Memorial Sloan Kettering
Cancer Center

survClust: An Outcome Weighted Learning Approach for Identifying Clinically Relevant Patient Subgroups from Large-scale Sequencing Data

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Motivation

- TCGA generated multidimensional omics data across 10,000 tumors across 33 tumor types
- The main TCGA studies primarily focused on molecular subtype analysis using unsupervised clustering
- We aim to develop a supervised learning approach for patient outcome weighted stratification

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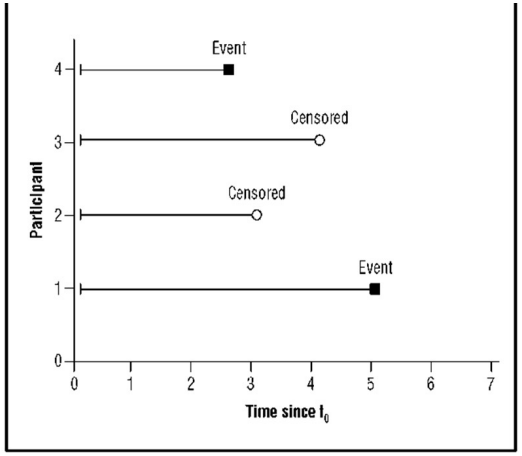
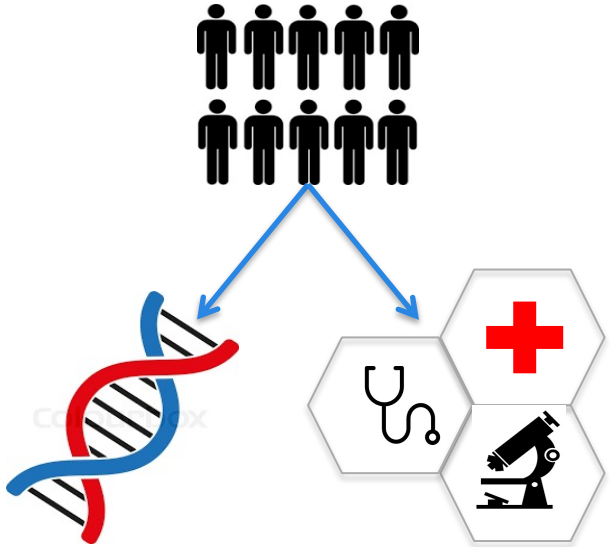


References:
1. Hoadley, Katherine A., et al. "Cell-of-origin patterns dominate the molecular classification of 10,000 tumors from 33 types of cancer." *Cell* 173.2 (2018): 291-304.

survClust



- DNA Methylation
- mRNA expression
- miRNA expression
- Copy Number
- Somatic Mutation
- Protein
- Mutation signature
- Single Cell Sequencing
- …

- Overall Survival
- Progression Free Survival
- Response (future work)

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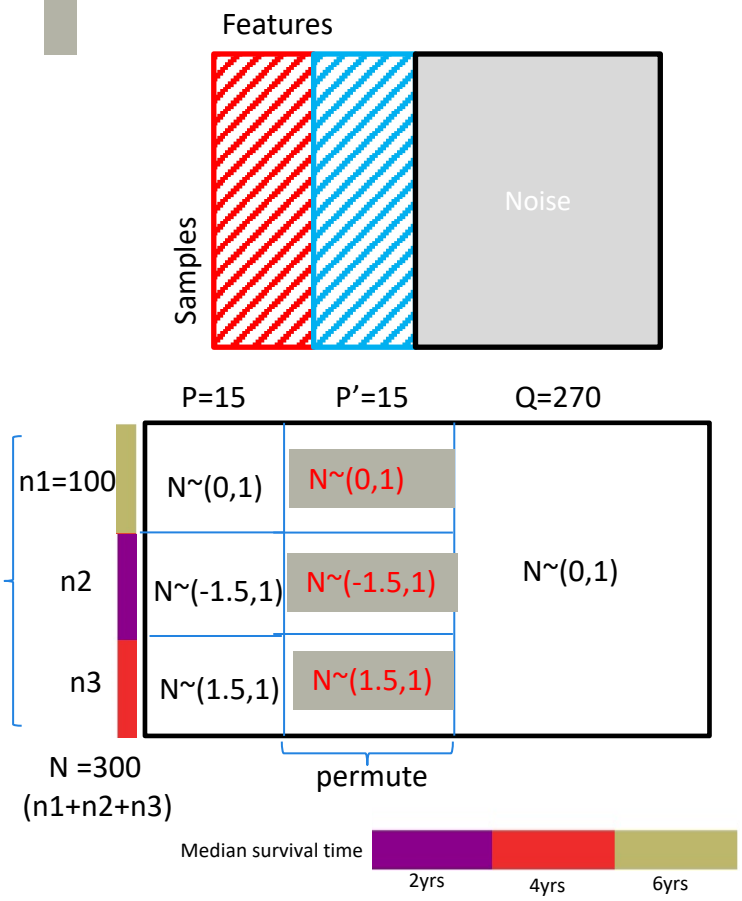
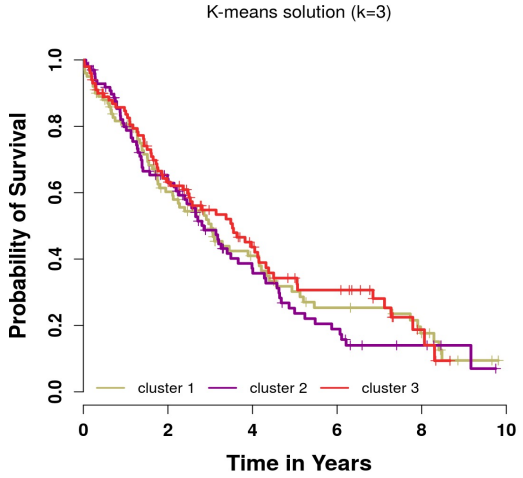
unsupervised vs supervised clustering via simulation

Typical data set

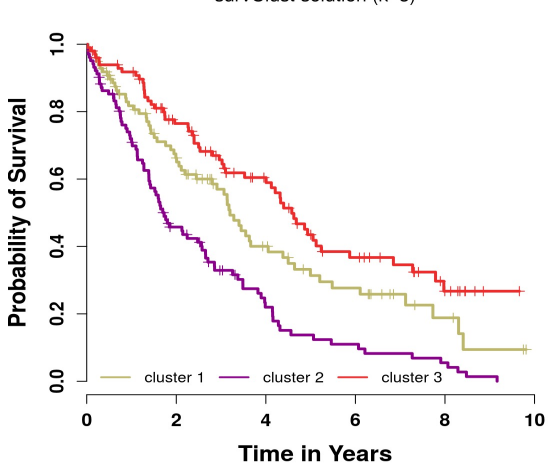


Unsupervised clustering solution*



	Cluster 1	Cluster 2	cluster 3
Truth Cluster 1	29	34	38
Truth Cluster 2	71	0	0
Truth Cluster 3	0	66	62

survClust solution



	Cluster 1	Cluster 2	cluster 3
Truth Cluster 1	0	0	100
Truth Cluster 2	0	100	0
Truth Cluster 3	100	0	0

* Unsupervised clustering solution was arrived by running *k-means* algorithm

survClust Workflow

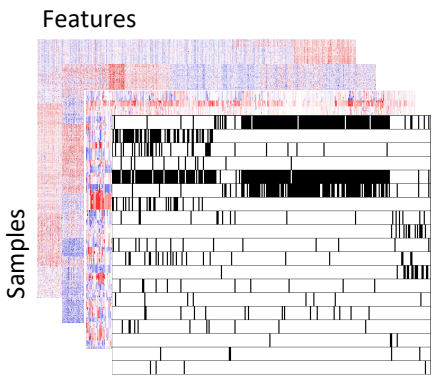
Raw Data → **getDist** → **combineDist** → **survClust**

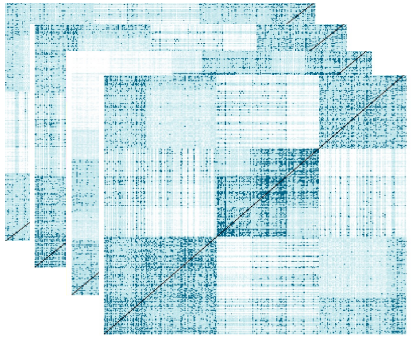
Various molecular platforms

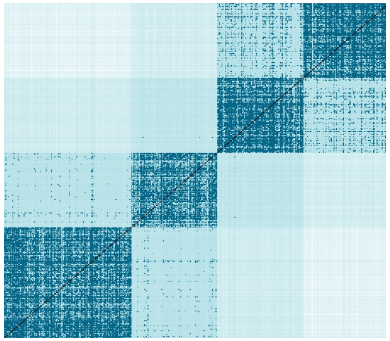
Weighted Distance Matrix

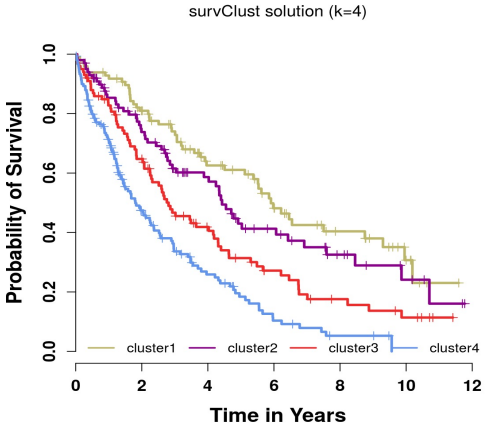
Integrated Distance Matrix

Cluster membership with survival difference





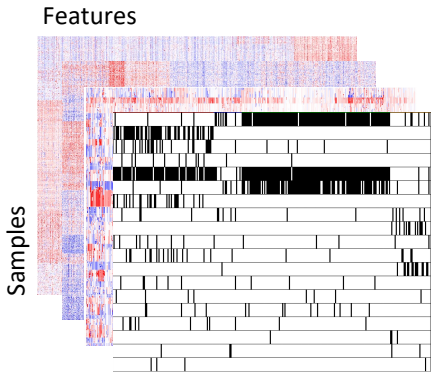




Step 1 – prepare input data

Raw Data

Various molecular platforms

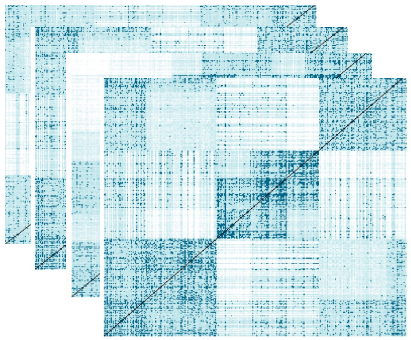


- Continuous data should be standardized across features (columns)
- This ensure that weights are interpretable.

Step 2- getDist

getDist

Weighted Distance Matrix



Consider a data type $\boldsymbol{X_m}$ (where, m=1, .., M data types) of varying samples(N_m) and features (p_m)

$\boldsymbol{a_p}$ and $\boldsymbol{b_p}$ are a pair of samples measured for p features

The weighted distance[1] –

$$d_w(\boldsymbol{a}, \boldsymbol{b}) = \sqrt{(\boldsymbol{a} - \boldsymbol{b})^T \boldsymbol{W} (\boldsymbol{a} - \boldsymbol{b})}$$

$$\boldsymbol{X'} = \boldsymbol{X} * \boldsymbol{W}^{1/2}$$

$$d_w(\boldsymbol{a'}, \boldsymbol{b'}) = d_w(\boldsymbol{b'}, \boldsymbol{a'}) = \sqrt{\sum_{j=1}^{p} (a_j' - b_j')^2}$$

- respectively, $\boldsymbol{W}$ is a $p \times p$ diagonal weight matrix with $\boldsymbol{W} = diag\{w_1, \ldots, w_p\}$.

- The scaling factor or weights w_p are obtained by fitting a univariate cox proportional model for each p –

$$h(t|\boldsymbol{x_j}) = h_o \times \exp(\boldsymbol{x_j^T} * \beta)$$

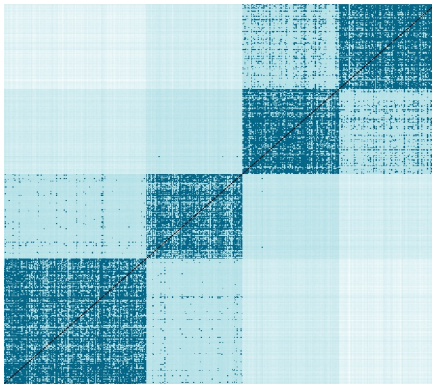
where j is the j[th] feature from $1 \ldots p$ features. t represents the survival time, $h(t)$ is the hazard function determined by p covariate, coefficient β determines the impact of covariate also known as w_p, and h_o is defined as baseline hazard.

References:
1. Xing, Eric P., et al. "Distance metric learning with application to clustering with side-information." *Advances in neural information processing systems*. 2003.

Integrate and perform survClust

combineDist

Integrated Weighted Distance Matrix



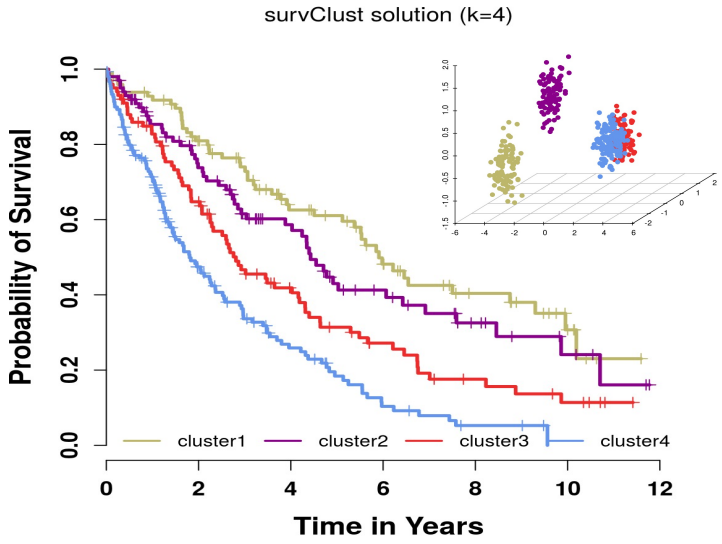
$$I_w = \frac{\sum_{m=1}^{M} D_m}{M}$$

Where,

D_m = weighted distance matrix of mth data type

survClust

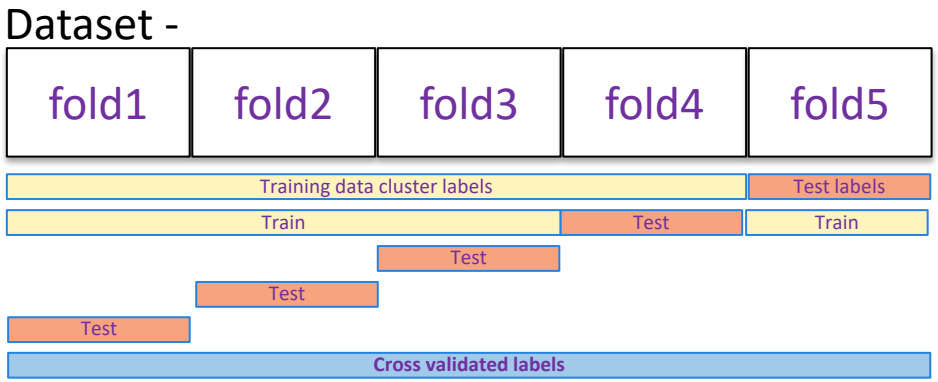
Cluster membership with survival difference



survClust then projects the integrated and weighted distance matrix in a lower dimensional space via multidimensional scaling and clustering sample points into subgroups via the K-means algorithm.

Overfitting is avoided by cross-validation

- We did 5-fold cross validation for 50 rounds of cross validation to arrive at a consolidated solution for a particular k cluster



Concludes one round of cross-validation

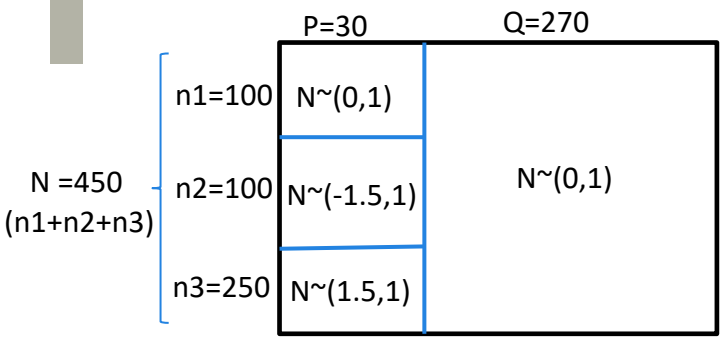
- Perform 50 such rounds – with random 5 splits of the data
- Collect 50 cross validated survClust predicted class labels for each k = 2 to 7

An example of cross validation and how to pick k

simulate two data types –

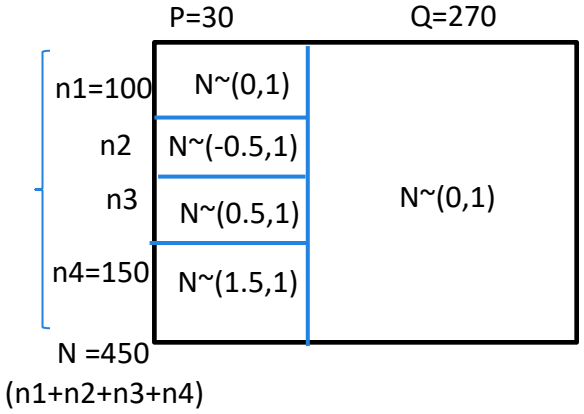
data type 1

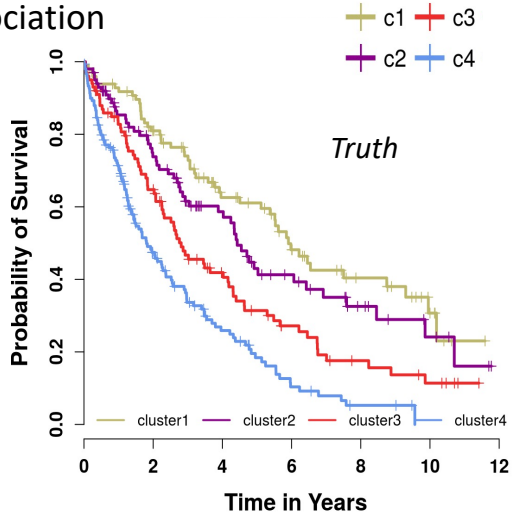
strong clusters, weak survival association

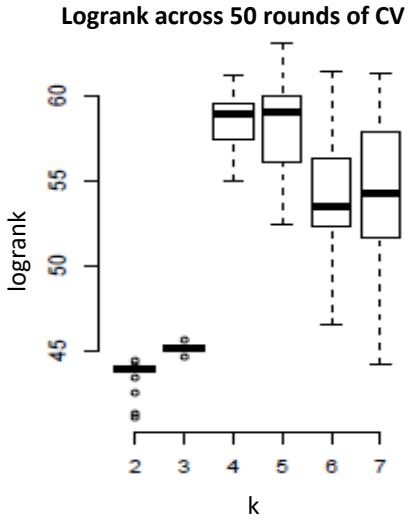


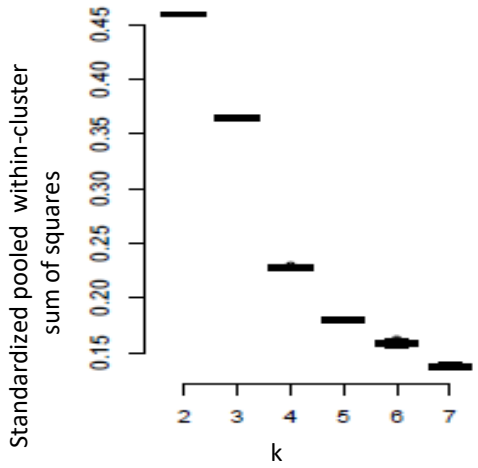
data type 2 –

weak clusters, strong survival association





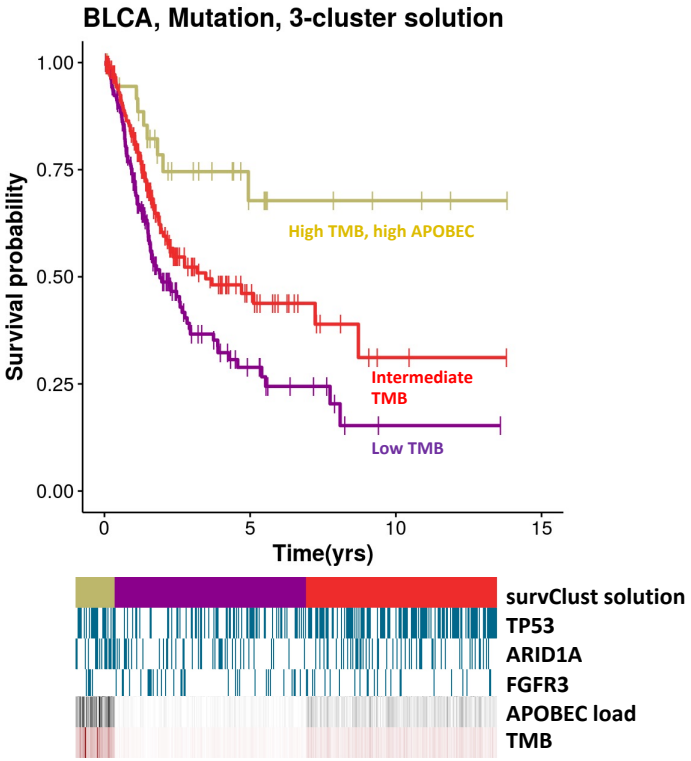




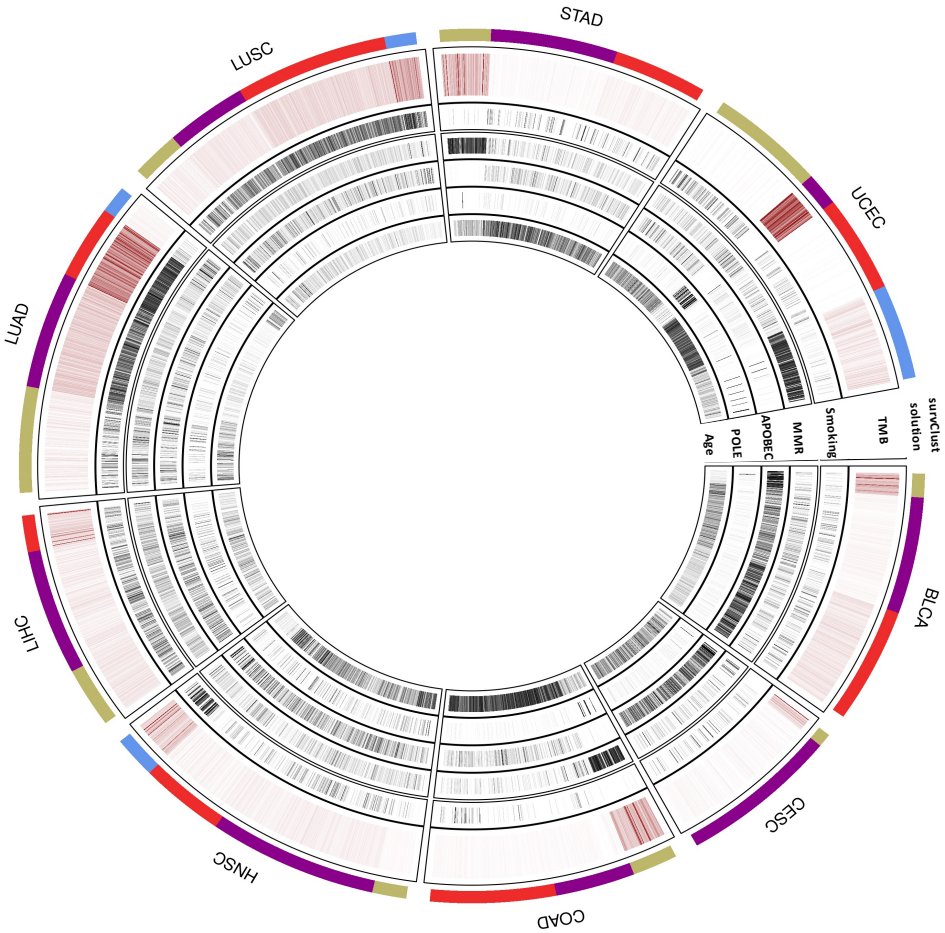
survClust labels	c1	c2	c3	c4
Simulated labels				
Cluster 1	100	0	0	0
Cluster 2	0	100	0	0
Cluster 3	0	0	100	0
Cluster 4	0	0	0	150

Mutation based stratification using survClust in TCGA datasets

a **Bladder Cancer (BLCA)**



b **A circomap showing survClust identified TMB patterns across cancer types**



c1 c3 c5
c2 c4 c6

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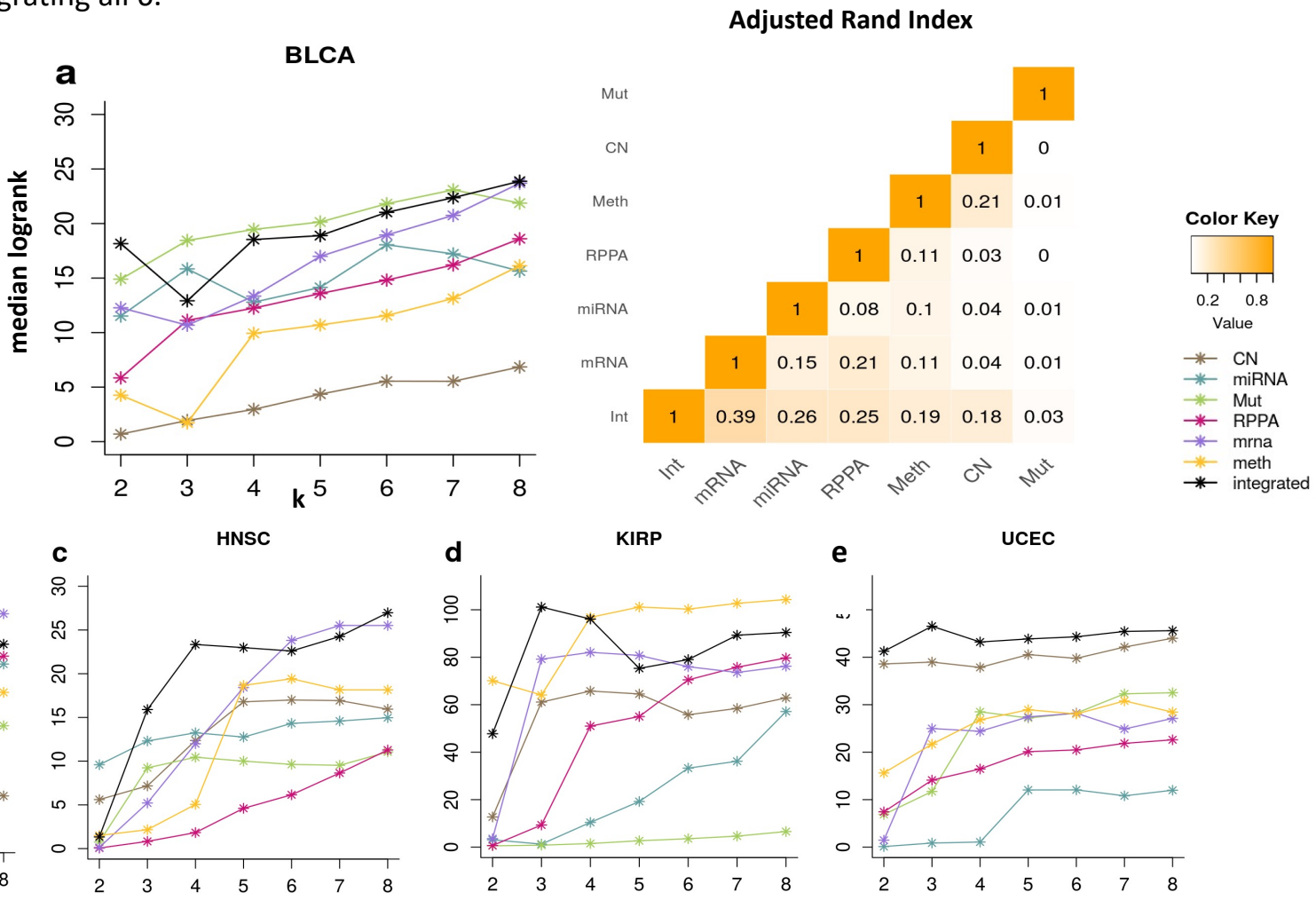
Integrative analysis of multiple platforms

survClust was run on each of the available 6 molecular platforms on each cancer type – Mutation, copy number, DNA Methylation, mRNA expression, miRNA expression and protein assay (RPPA), and integrating all 6.



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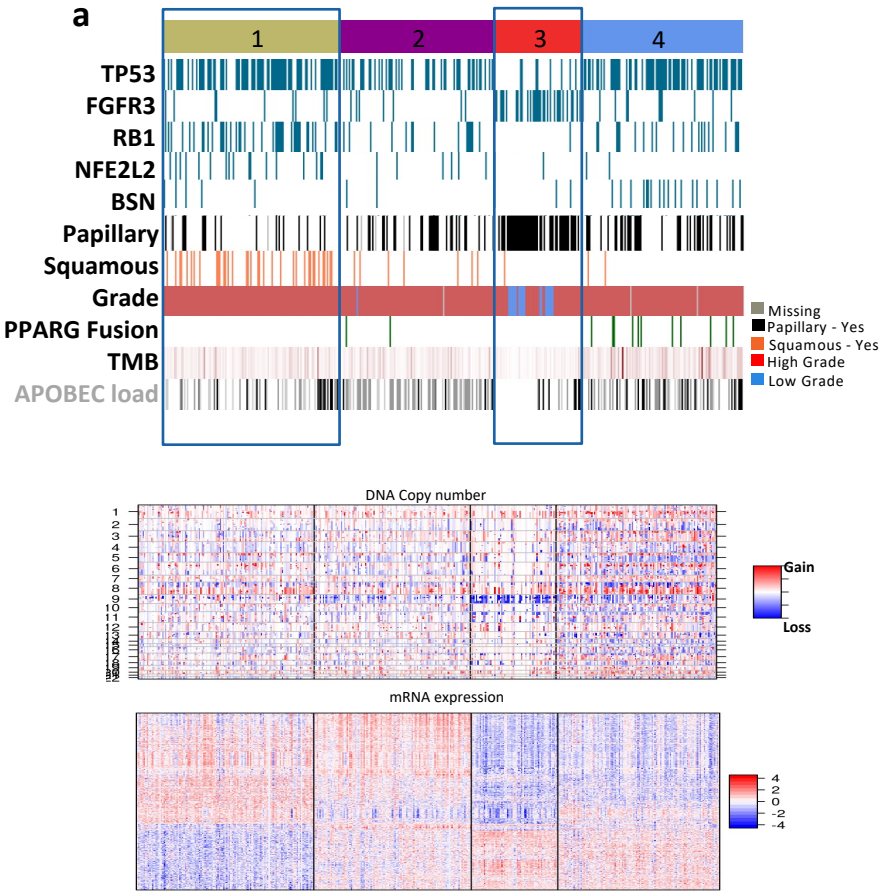
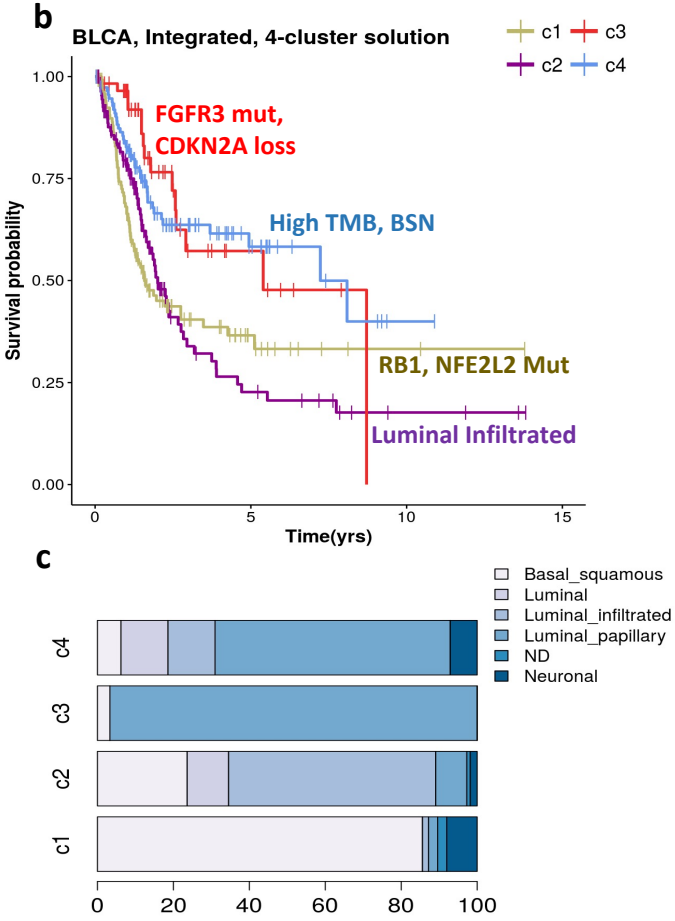
Integrated solution identified by survClust on TCGA BLCA cohort





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Conclusion

- Developed a supervised learning approach for survival outcome-weighted molecular stratification

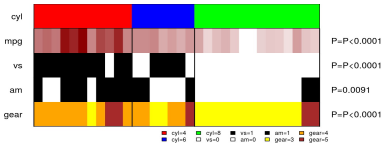
- Application to somatic mutation data led to stratifications associated with mutational burden and hyper-mutation signatures corresponding to distinct mutagenic processes

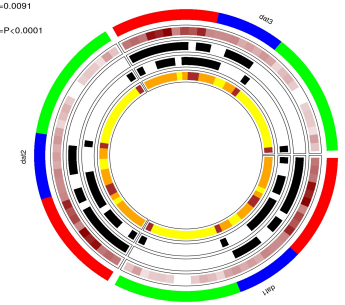
- The integration of multiple data platforms led to more refined outcome stratifications than individual platform derived clustering results in the majority of the cancer types in our analysis

- Developed annotation tools (*circomap, panelmap*) to visualize the association of molecular and clinical information with the subtypes

  R package *panelmap* and function *circomap* –

  found here – https://github.com/arorarshi/panelmap





- *survClust* – developmental version

  Happy to talk! - email – arshiaurora@gmail.com

  check my Github repository when it's published!

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Thank you!