Informatics links between histological features and genetics in cancer

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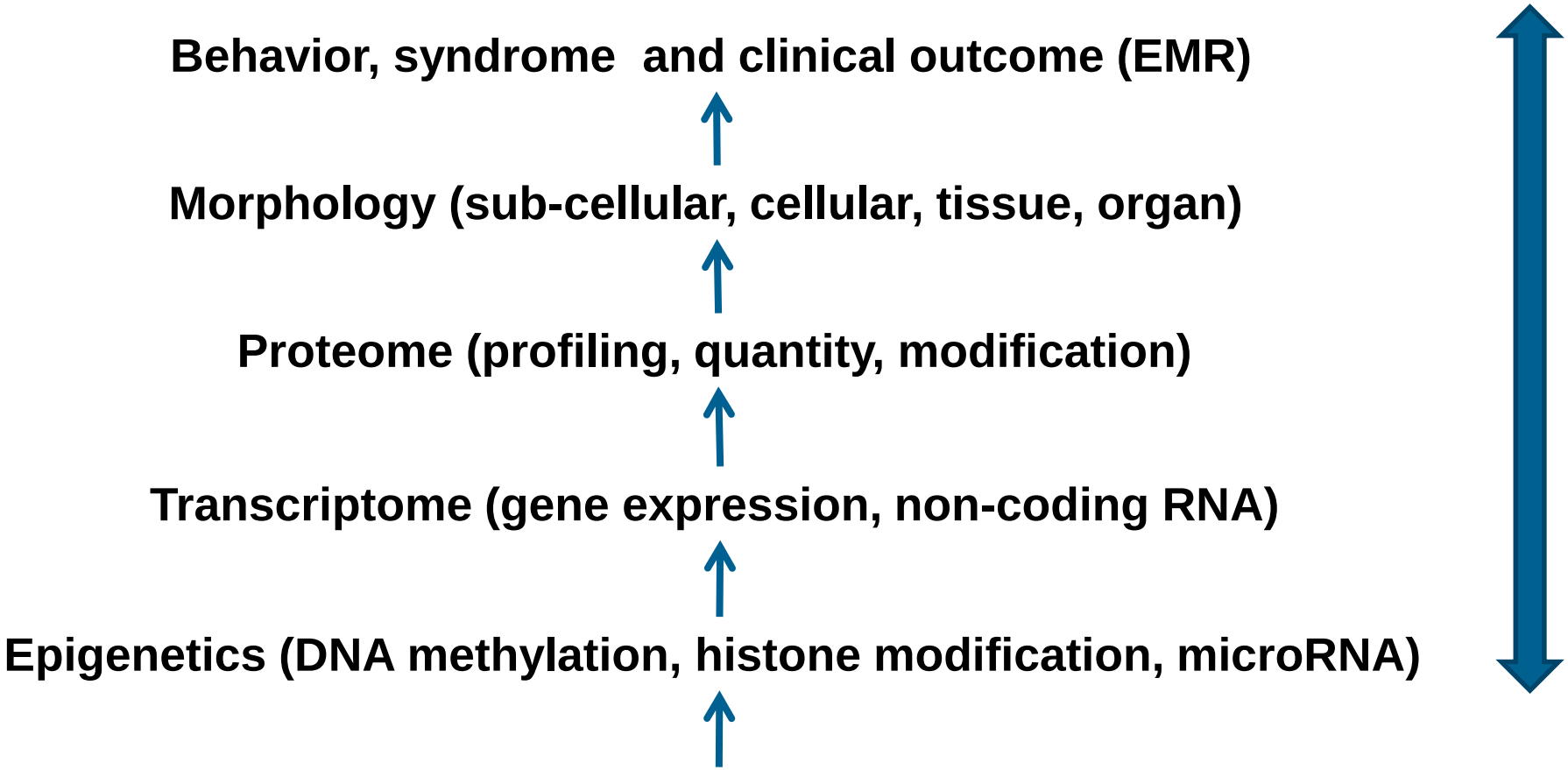
The Ohio State University Wexner Medical Center

June 13, 2016

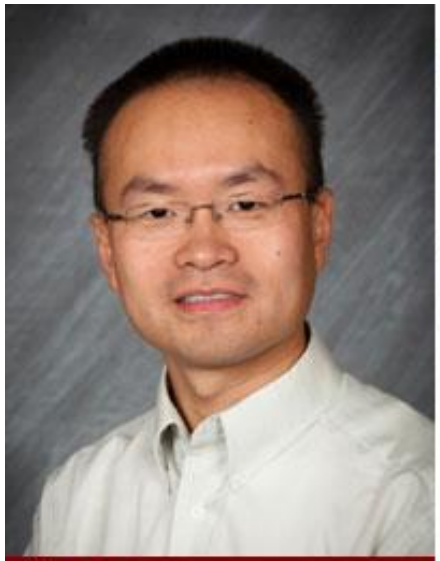
Wexner Medical Center

Data Integration

- **Integrative genomics / trans-omics approach**



Team



Huang

Machiraju

Jeff Baumes, Kitware

Jie Zhang

David Manthey, Kitware

dical Center

Leveraging

- NCI CPTAC Contract
  - Integrate proteomics data from CPTAC project
  - High performance computing (GPU and cluster)

Catalyurek

HPC

Mallick

Proteomics

NATIONAL CANCER INSTITUTE

CLINICAL PROTEOMIC TUMOR ANALYSIS CONSORTIUM

OHIO STATE Wexner Medical Center

4

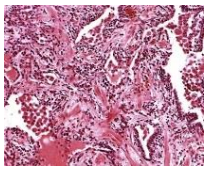
Tasks

Aim 1 – Develop software libraries for integrative genomics in cancer research, specifically for ***integrating genomic, histological images and clinical data for cancer biomarker discovery and subtyping***.

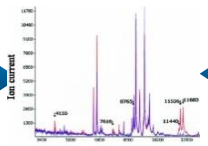
Aim 2 – Develop an integrative and expandable open source platform for *managing, analyzing, and integrating multiple data types* in integrative genomics for cancer with ***visual analytic capabilities*** for cancer biomarker discovery.

Aim 3 – Test the completed ***software platform*** with cancer systems biology studies and build ***an ecosystem based on the open source framework for integrative genomics*** and in particular for imaging genomics in cancer.

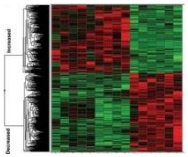
From Correlation to Integration



Pathology



Proteome

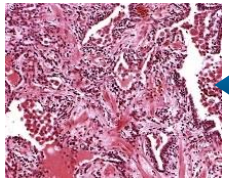


Transcriptome

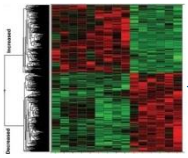
Correlative Study

- Triple Negative Breast Cancer
- Breast Cancer Proteomics

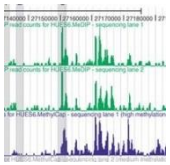
Applications



Pathology



Transcriptome

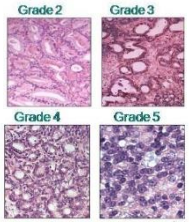


Epigenome

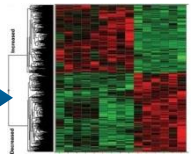
Model-based Study

- Lung Adenocarcinoma

Applications



Clinical Attributes



Transcriptome

Integrative Clustering

Breast Cancer Patient Stratification

- A two-step algorithm
- Molecular regularized algorithm

Applications

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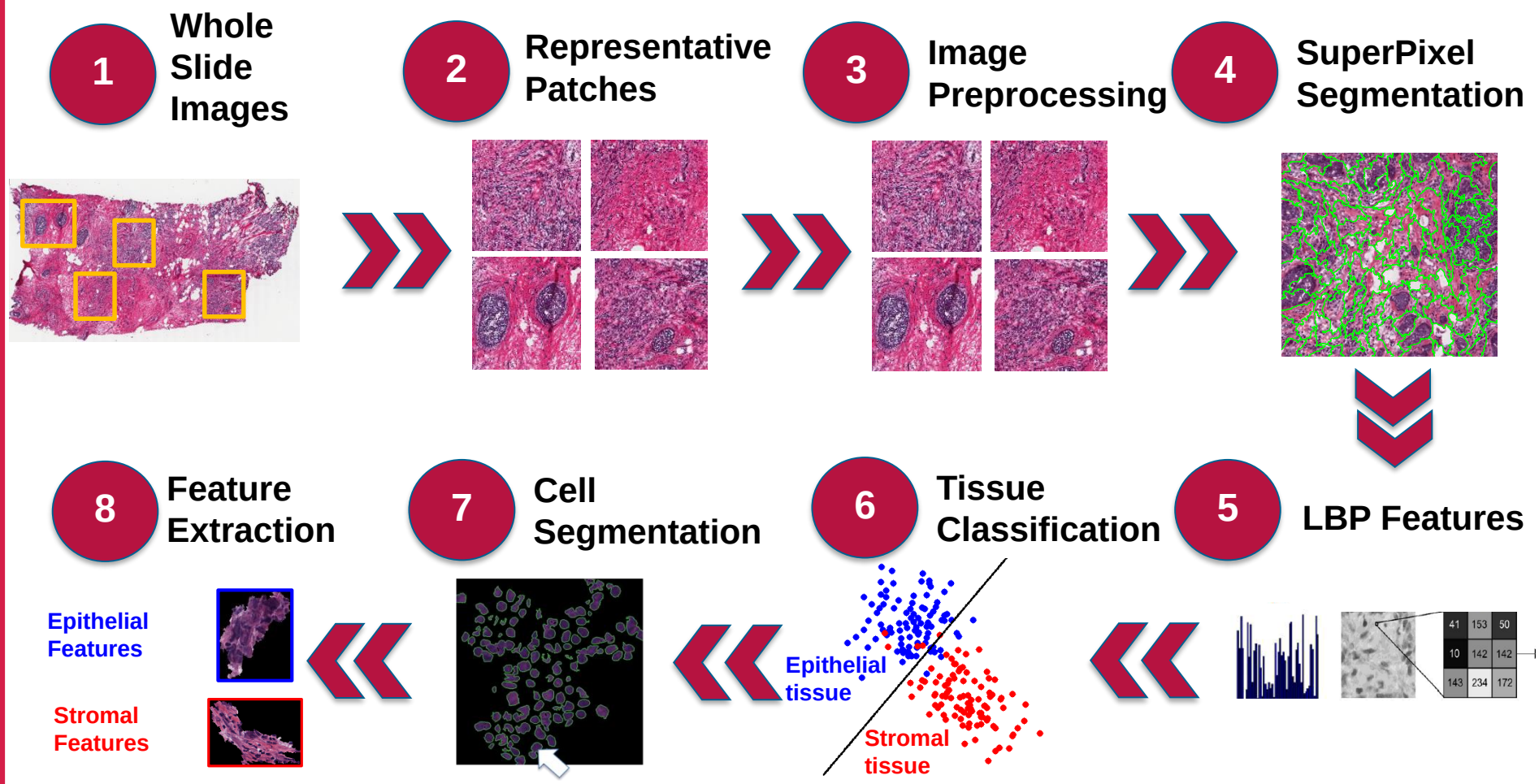
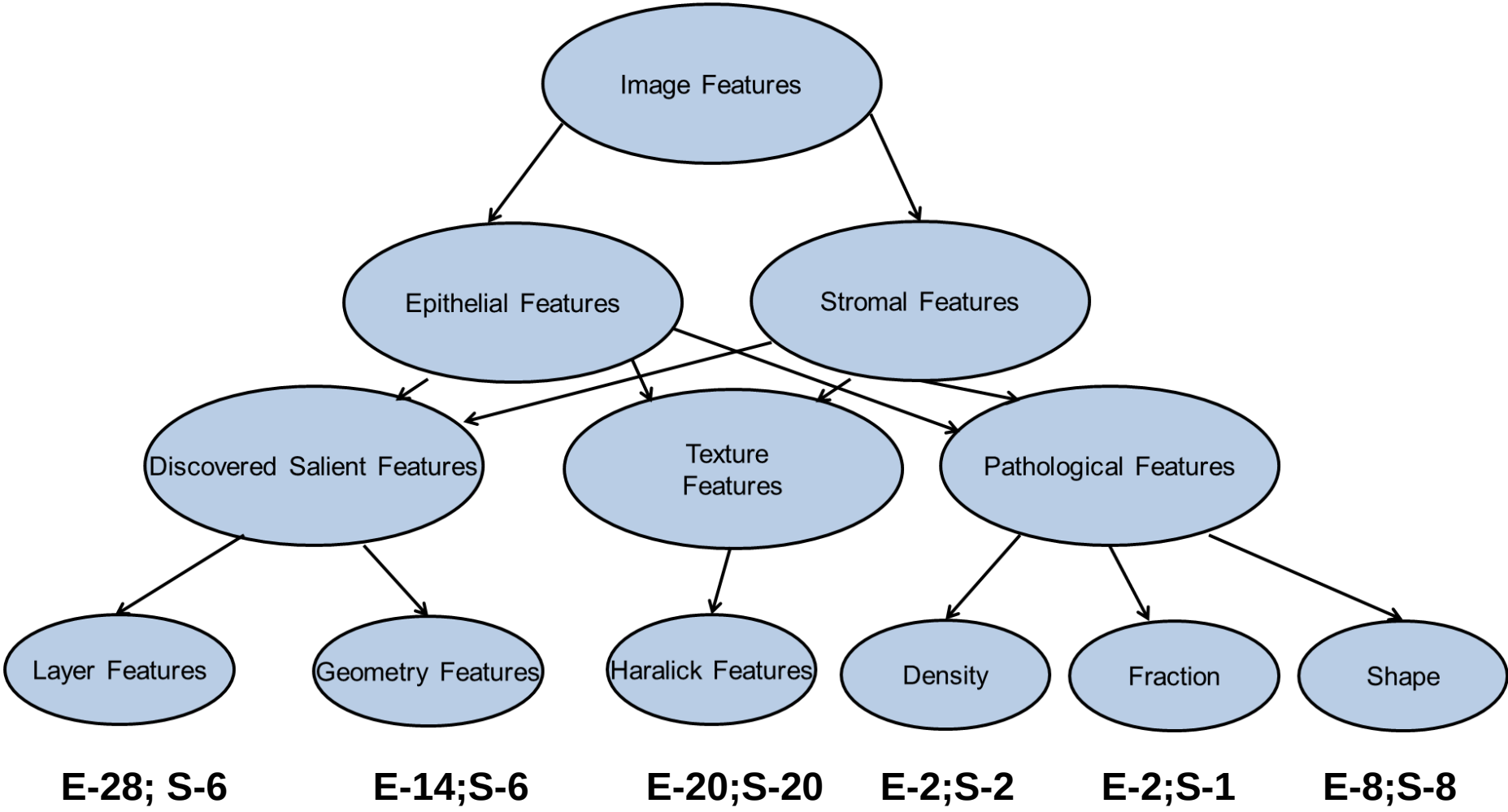
Pipeline Overview



Feature Extraction



E:epithelial features;S:stromal features

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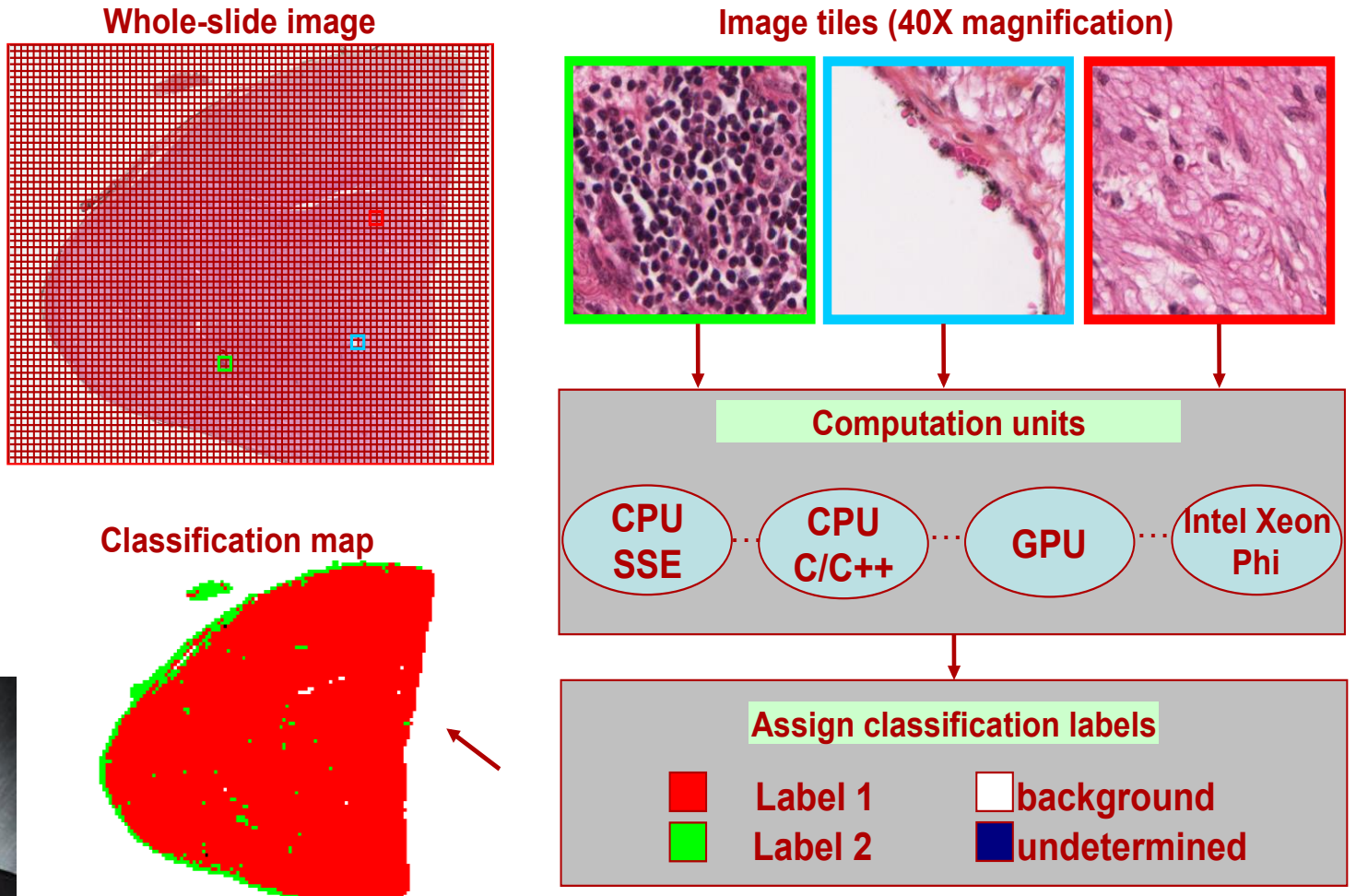
Image Analysis



Catalyurek

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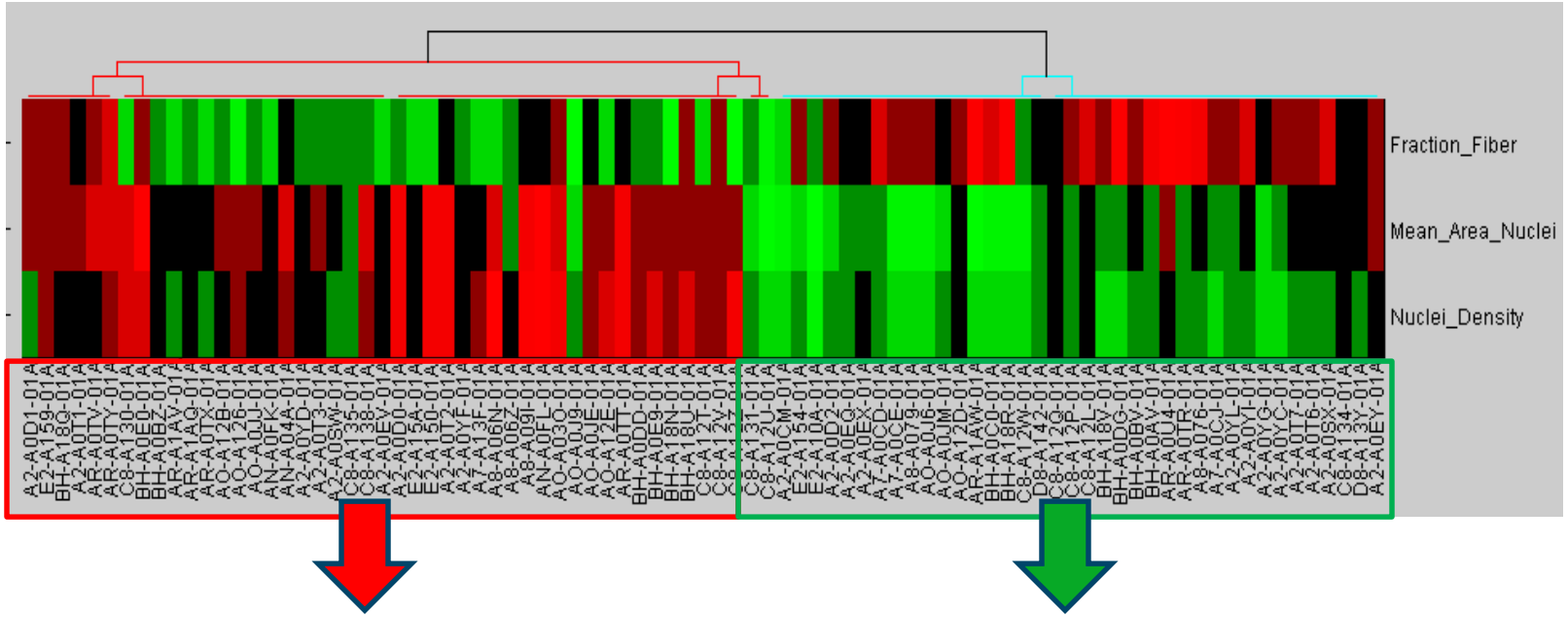
Patient Stratification on Morphology



Hierarchical clustering of breast cancer patients based on imaging features.

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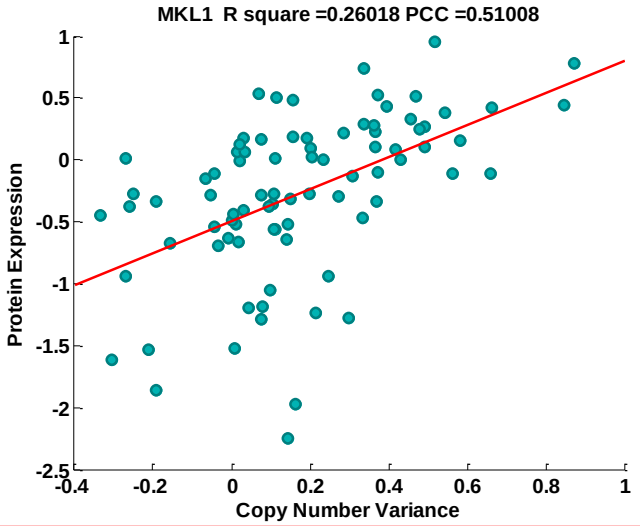
Associated Protein Co-Expression Network

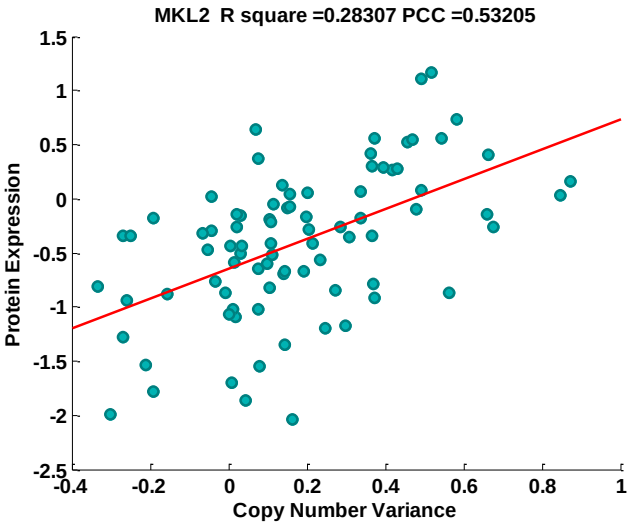
- Identified 124 protein co-expression networks
- 4 protein networks differentially expressed

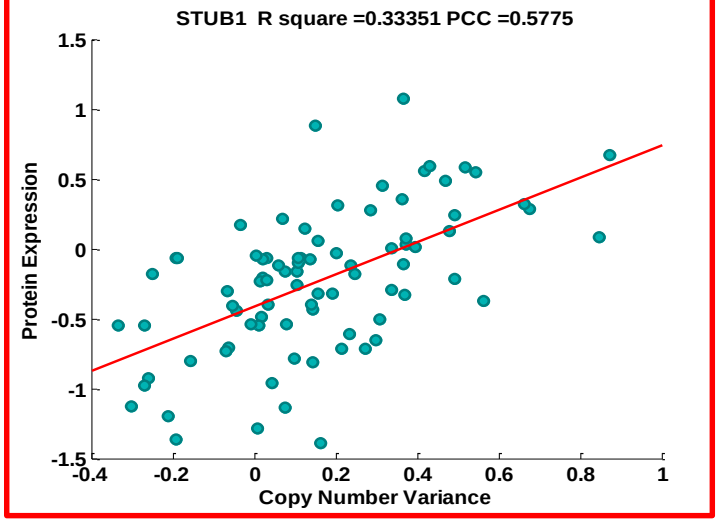
Protein Networks	Proteins in the Networks	Cytoband	pValue	Enriched Cytobamds	Top GO Molecular Functions (pValue)	Note
1	MYOCD	17p11.2	3.880E-2	16p13 P – value = 2.170E-5	smooth muscle cell differentiation(8.184 E-7); muscle cell differentiation(1.889 E-4); regulation of transforming growth factor beta receptor signaling pathway.	Enriched in 16q13
	MKL1	22q13	5.986E-3			
	MKL2	*16p13.12*	2.306E-3			
	FLYWCH2	*16p13.3*	2.170E-5			
	CISD3	17q12	1.439E-1			
	HN1L	*16p13.3*	2.170E-5			
	STUB1	*16p13.3*	2.170E-5			
	SUCLG1	2p11.2	1.536E-2			

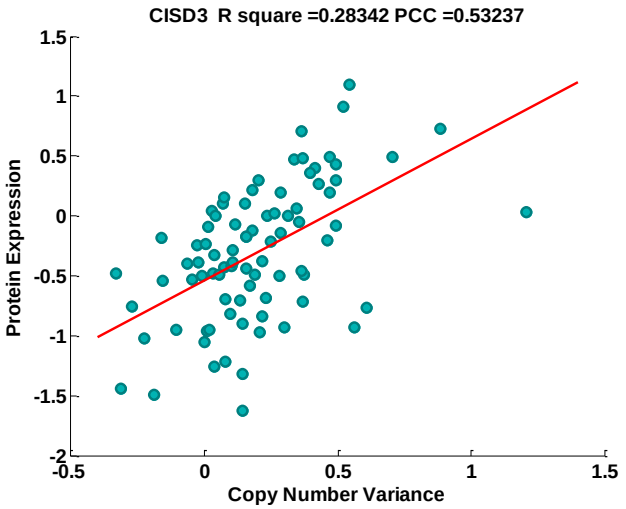
DNA Copy Number Variance

Protein Networks	Proteins in the Networks
1	MYOCD
	MKL1
	MKL2
	FLYWCH2
	CISD3
	HN1L
	STUB1
	SUCLG1









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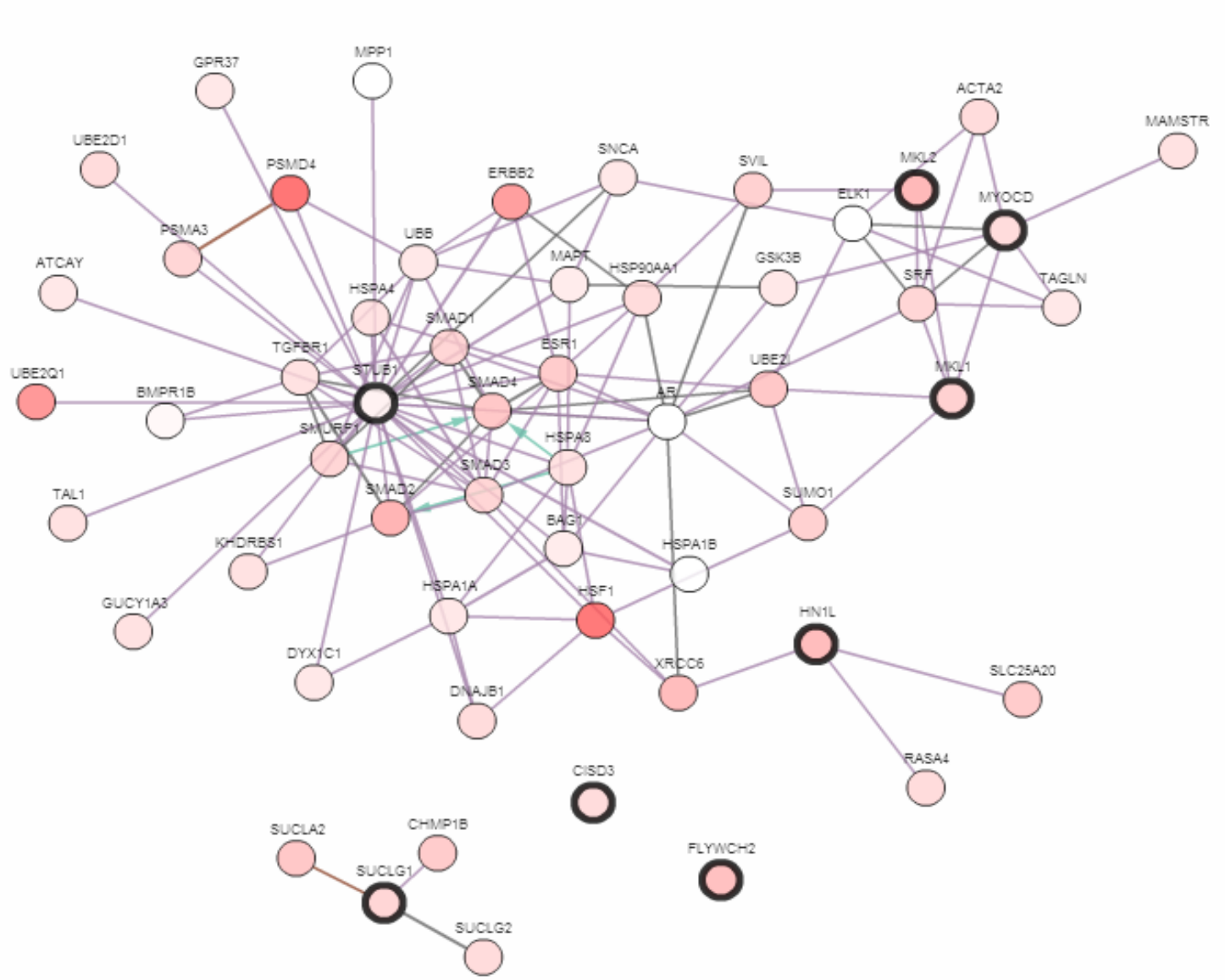
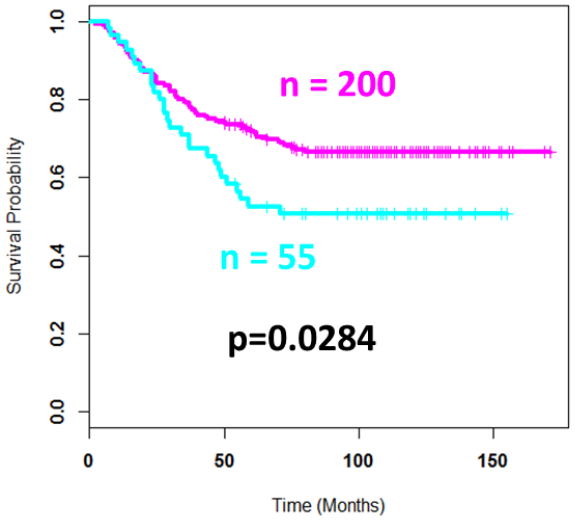
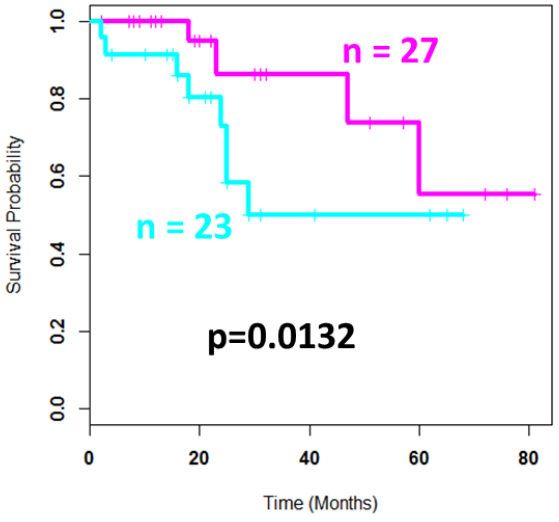
STUB1 gene as a hub gene



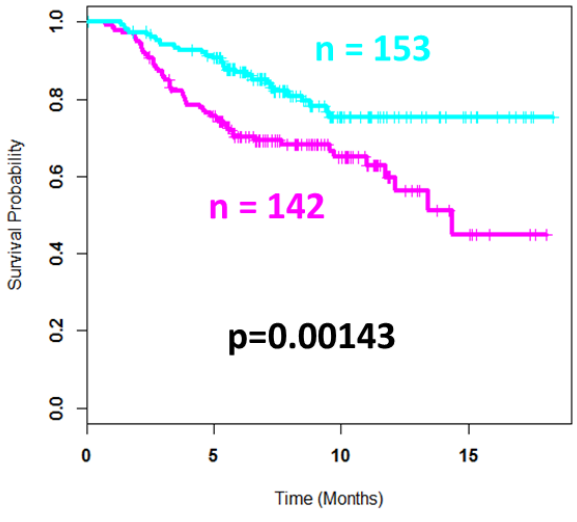
Prognosis Validation



A



B



C

Wang Perou NKI

Kaplan–Meier survival curves of prognostic model on multiple public breast cancer datasets. From left to right: Wang, Perou and NKI data respectively.

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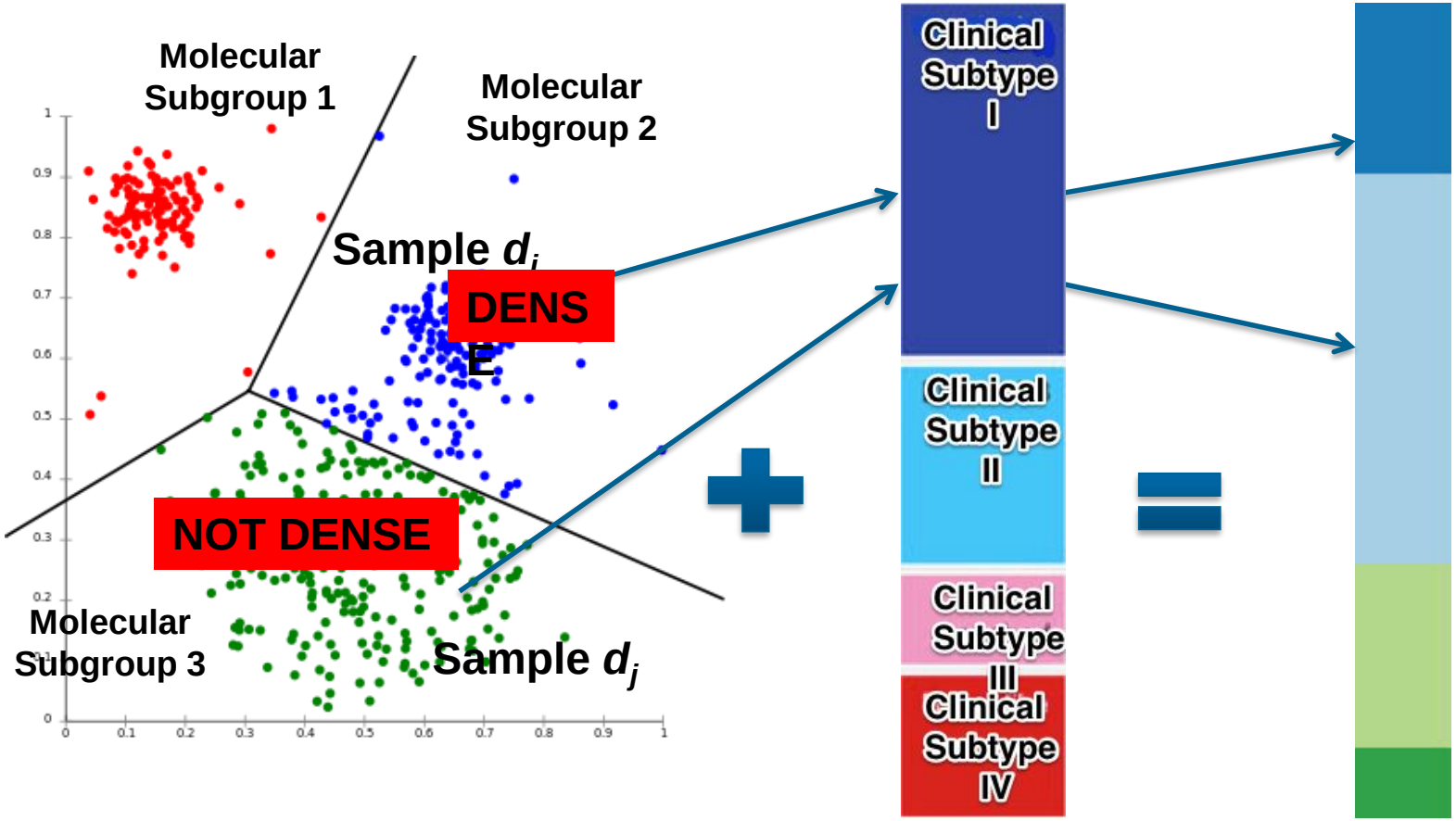
Concept



Wang et al, Methods, 2013

The Algorithm

Algorithm 1: Molecular Regularized Consensus Patient Stratification

Data: Similarity Matrix $\widetilde{S}$, Molecular Density Weight Matrix W, the number of clusters in final consensus k, MaxIter, precision ϵ

Result: Cluster indicator matrix U.

initialize $\widetilde{U}^{(1)} > 0$, $t = 1$, $\Delta = +\infty$;

while $t < MaxIter$ *and* $\Delta > \epsilon$ **do**

Update $\widetilde{U}_{ij}^{(t+1)} \leftarrow \widetilde{U}_{ij}^{(t)} \sqrt{\frac{[(W \circ S)\widetilde{U}D]_{ij}}{[(W \circ \widetilde{U}D\widetilde{U}^T)\widetilde{U}D]_{ij}}}$;

Update $D_{ij}^{(t+1)} \leftarrow D_{ij}^{(t)} \sqrt{\frac{[\widetilde{U}^T(S \circ W)\widetilde{U}]_{ij}}{[\widetilde{U}^T(\widetilde{U}D\widetilde{U}^T \circ W)\widetilde{U})]_{ij}}}$;

Compute $\Delta = \|\widetilde{S} - W \circ (\widetilde{U}D\widetilde{U}^T)\|_F^2$;

$t = t + 1$;

end

Discretize $\widetilde{U}$ to binary membership matrix.

Algorithm 1: Molecular Regularized Consensus Patient Stratification

Wang C, Machiraju R, Huang K, *Methods*, 2014

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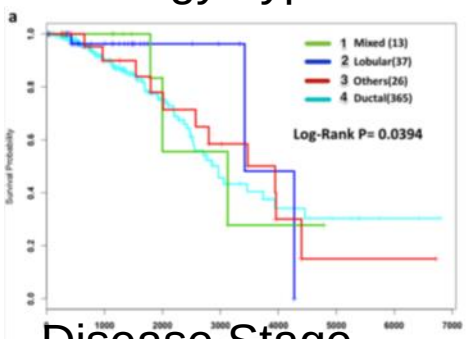
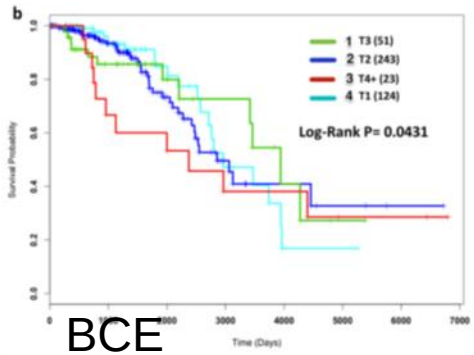
Prognosis

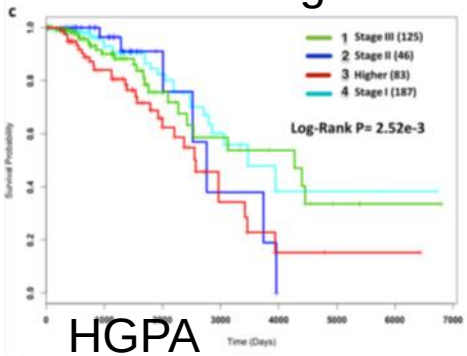
Histology Type



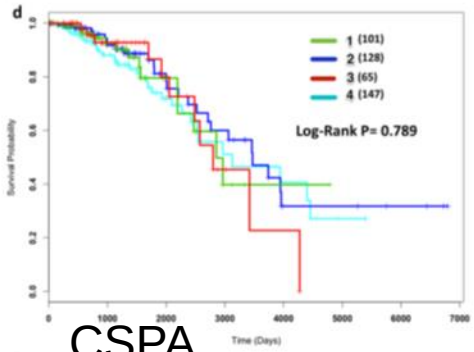
Tumor Grade



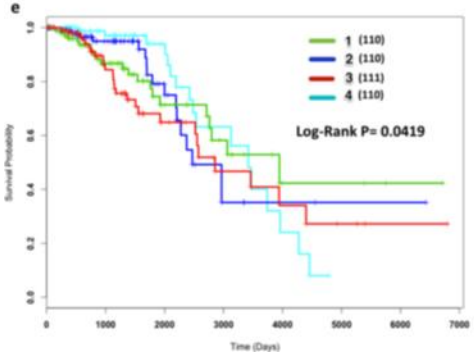
Disease Stage



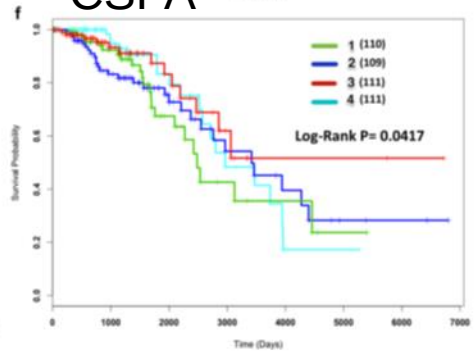
BCE



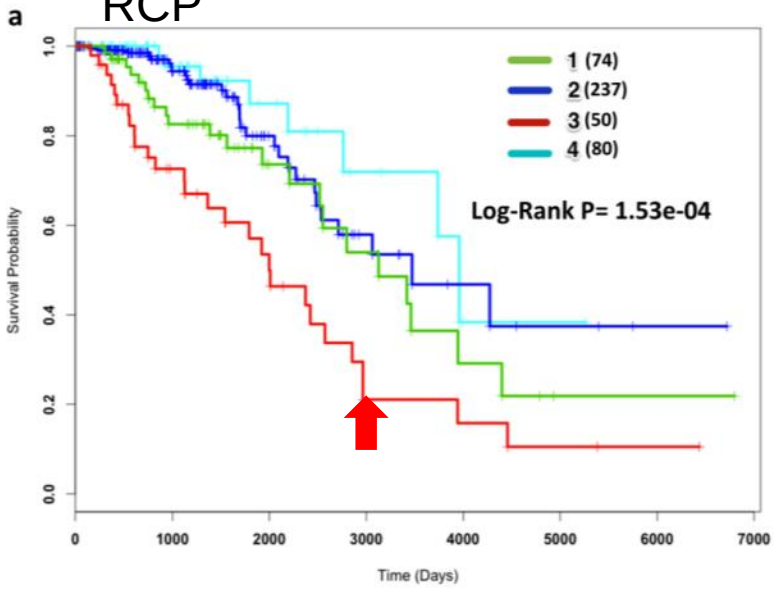
HGPA



CSPA



RCP



Wang C, Machiraju R, Huang K, *Methods*, 2014

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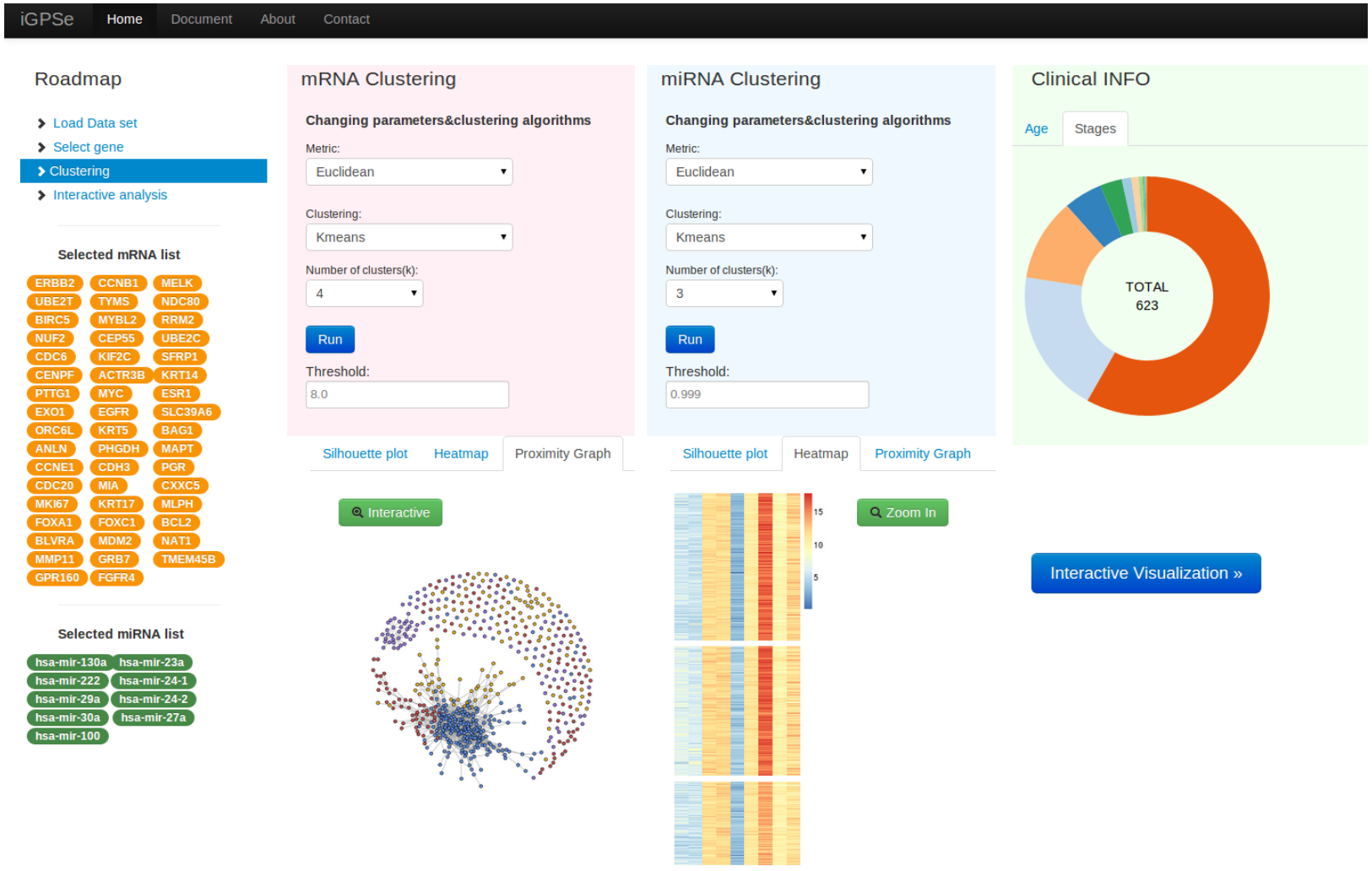
Visualization



Ding et al, BMC Bioinformatics, 2014

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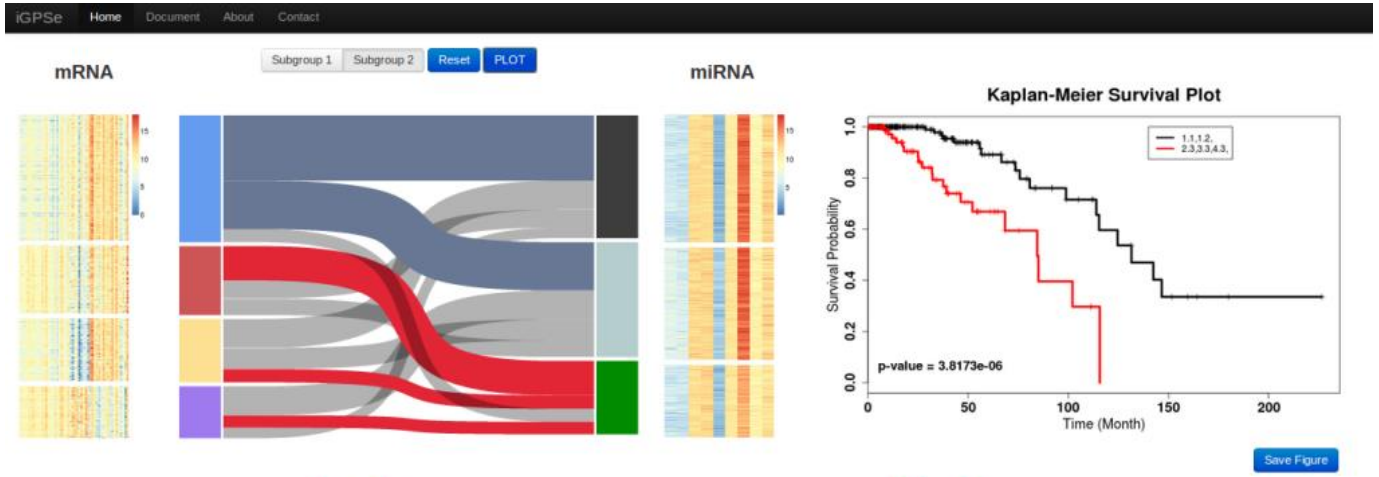
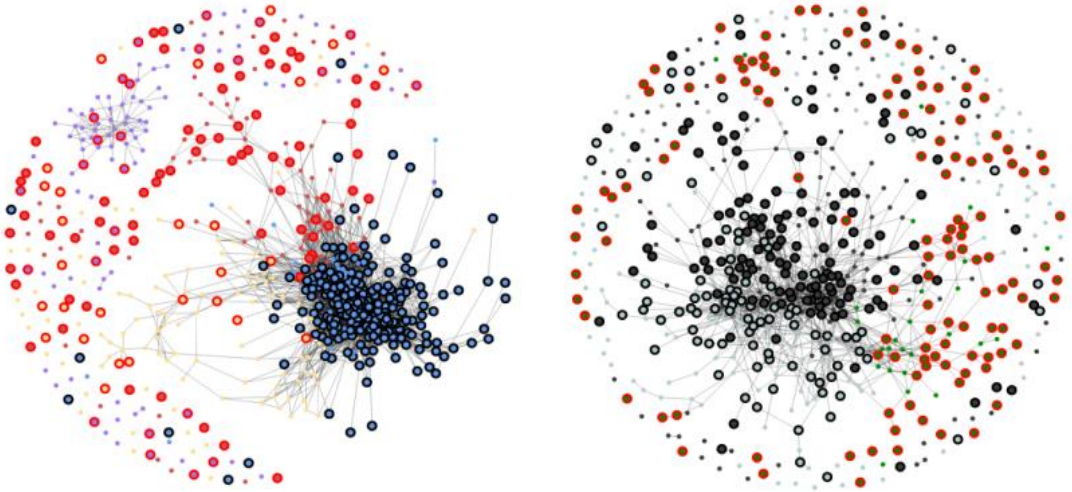
Interactive Patient Stratification





Ding et al, BMC Bioinformatics, 2014

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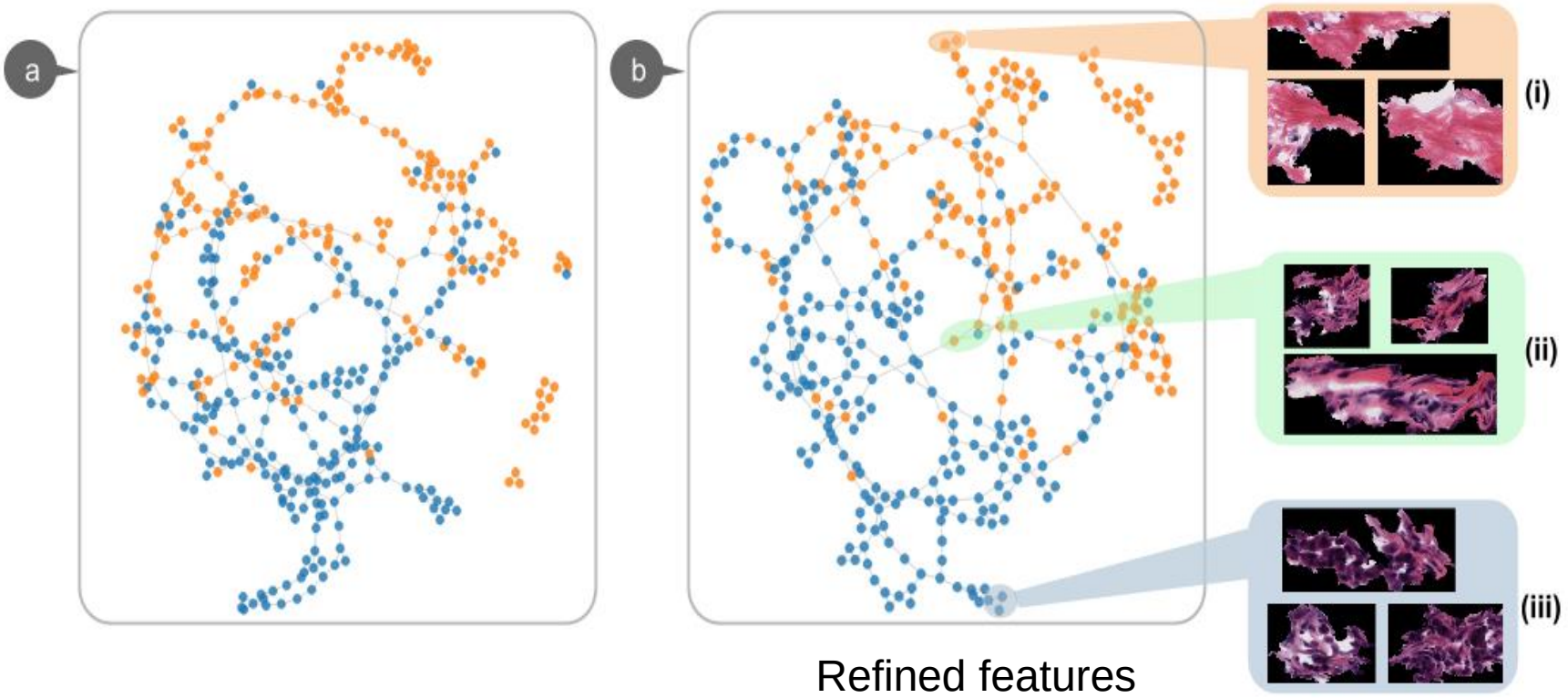
Graphie – Visual Analytics of Imaging Features



Refined features

Ding *et al. BMC Bioinformatics* 2015, **16**(Suppl 11):S10
http://www.biomedcentral.com/1471-2105/16/S11/S10

BMC Bioinformatics

RESEARCH Open Access

GRAPHIE: graph based histology image explorer

Hao Ding[1], Chao Wang[3], Kun Huang[2*], Raghu Machiraju[1*]

From 5th Symposium on Biological Data Visualization
Dublin, Ireland. 10-11 July 2015

biovis

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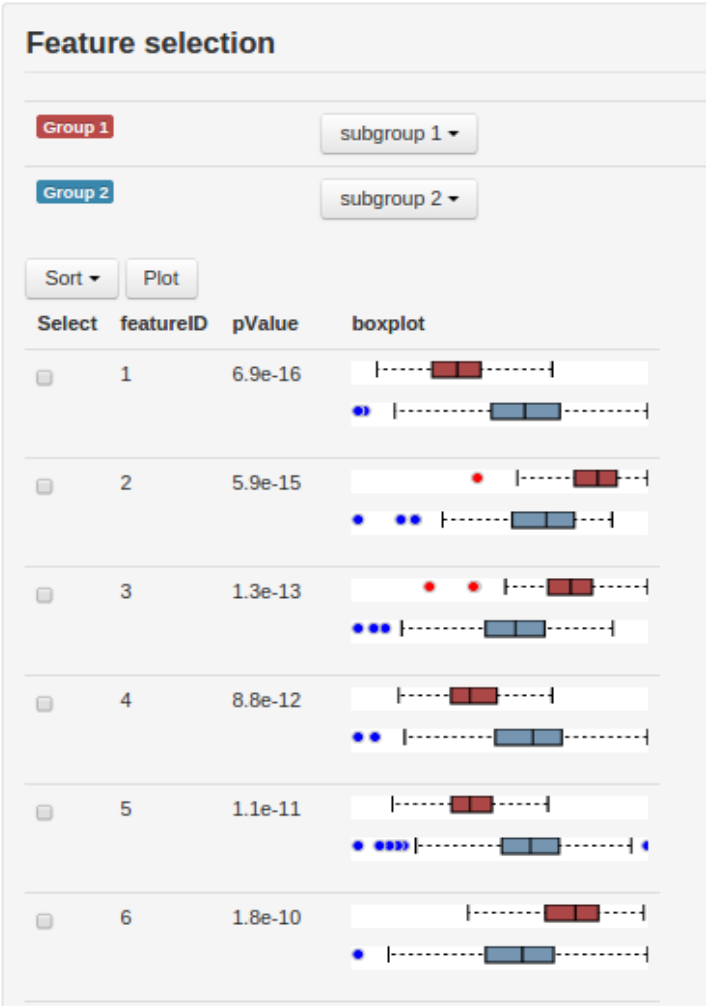
Graphie –Feature Selection

Examine feature distinctiveness for groups of images.

- Student's t-test
- Boxplots
- Re-generate with selected feature subset



biovis

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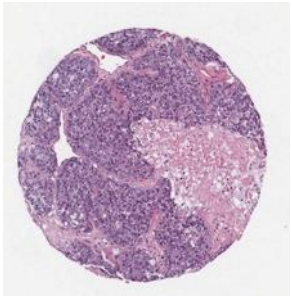
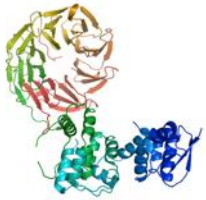
Combining Graphie, iGPSE, & SUMO

Histology images



Genome

Epigenome



Proteome

Subtype Analysis

Integrative Biomarkers

Molecular behaviours

...

biovis

http://osumo.org/

Kitware

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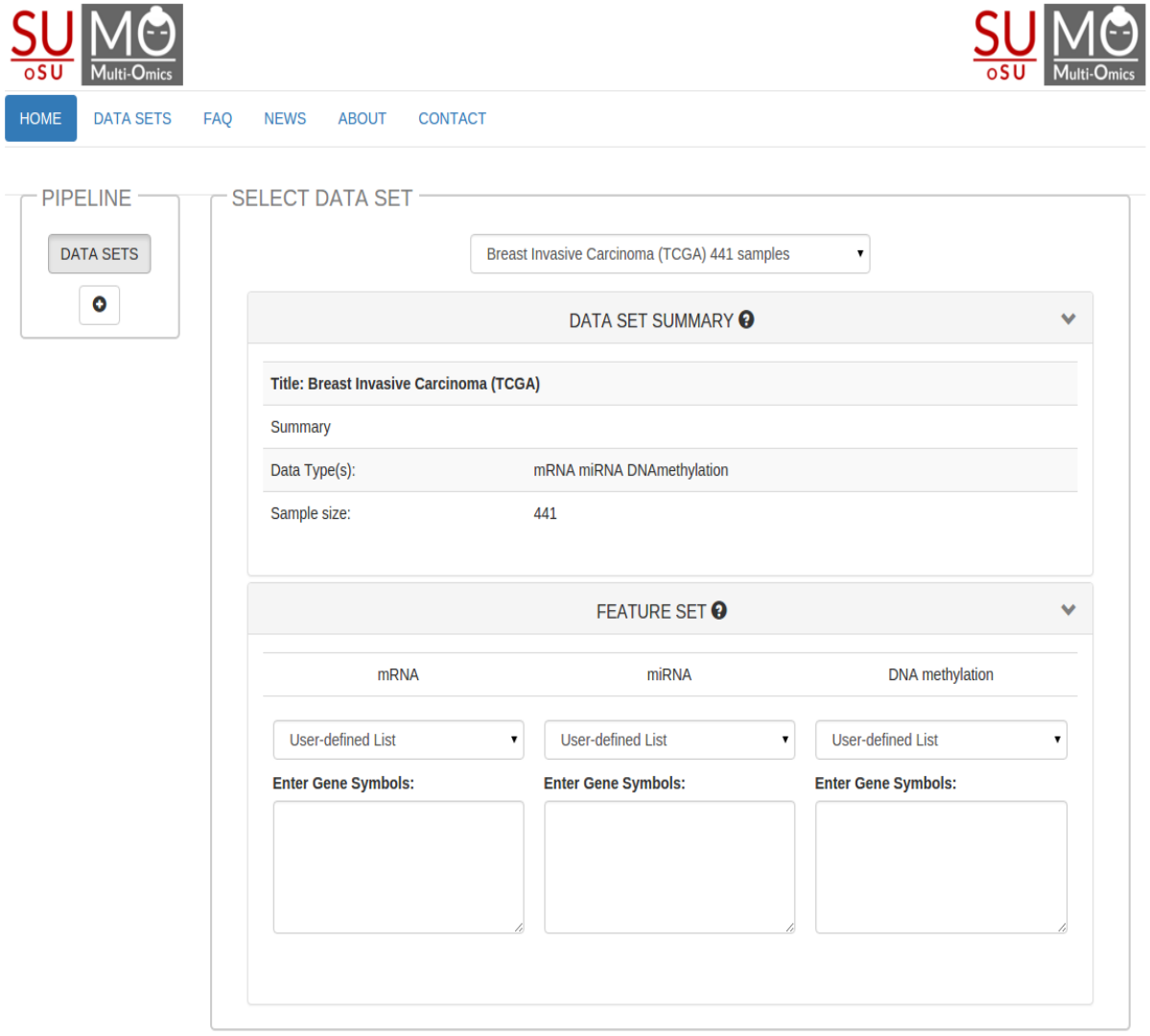
(O)SUMO



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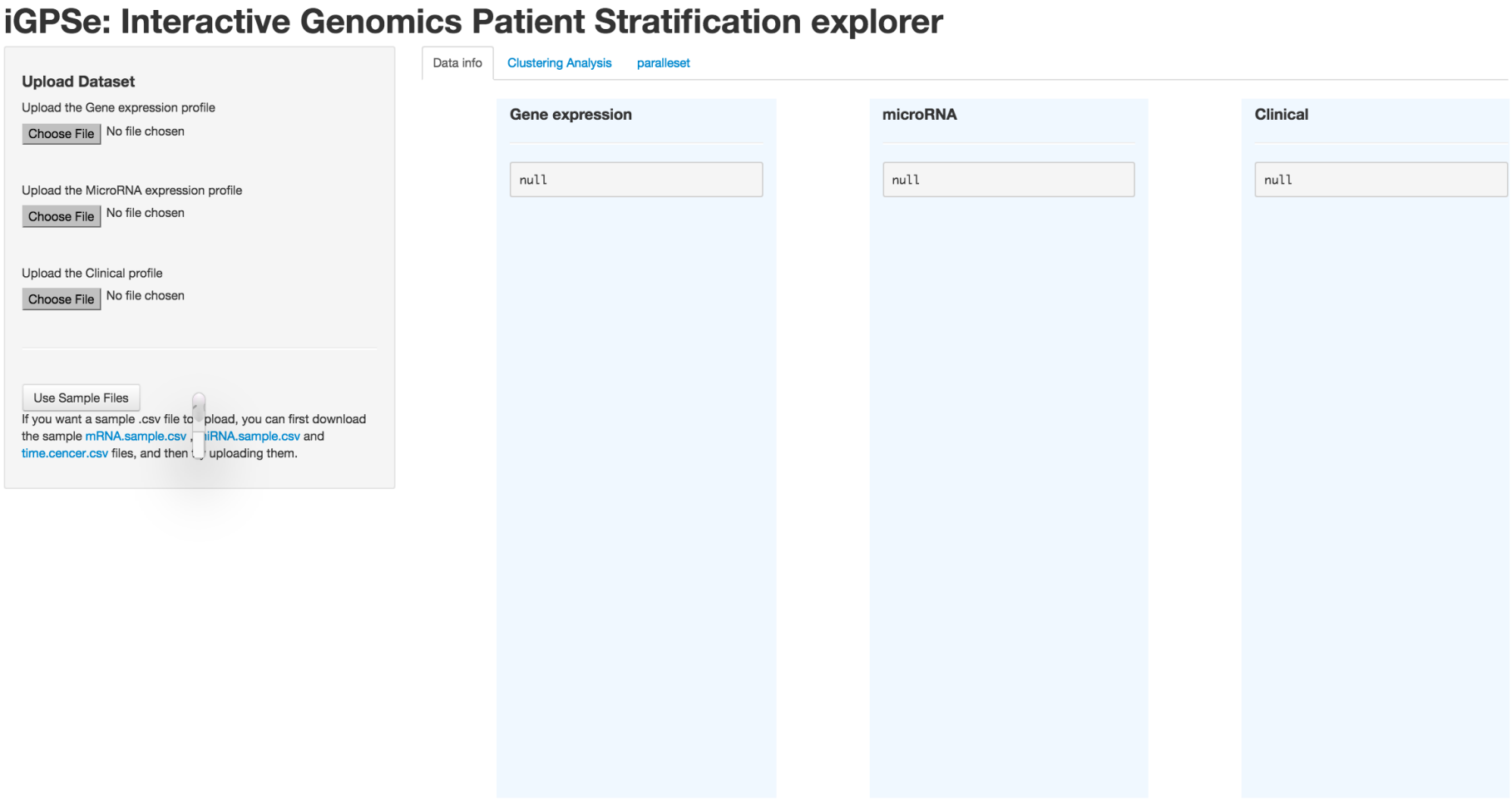
23

State of (O)SUMO



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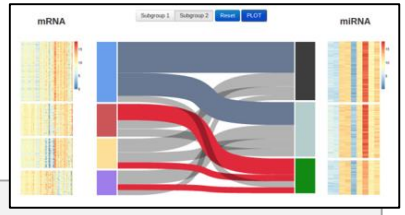
SUMO Architecture

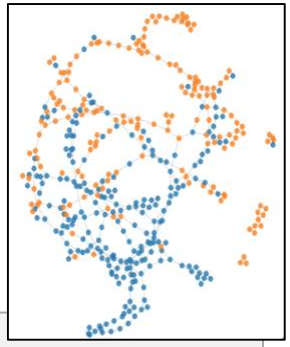
Adding workflows

JSON metadata for tasks

R/Python source



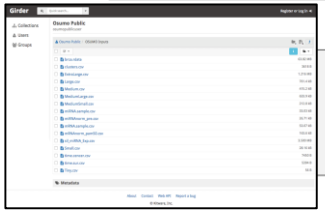
iGPSe



Graphie

...

SUMO (workflow management, UI)



Girder (authentication, data management)

Girder Worker (analysis execution)

```
blur_image = {
   'inputs': [
      {'name': 'blur_input', 'type': 'image', 'format': 'pil'},
      {'name': 'blur_radius', 'type': 'number', 'format': 'number'}
   ],
   'outputs': [{'name': 'blur_output', 'type': 'image', 'format': 'pil'}],
   'script': '''
from PIL import ImageFilter
blur_output = blur_input.filter(ImageFilter.GaussianBlur(blur_radius))
'''
}
```

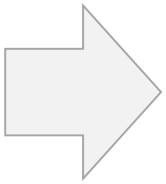
Basic Workflow - Silhouette Plot

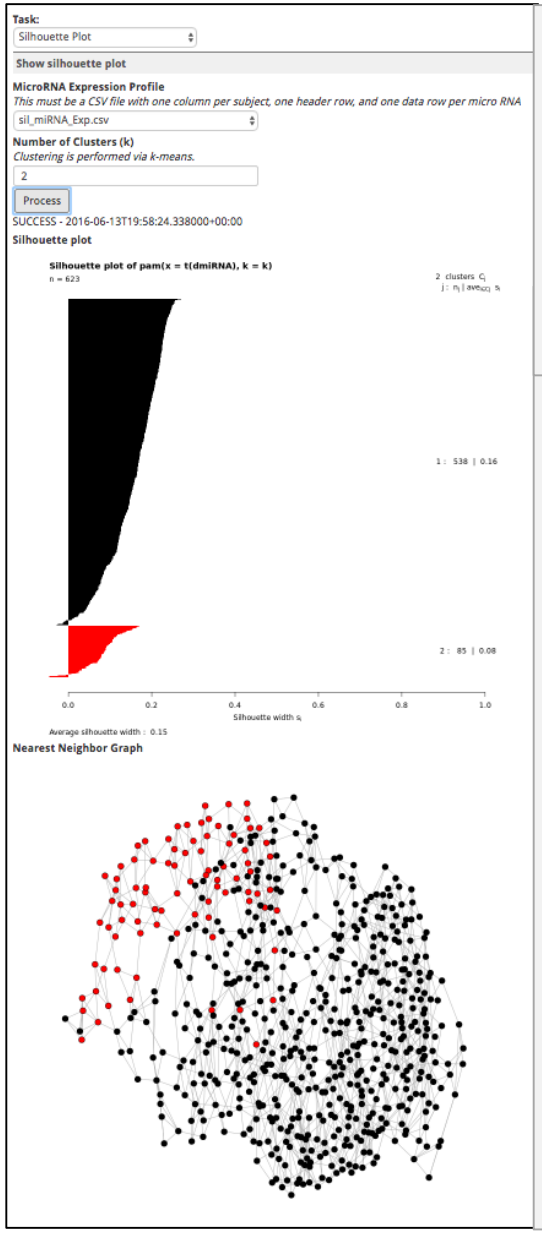
Input / output descriptions

```
---

name: "Silhouette Plot"

description: "Show silhouette plot"

fallbackUser: "osumopublicuser"

task:
  name: silhouette
  mode: r

  script: >
      @include(silhouette.r)

  inputs:
    - name: sil_input_path
      type: string
      format: text
    - name: silhouette_clusters
      type: number
      format: number

  outputs:
    - name: dataplot1
      target: filepath
      type: image
      format: png
    - name: dataplot2
      target: filepath
      type: image
      format: png

inputs:
  - key: sil_input_path
    name: "MicroRNA Expression Profile"
    description: "miRNA data."
    type: file
    subtype: rdata
    preferredNames: "^sil_.*csv$"
    notes: "This must be a CSV file with one column per subject, one hea
  - key: silhouette_clusters
    name: "Number of Clusters (k)"
    description: "The number (k) of clusters used in calculations"
    type: integer
    default: 2
    format: number
    notes: "Clustering is performed via k-means."

parameters:
  - key: targetFolderId
    name: "Target Folder"
    type: folder
    input: false

outputs:
  - key: dataplot1
    show: image
    parentType: "folder"
    parent: "parameter:targetFolderId"
    name: "dataplot1.png"
    dataType: "image"
    dataFormat: "png"
    displayName: "Silhouette plot"
  - key: dataplot2
    show: image
    parentType: "folder"
    parent: "parameter:targetFolderId"
    name: "dataplot2.png"
    dataType: "image"
    dataFormat: "png"
    displayName: "Nearest Neighbor Graph"
```

R script

```
# Read Data
dmiRNA = read.csv(sil_input_path)

#clustering
color <- palette()
require(cluster)
k <- silhouette_clusters
cl <- pam(t(dmiRNA),k)
si <- silhouette(cl)

localdir = Sys.getenv('tempdir', unset=tempdir())
dataplot1 = tempfile('plot', tmpdir=tempdir, fileext='.png')
png(filename=dataplot1, width=800, height=800, units="px")

plot(si, col=color[1:k], border=NA) # with cluster-wise coloring

dev.off()


# plot the graph
require(ecod)
require(igraph)
ADJmiRNA <- as.matrix(dist(t(dmiRNA)))
g <- nng(ADJmiRNA, k=3)
g <- as.undirected(g)
V(g)$color <- color[cl$clustering]

localdir = Sys.getenv('tempdir', unset=tempdir())
dataplot2 = tempfile('plot', tmpdir=tempdir, fileext='.png')
png(filename=dataplot2, width=800, height=800, units="px", pointsize=8)

plot(g, vertex.size=3, layout=layout.kamada.kawai, vertex.label=NA)

dev.off()
```





Inputs

Any Girder-uploaded dataset, access controlled

Outputs

May be static R charts or interactive D3 plots

Outputs are stored in user's Girder space

al Center

2-Stage Workflow - iGPSe

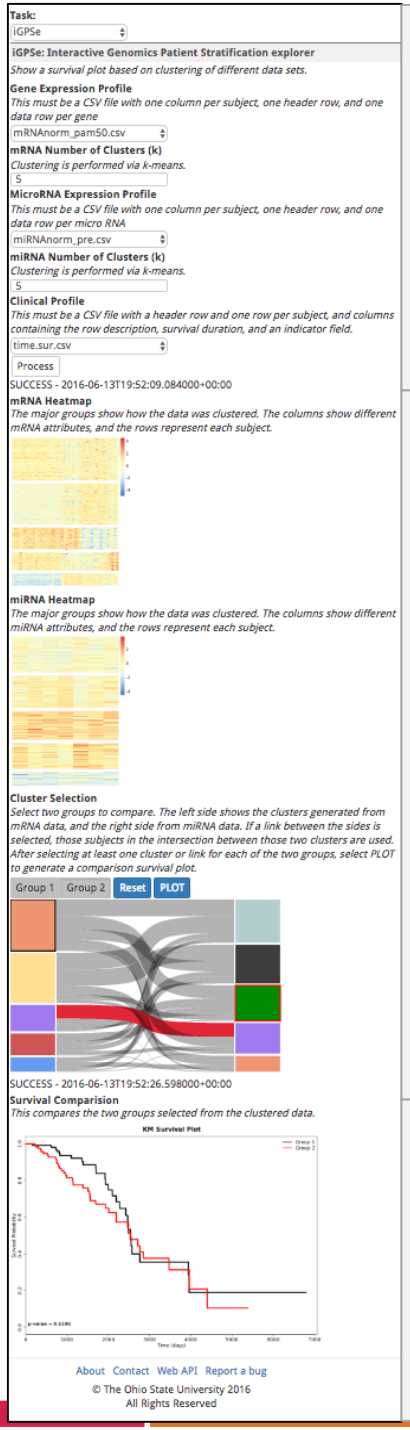
JSON metadata for Stage 1

R source for Stage 1

Workflow link between stages

JSON metadata for Stage 2

R source for Stage 2



Stage 1 Inputs

Genetic and clinical datasets

Stage 1 Outputs

Two static R cluster heatmaps

One interactive D3 set selection that serves as Stage 2 input

Stage 2 Output

Survivability plot for selected sets

SUMO

Initial application available at http://osumo.org

Plan for more machine learning algorithms (consensus learning, multiview learning) for data integration on SUMO

Pan-cancer study as driven application

We welcome

- ✧ Beta users
- ✧ Use cases and workflows to deploy
- ✧ Open-source contributionshttps://github.com/osumo/osumo

Demonstration

- https://www.youtube.com/watch?v=d96h4EnwRxY

More Comprehensive Workflow Proposed