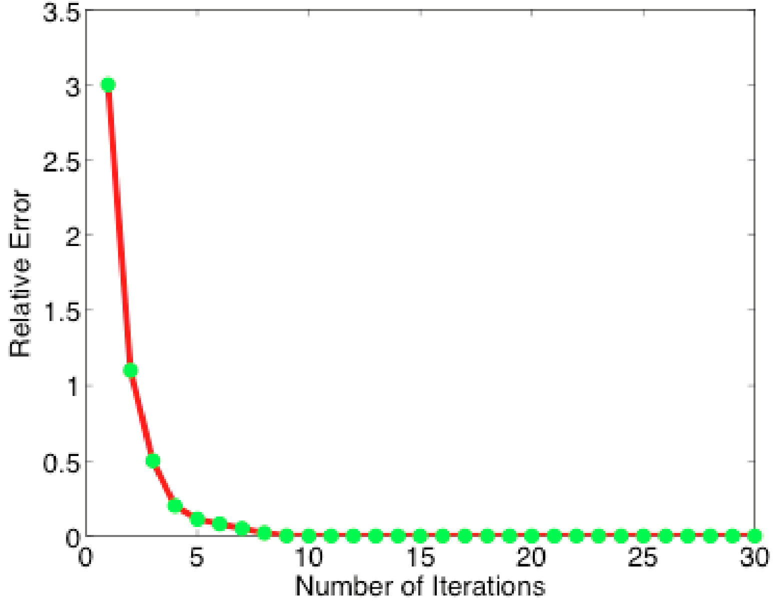
Silhouette score (cluster homogeneity)

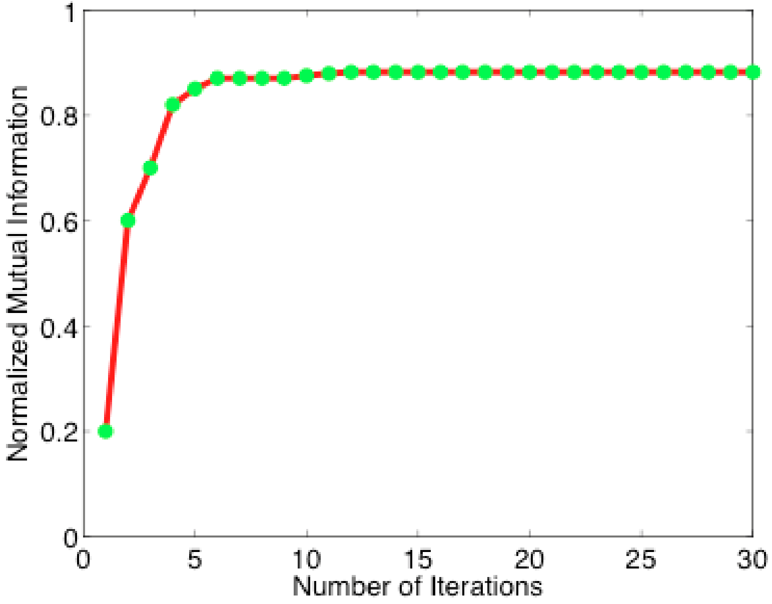
Running time

Simulation 1 – complementarity



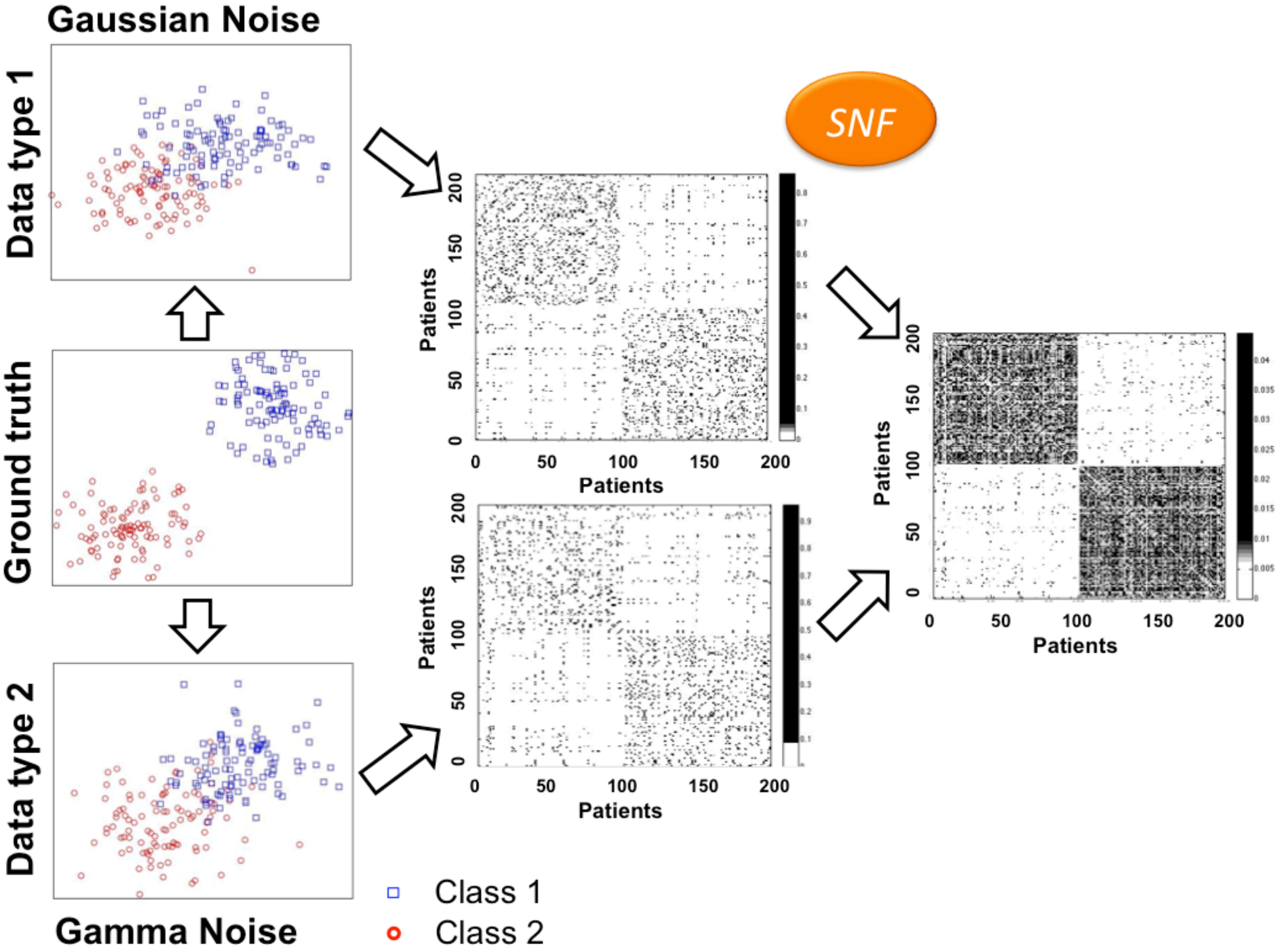
Simulation 1 convergence



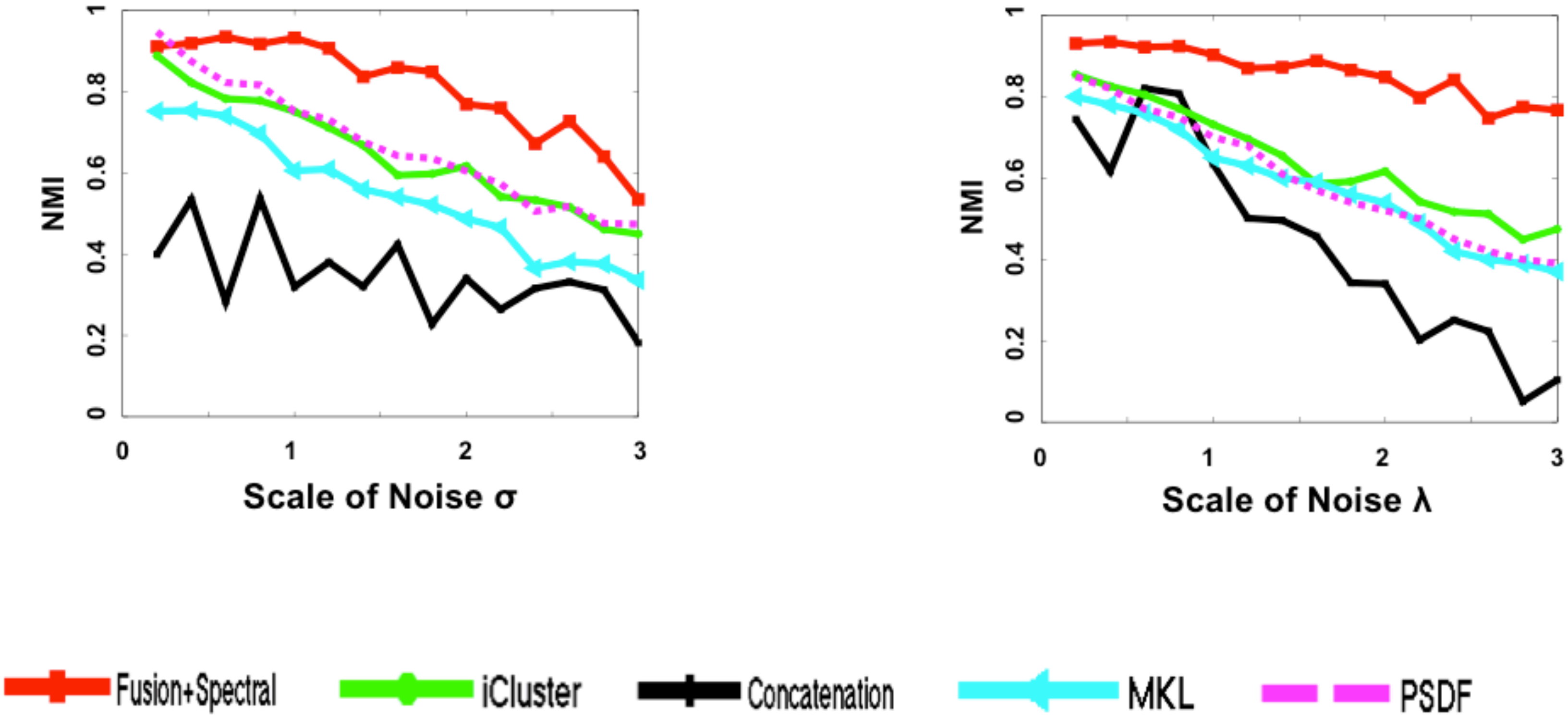


20% of patients are mislabeled

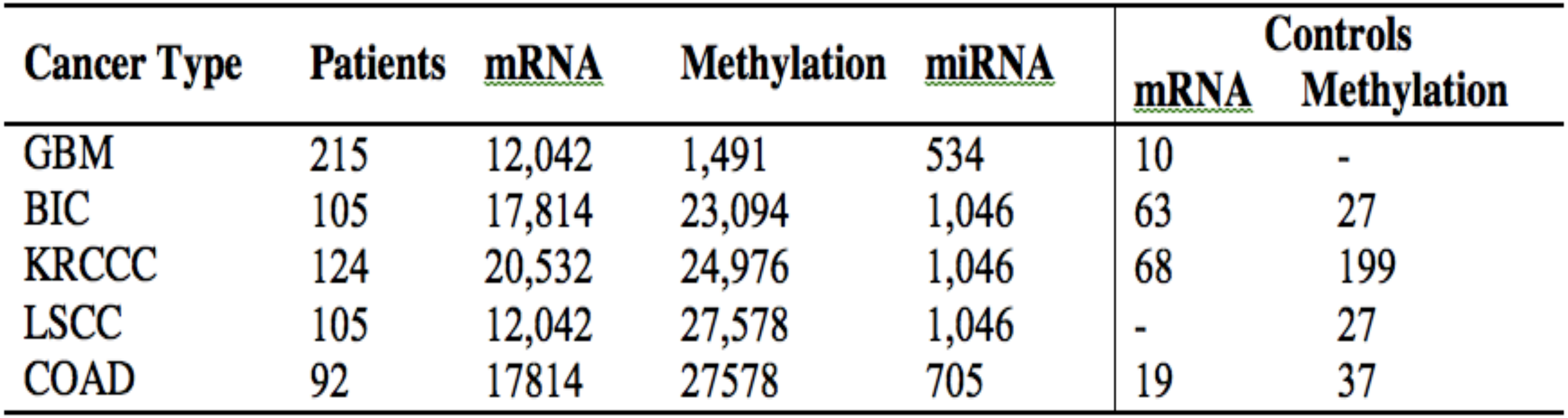
Simulation 2 - removing noise



Simulation 2 - removing noise



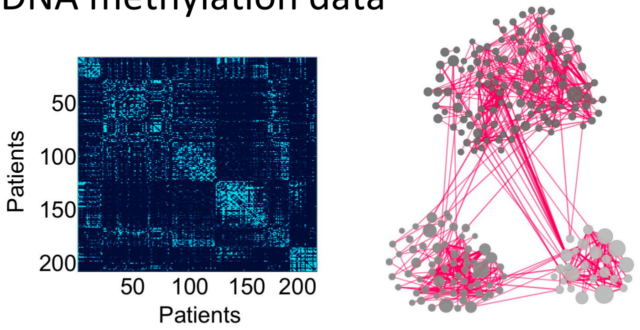
TCGA Data



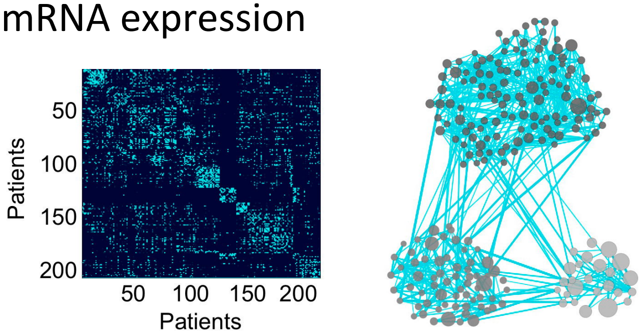
Cancer Type	Patients	mRNA	Methylation	miRNA	Controls	
					mRNA	Methylation
GBM	215	12,042	1,491	534	10	-
BIC	105	17,814	23,094	1,046	63	27
KRCCC	124	20,532	24,976	1,046	68	199
LSCC	105	12,042	27,578	1,046	-	27
COAD	92	17814	27578	705	19	37

Case study: Glioblastoma

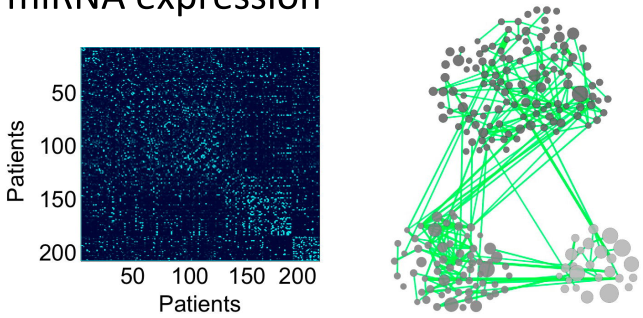
DNA methylation data



mRNA expression



miRNA expression



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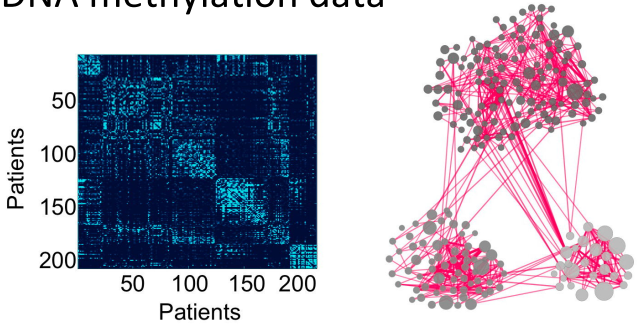
Case study: Glioblastoma

DNA methylation data



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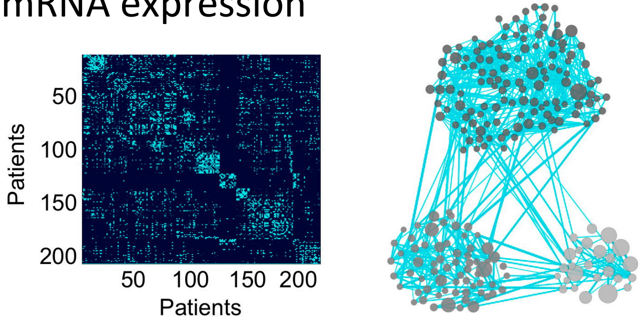
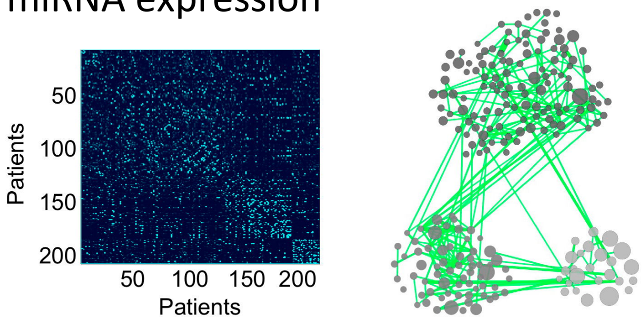
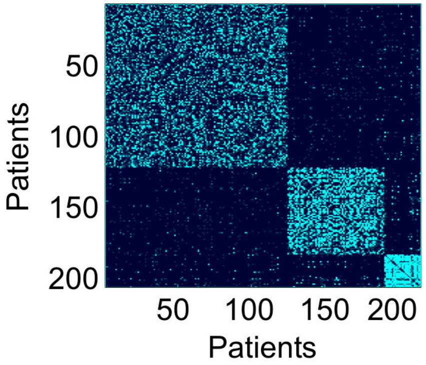
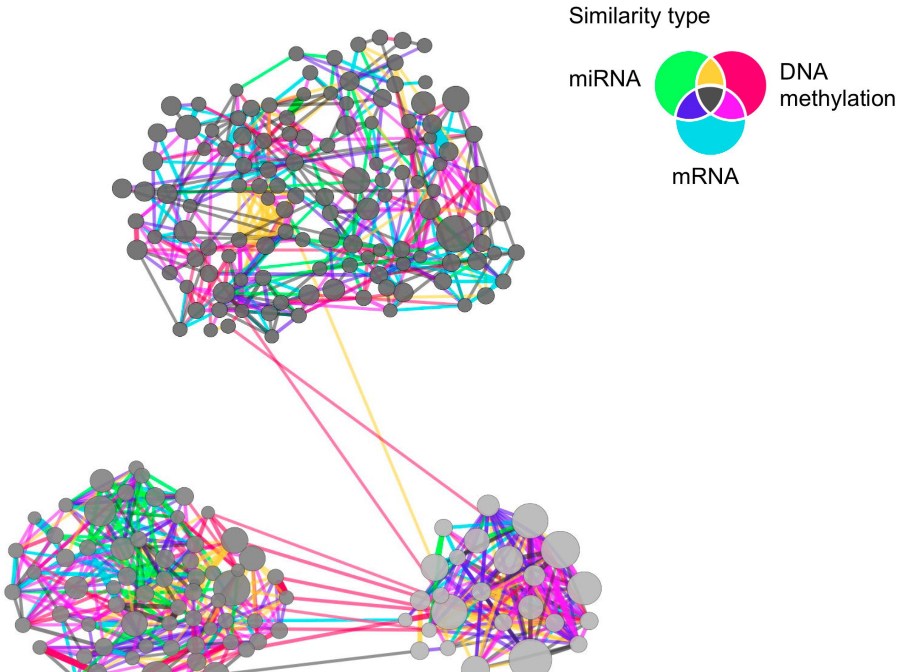


miRNA expression



FUSED





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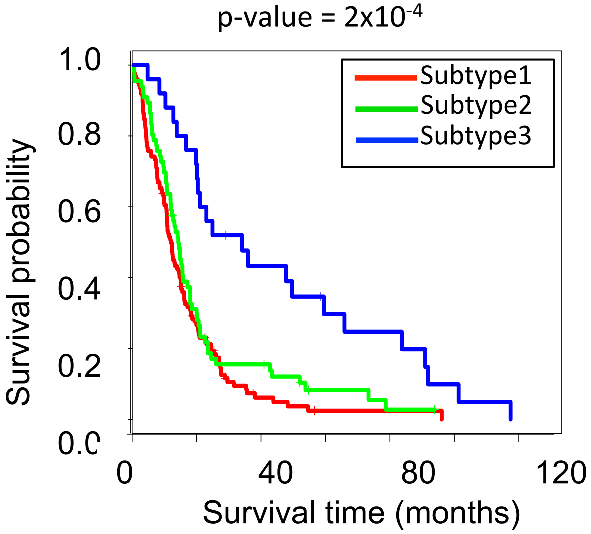
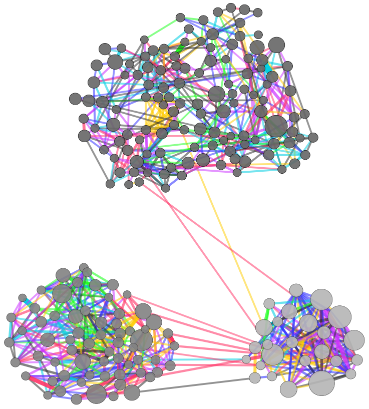
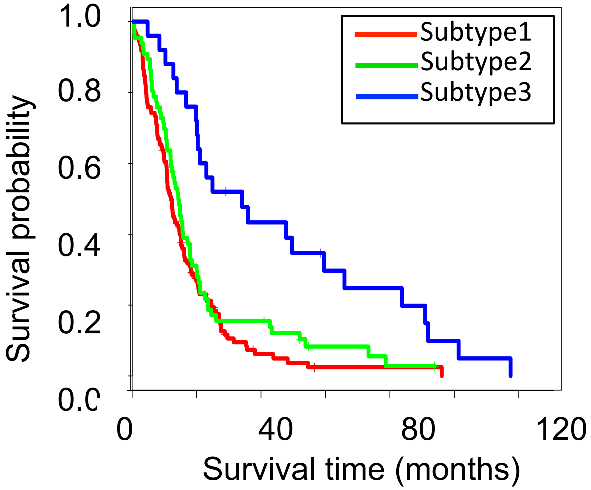
Clinical properties of the subtypes

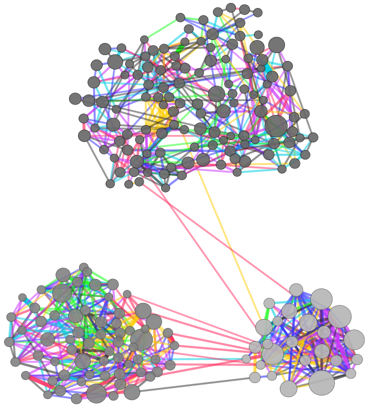


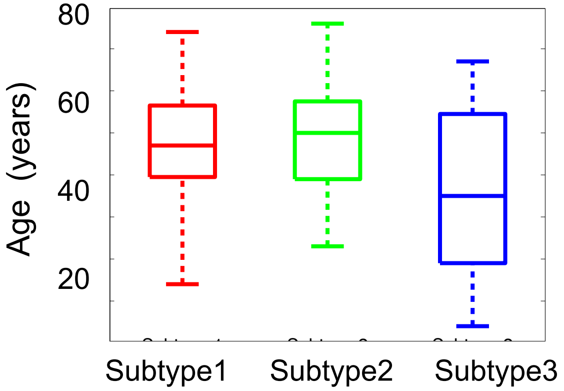


Clinical properties of the subtypes

p-value = $2x10^{-4}$



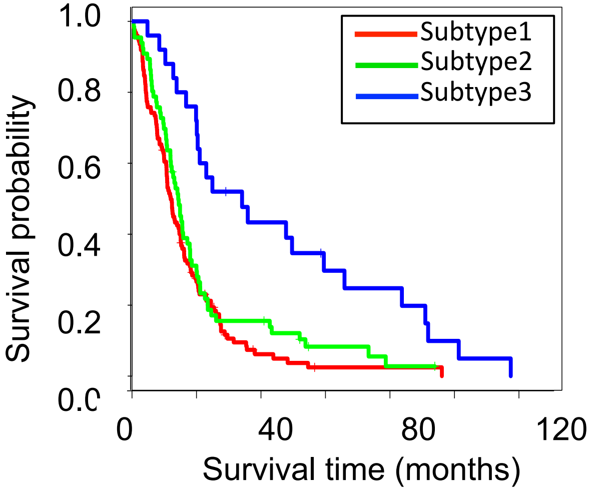


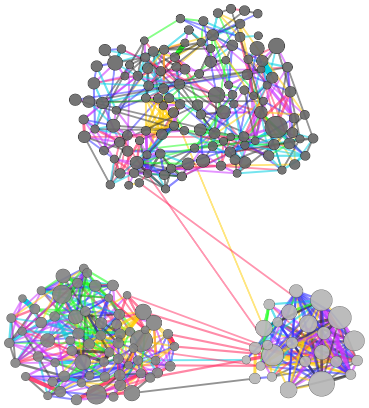


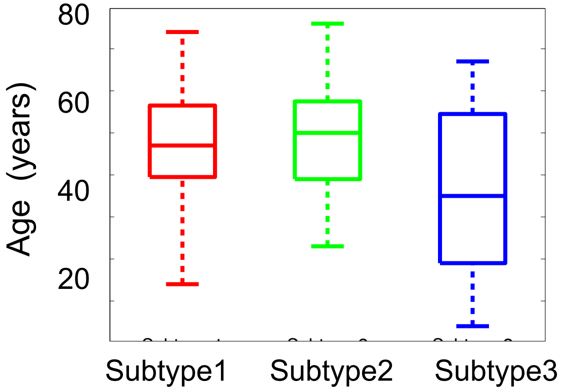
p-value = $3x10^{-5}$

Clinical properties of the subtypes

p-value = $2x10^{-4}$

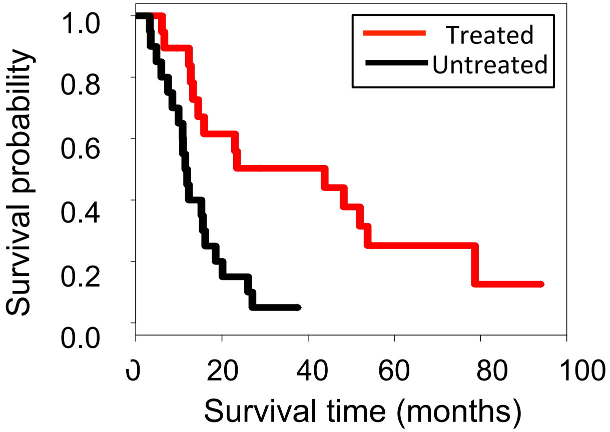






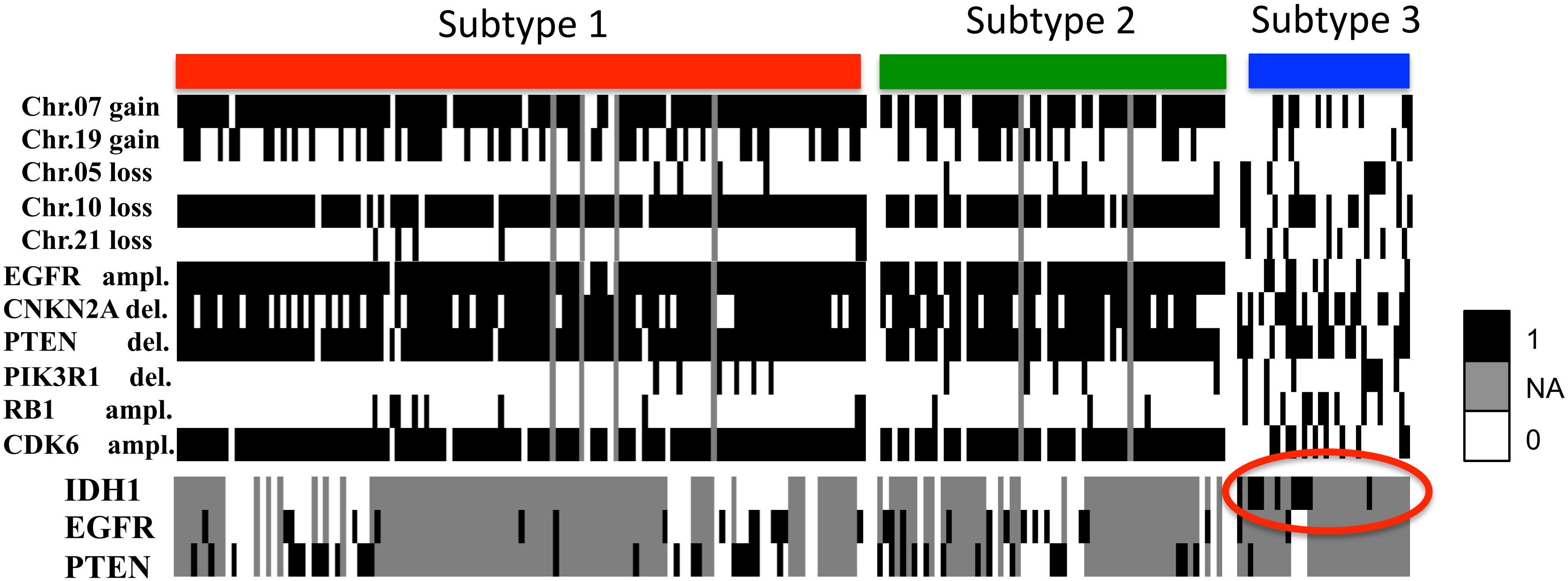
p-value = $3x10^{-5}$

Subtype 1



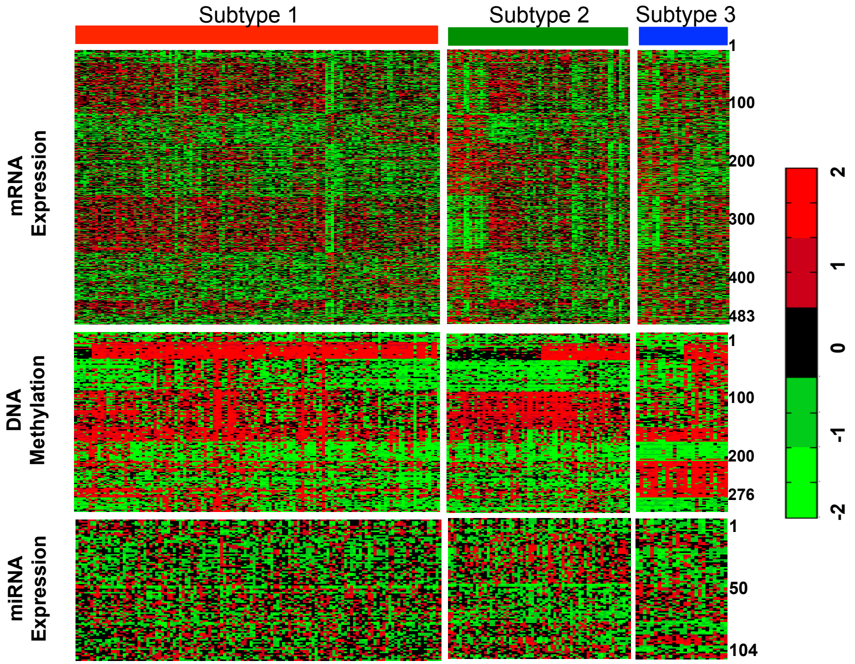
p = 0.001

Biological characterization of the subtypes



Feature Selection

Standard t-test
Differential analysis



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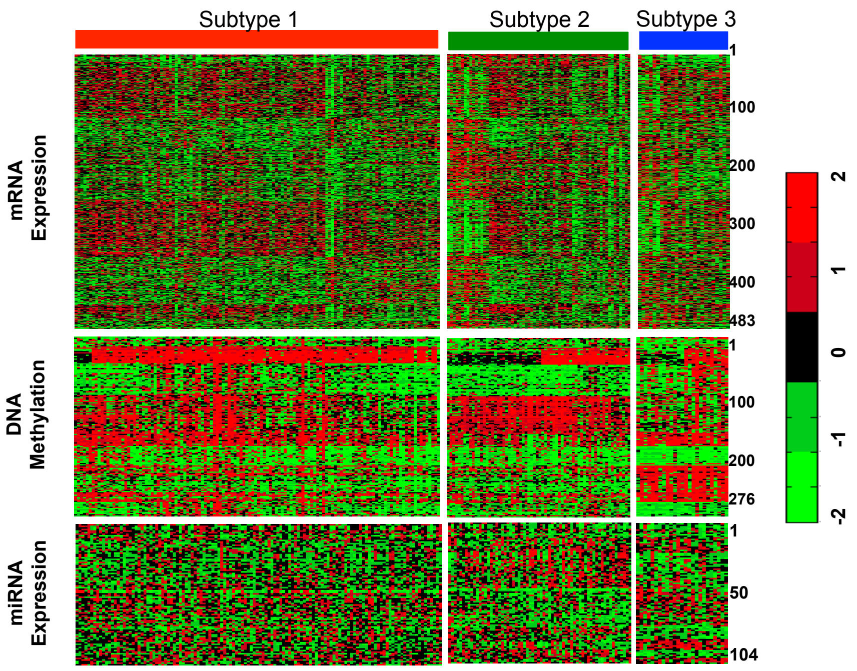
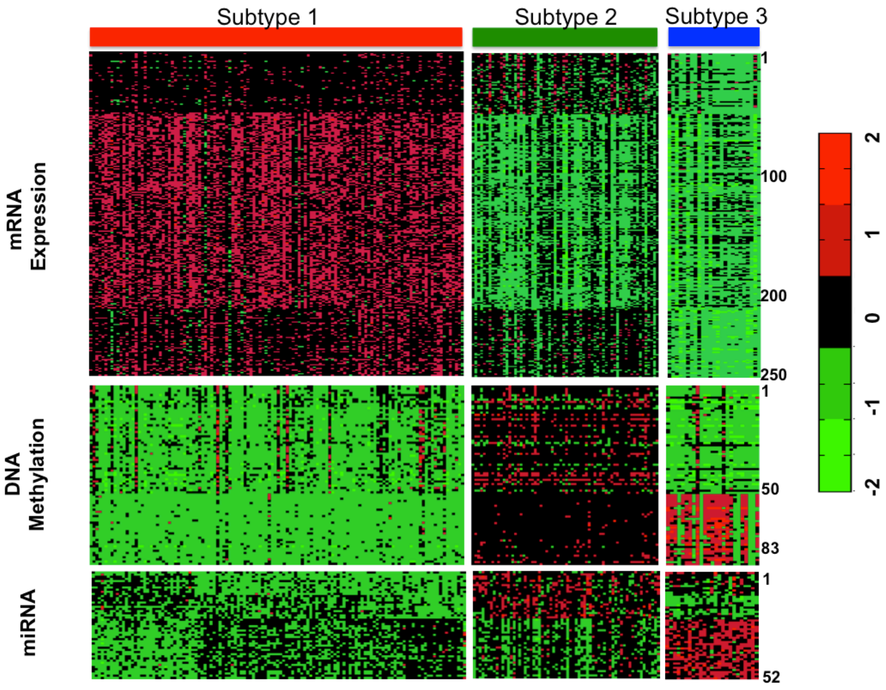
Feature Selection

Standard t-test Differential analysis



Network-based NMI Differential analysis



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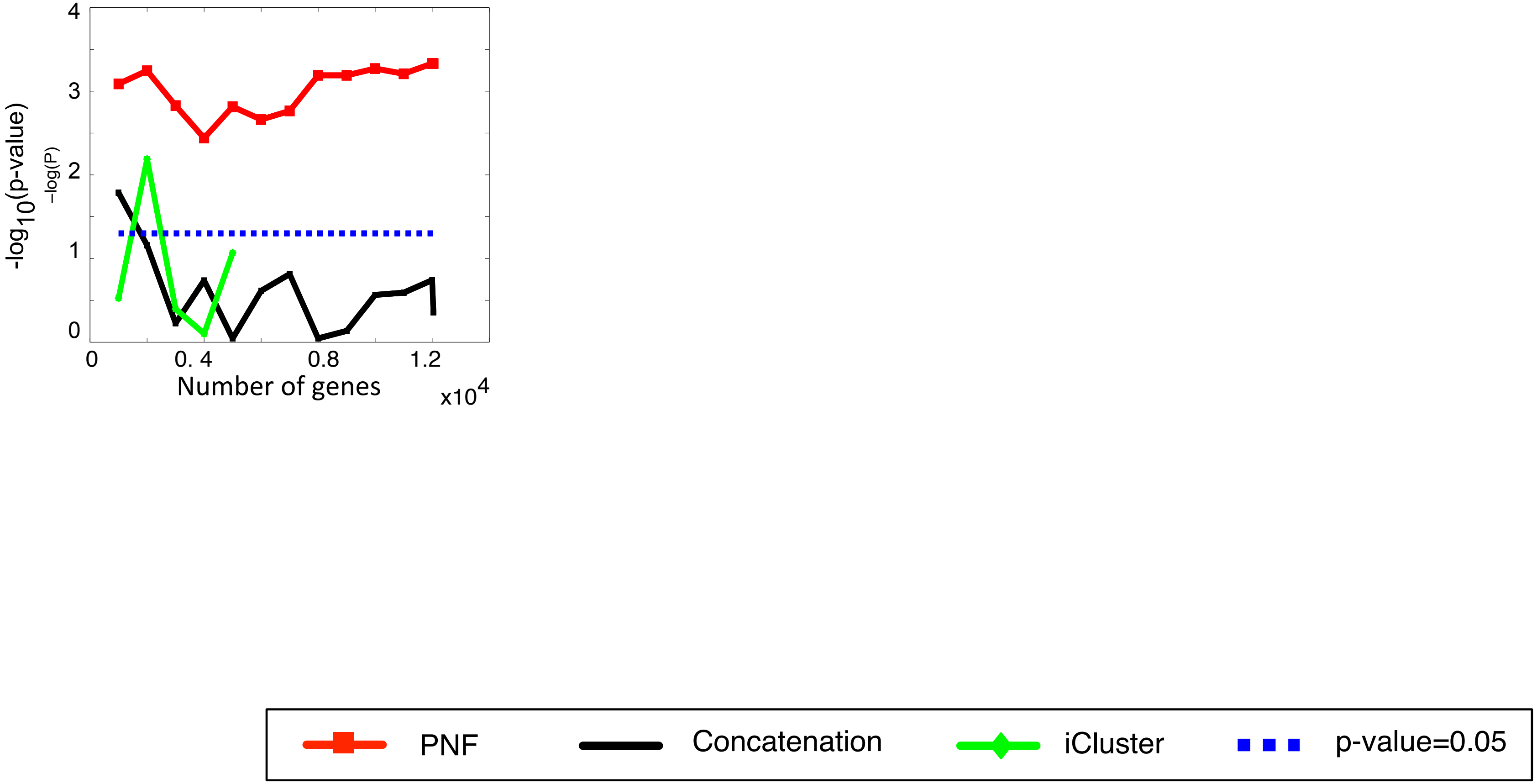
Gene Pre-selection in GBM



Genes are ordered by significance of the differential values between tumor and normal

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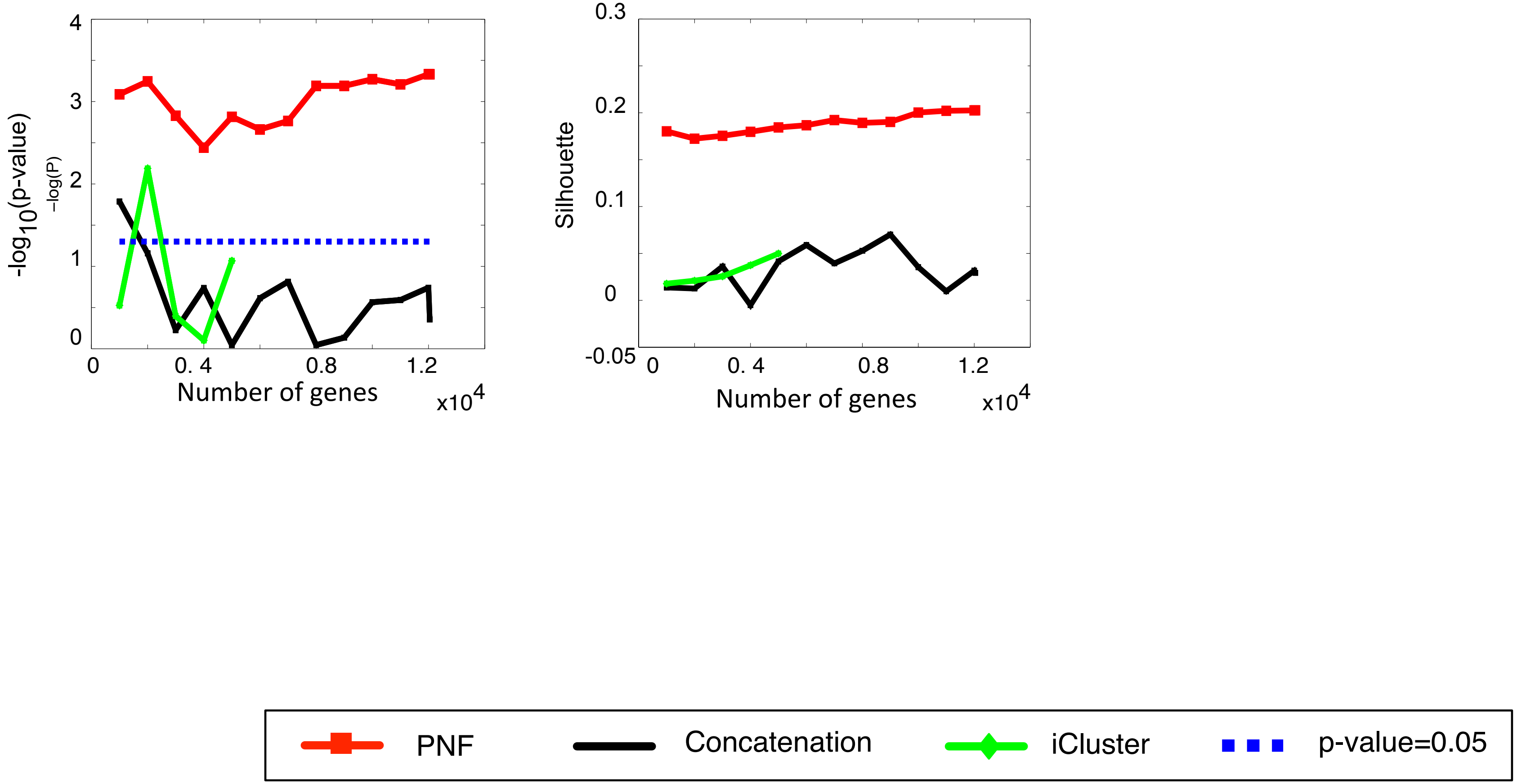
Gene Pre-selection in GBM



Genes are ordered by significance of the differential values between tumor and normal

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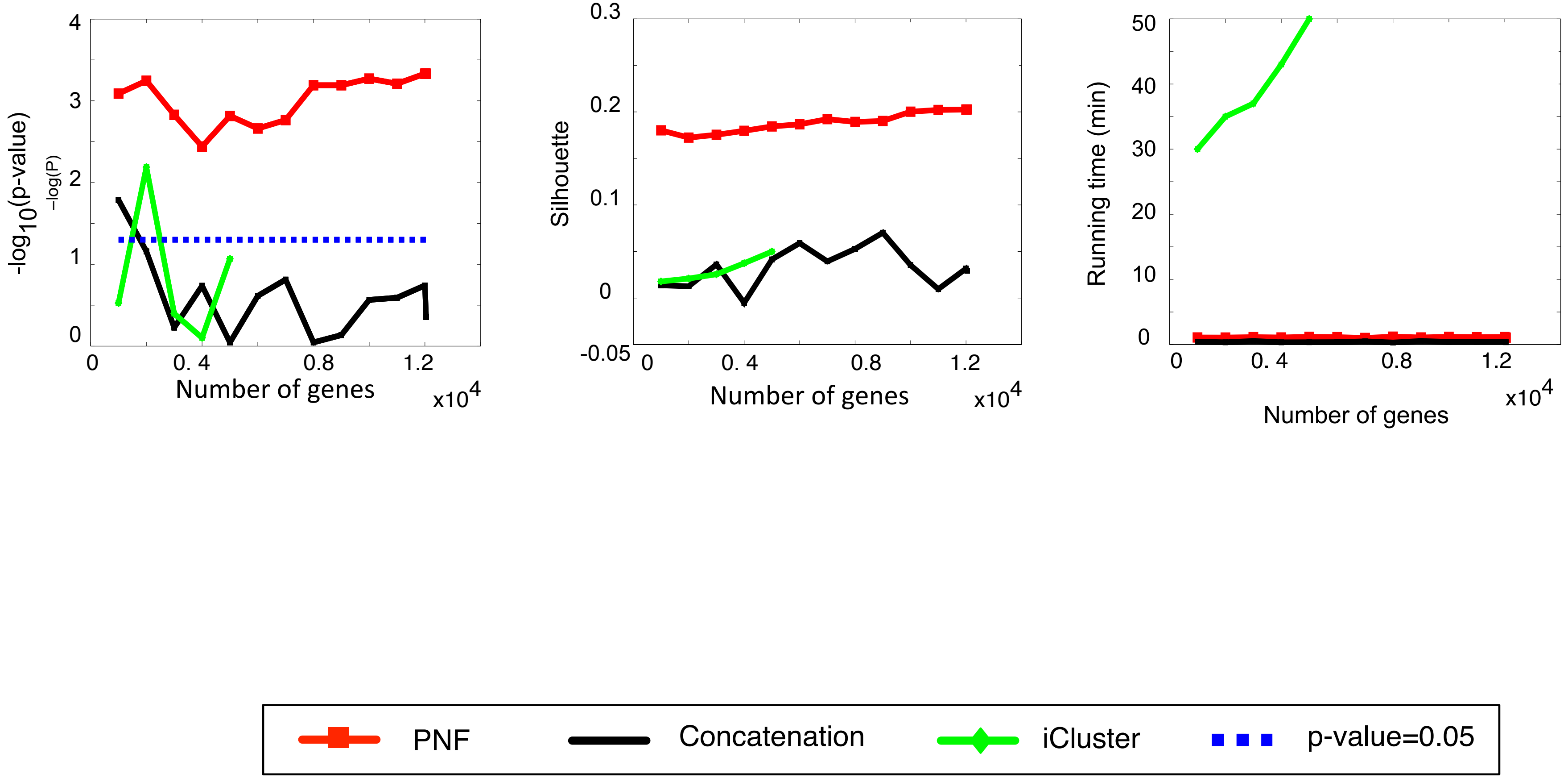
Gene Pre-selection in GBM



Genes are ordered by significance of the differential values between tumor and normal

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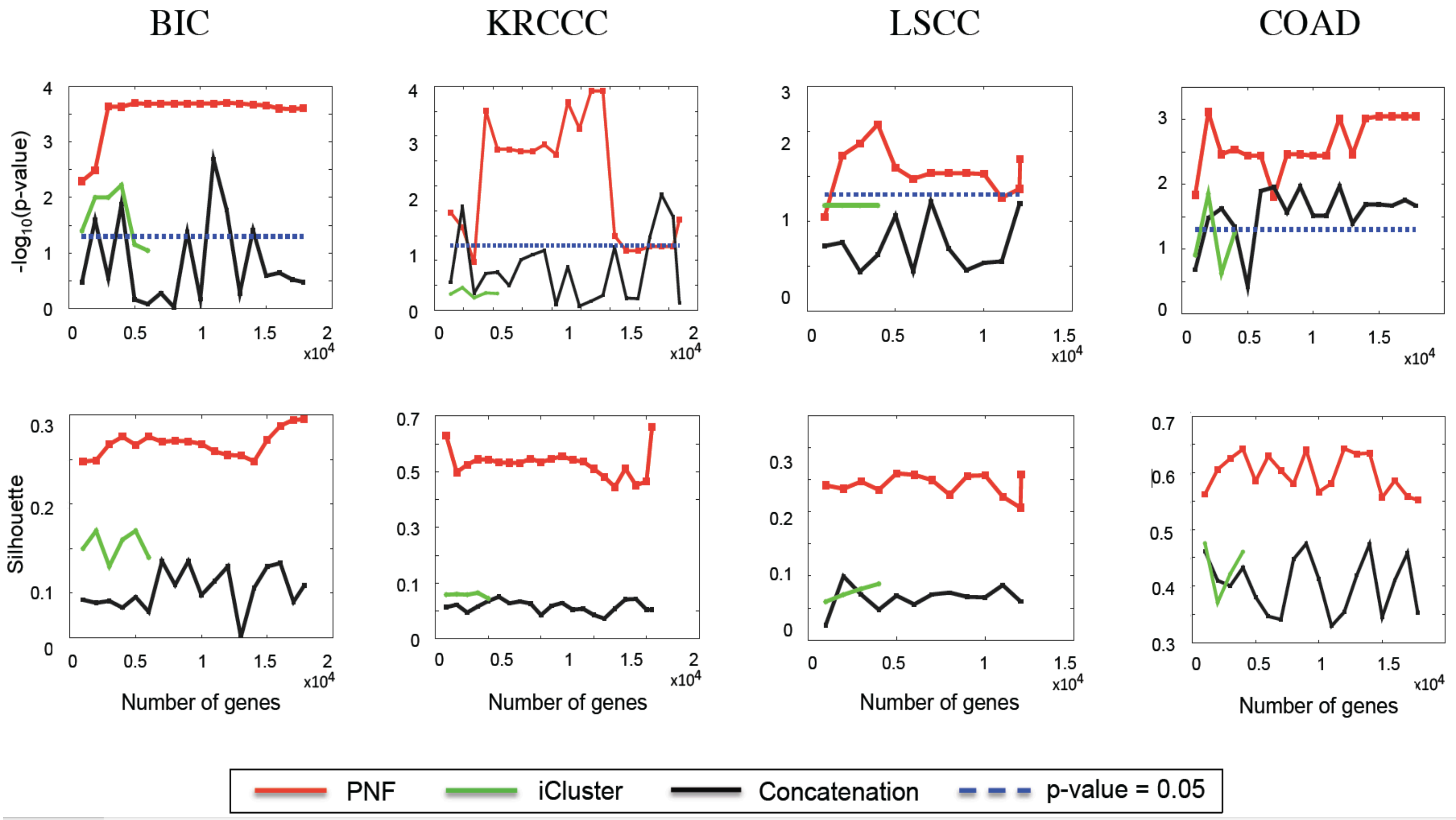
Gene pre-selection across cancers



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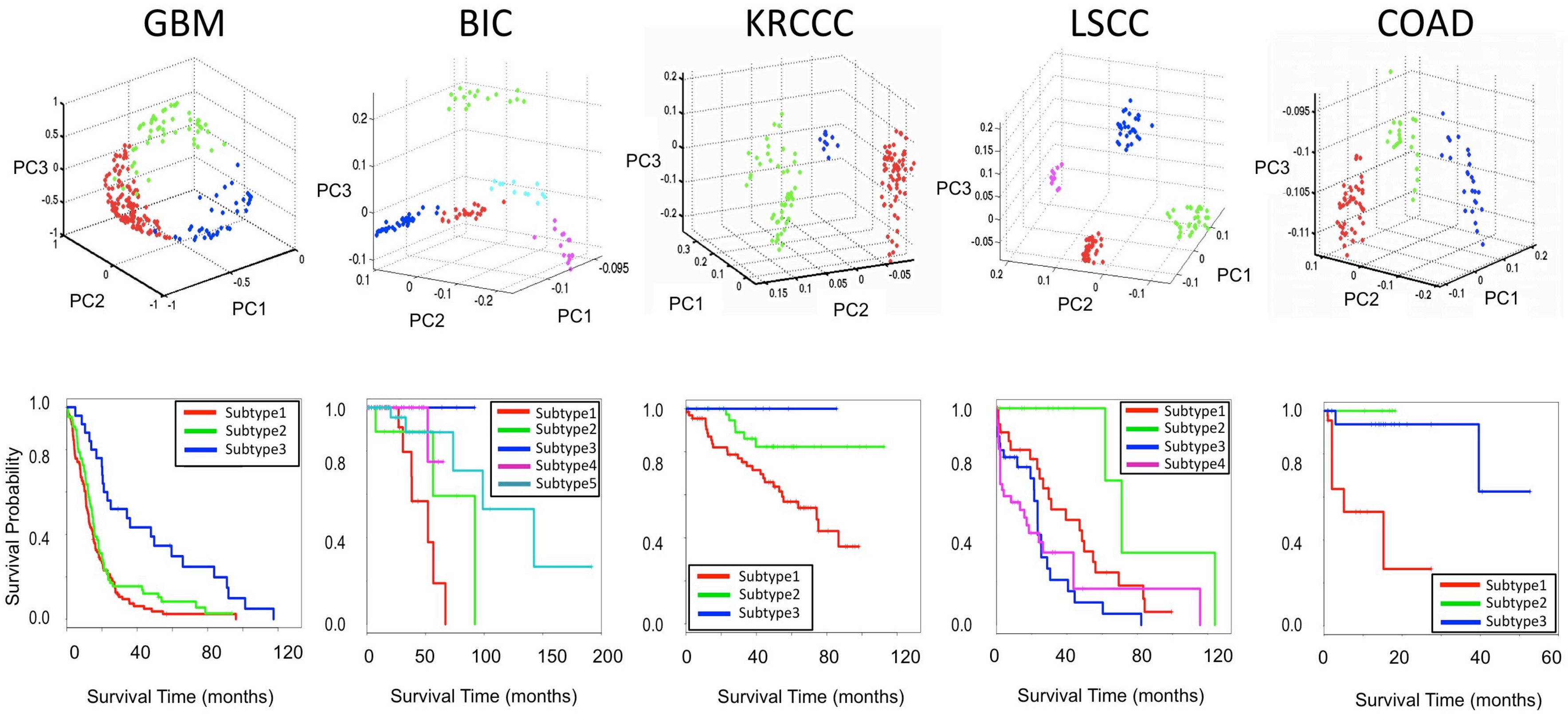
Clustering of the network



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Patient networks framework advantages

✓ Creates a unified view of patients based on multiple heterogeneous sources

✓ Integrates gene and non-gene based data

✓ No need to do gene pre-selection

✓ Robust to different types of noise

✓ Scalable

Patient networks

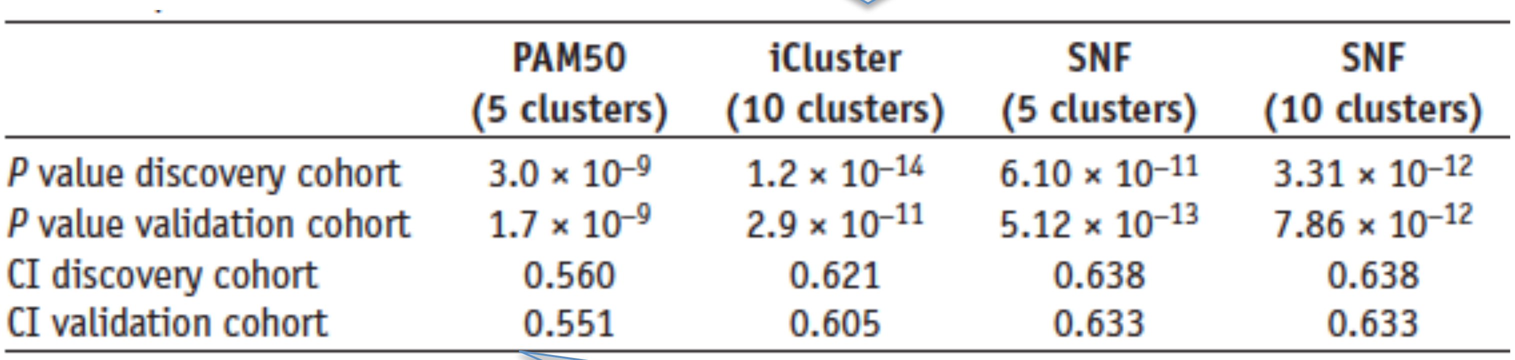
- ✓ Obtain superior results on regular tasks such as subtyping
- ✓ No fea re pre-se ion
- ✓ Imputatio
- ✓ Can e hout imputi

Transformative power of patient networks

Breast Cancer (METABRIC example)

CNV and expression data
Discovery: 997 patients
Validation: 995 patients

Nature, 2012



	PAM50 (5 clusters)	iCluster (10 clusters)	SNF (5 clusters)	SNF (10 clusters)
P value discovery cohort	3.0×10^{-9}	1.2×10^{-14}	6.10×10^{-11}	3.31×10^{-12}
P value validation cohort	1.7×10^{-9}	2.9×10^{-11}	5.12×10^{-13}	7.86×10^{-12}
CI discovery cohort	0.560	0.621	0.638	0.638
CI validation cohort	0.551	0.605	0.633	0.633

established

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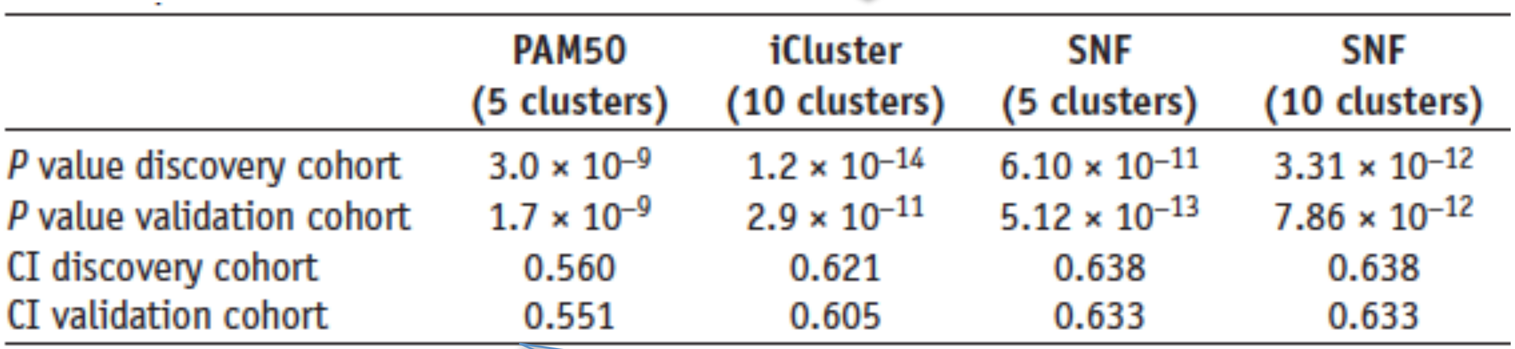

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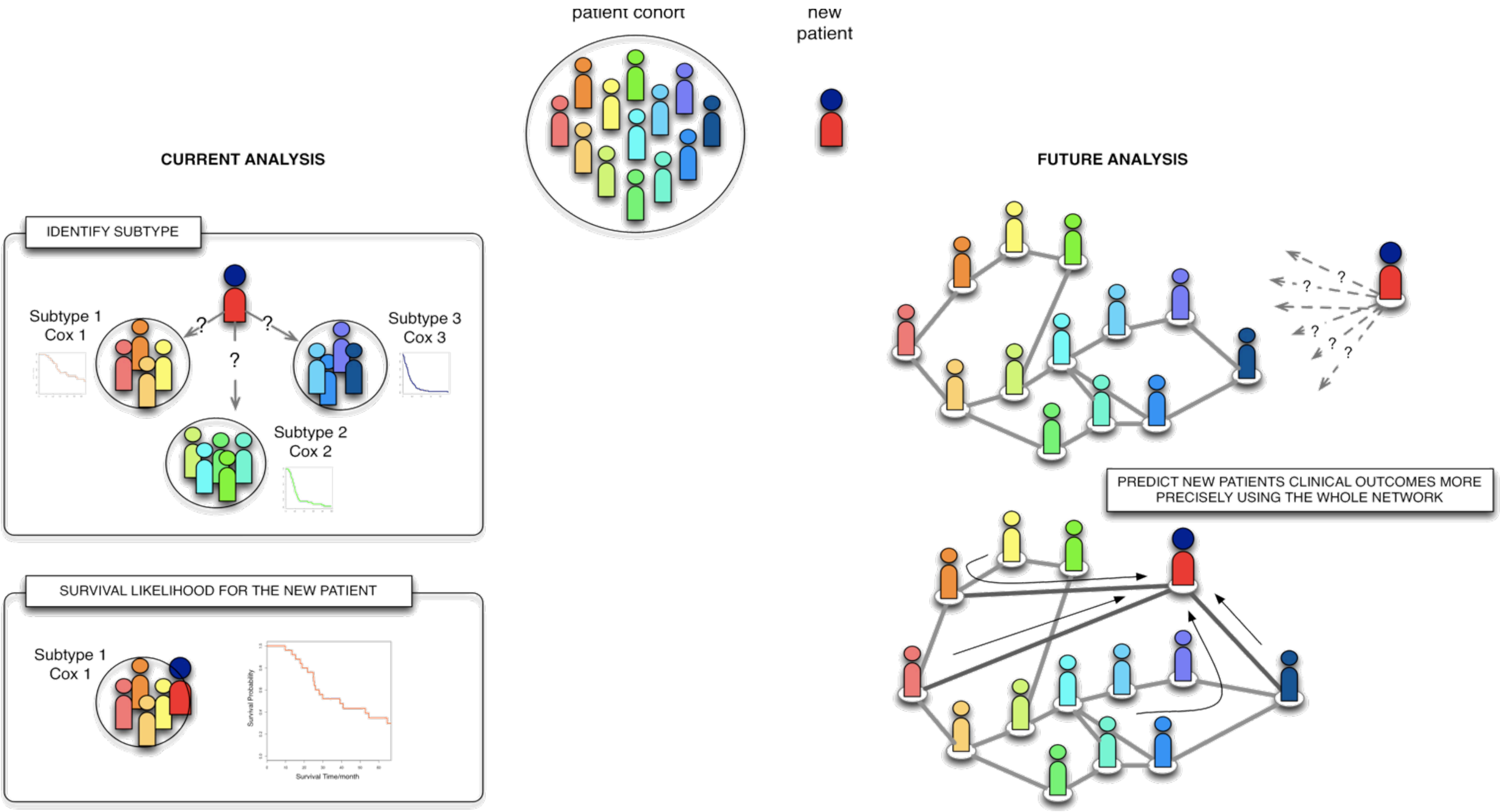
established

So how many subtypes are there really in breast cancer?

Predicting using the network



patient cohort

new patient

CURRENT ANALYSIS

IDENTIFY SUBTYPE

Subtype 1
Cox 1

Subtype 3
Cox 3

Subtype 2
Cox 2

SURVIVAL LIKELIHOOD FOR THE NEW PATIENT

Subtype 1
Cox 1

FUTURE ANALYSIS

PREDICT NEW PATIENTS CLINICAL OUTCOMES MORE PRECISELY USING THE WHOLE NETWORK

Predicting using the network

Cox objective $$lp(z) = \sum_{i=1}^{n} \delta_i \left(\mathbf{X}_{\boldsymbol{i}}^{\boldsymbol{T}} z - \log\left(\sum_{j \in \boldsymbol{R}(\boldsymbol{t_i})} \exp\left(\mathbf{X}_{\boldsymbol{j}}^{\boldsymbol{T}} z \right) \right) \right)$$

Predicting using the network

Cox objective

$$lp(z) = \sum_{i=1}^{n} \delta_i \left(\mathbf{X}_{\boldsymbol{i}}^{\boldsymbol{T}} z - \log\left(\sum_{j \in \boldsymbol{R}(\boldsymbol{t_i})} \exp\left(\mathbf{X}_{\boldsymbol{j}}^{\boldsymbol{T}} z\right) \right)\right)$$

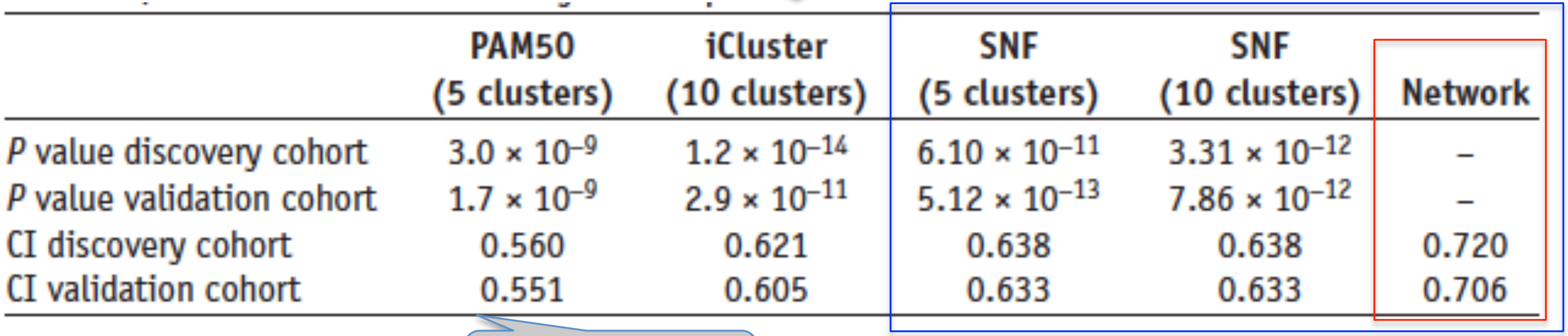
Our network-regularized objective

$$lp(\boldsymbol{z}) = \sum_{i=1}^{n} \delta_i \left(X_{\boldsymbol{i}}^{\boldsymbol{T}} \boldsymbol{z} - \log\left(\sum_{j \in \boldsymbol{R}(\boldsymbol{t_i})} \exp(X_{\boldsymbol{j}}^{\boldsymbol{T}} \boldsymbol{z}) \right)\right) - \lambda \sum_{i} \sum_{j} (X_{\boldsymbol{i}}^{\boldsymbol{T}} \boldsymbol{z} - X_{\boldsymbol{j}}^{\boldsymbol{T}} \boldsymbol{z})^2 w_{ij}$$

Predicting using the network
Breast Cancer (METABRIC example)

CNV and expression data
Discovery: 997 patients
Validation: 995 patients

Nature, 2012



	PAM50 (5 clusters)	iCluster (10 clusters)	SNF (5 clusters)	SNF (10 clusters)	Network
P value discovery cohort	3.0×10^{-9}	1.2×10^{-14}	6.10×10^{-11}	3.31×10^{-12}	–
P value validation cohort	1.7×10^{-9}	2.9×10^{-11}	5.12×10^{-13}	7.86×10^{-12}	–
CI discovery cohort	0.560	0.621	0.638	0.638	0.720
CI validation cohort	0.551	0.605	0.633	0.633	0.706

established