Biomarker signatures discovery to support cancer diagnosis

Towards an accurate and robust machine learning strategy

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Context

- Diagnosis of Breast Cancer
- Breast Cancer treatment response
- Design of **short** biomarker signatures

From Omics to Clinics

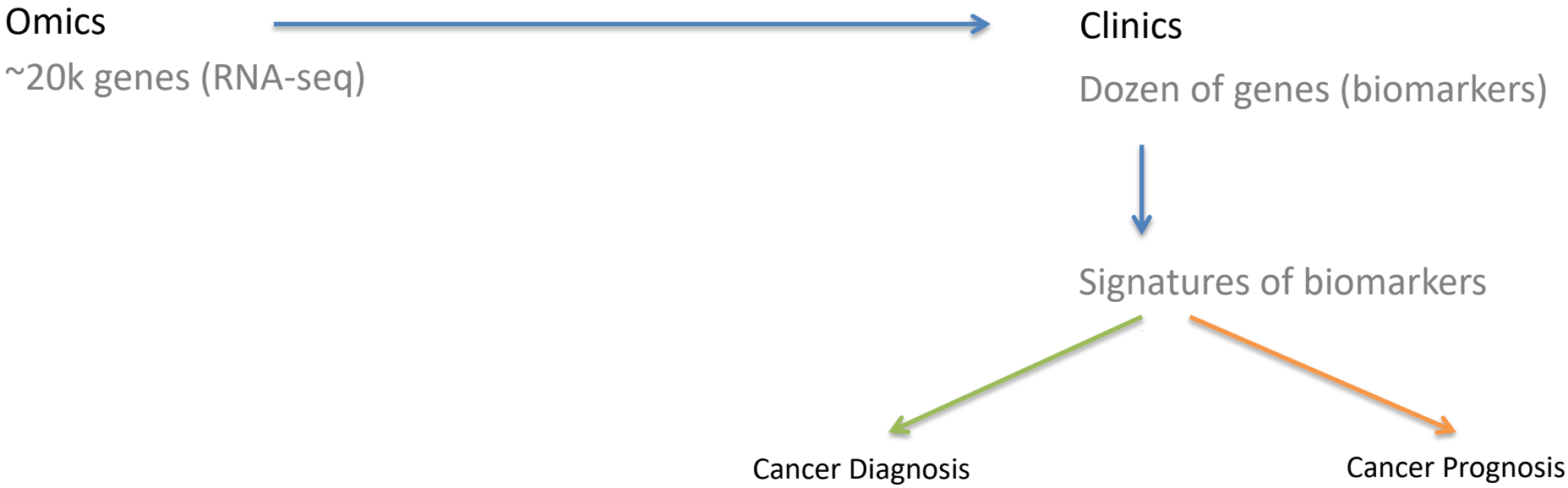
Omics

~20k genes (RNA-seq)

Clinics

Dozen of genes (biomarkers)

From Omics to Clinics



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Signatures of biomarkers

Robust and precise

From Omics to Clinics

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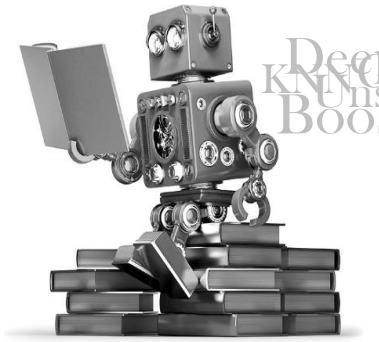

Deep Learning
SVM
KNN
Genetic Algorithm
Unsupervised Clustering
Boosting
Neural Networks
Random Forest

Clinics

Dozen of genes (biomarkers)

Signatures of biomarkers

Robust and precise
Models and signatures

From Omics to Clinics

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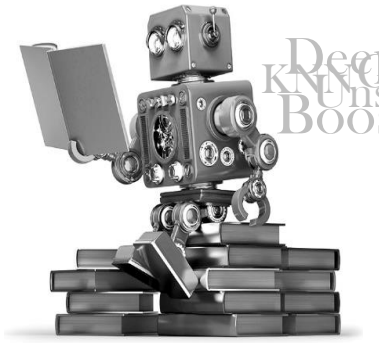

Deep Learning SVM KNN Genetic Algorithm Unsupervised Clustering Boosting Neural Networks

Random Forest

R implementations of Random Forest algorithm proposed by *[Breiman et al. 2001]*

Clinics

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Robust and precise Models and signatures

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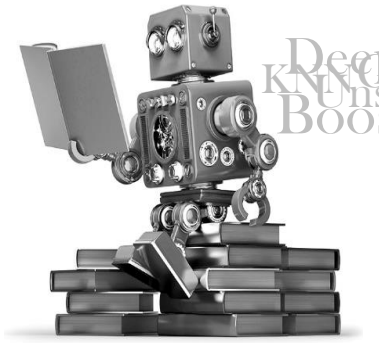

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Robust and precise Models and signatures ???

Objectives

Toward a robust RF method for the Biological question asked

Which method is suitable for which dataset (platform/technology) ?

Objectives

- Empirical comparison of random forest based methods
- Differences/Similarities of RF methods ➔ groups of methods
- Designing a high stability score to rank RF methods

Toward a robust RF method for the Biological question asked

Which method is suitable for which dataset (platform/technology) ?

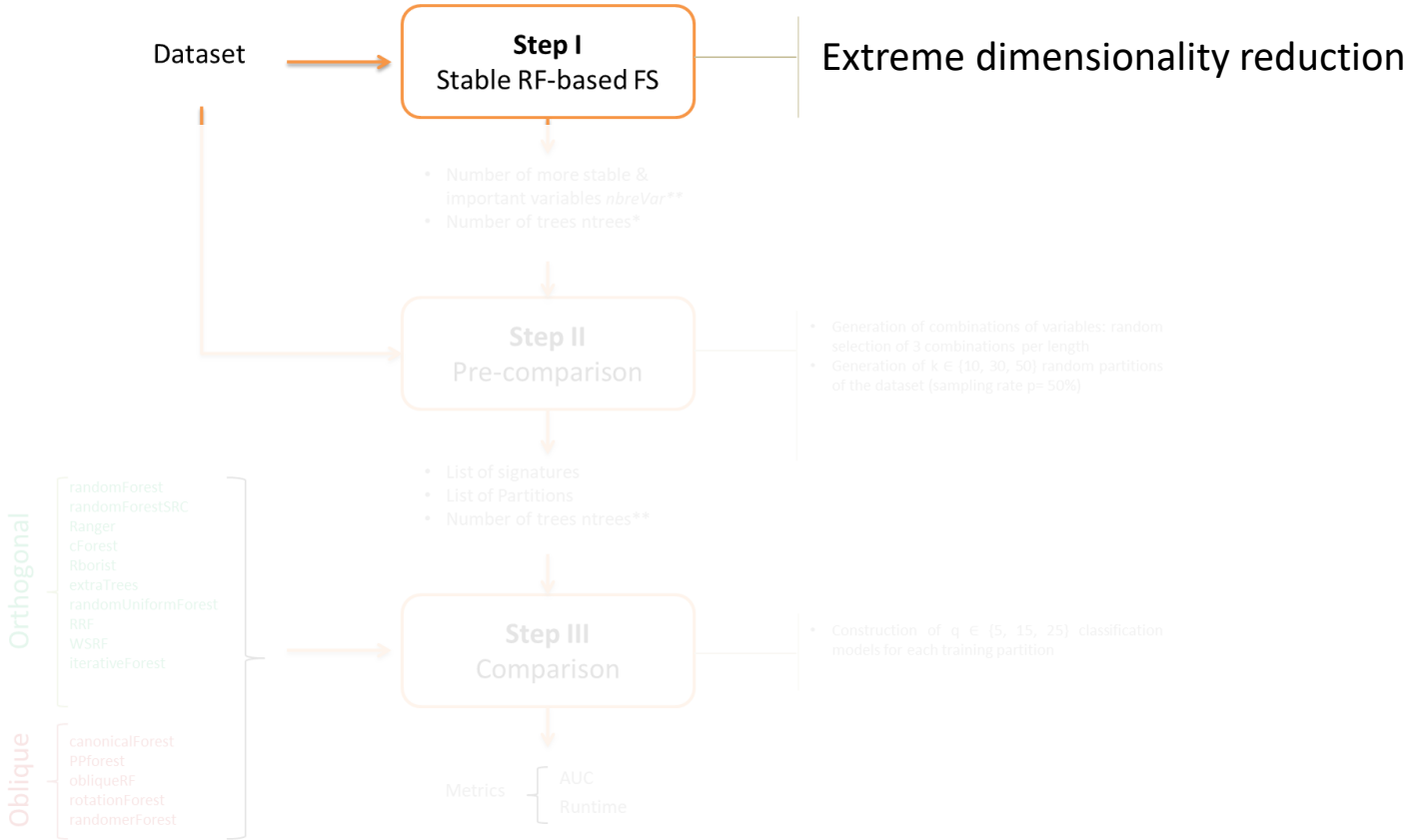
Materials and Methods

- **Datasets (Perfectly balanced)**
    - TCGA-BRCA (RPKM): 182 samples x 9560 genes
    - TCGA-LUSC (RPKM): 96 samples x 9262 genes

- **Main classification question**

The difference between paired **Tumor / Normal** samples will be used as a **strong classification** parameter, allowing for **strong** modeling only

Overview of the method



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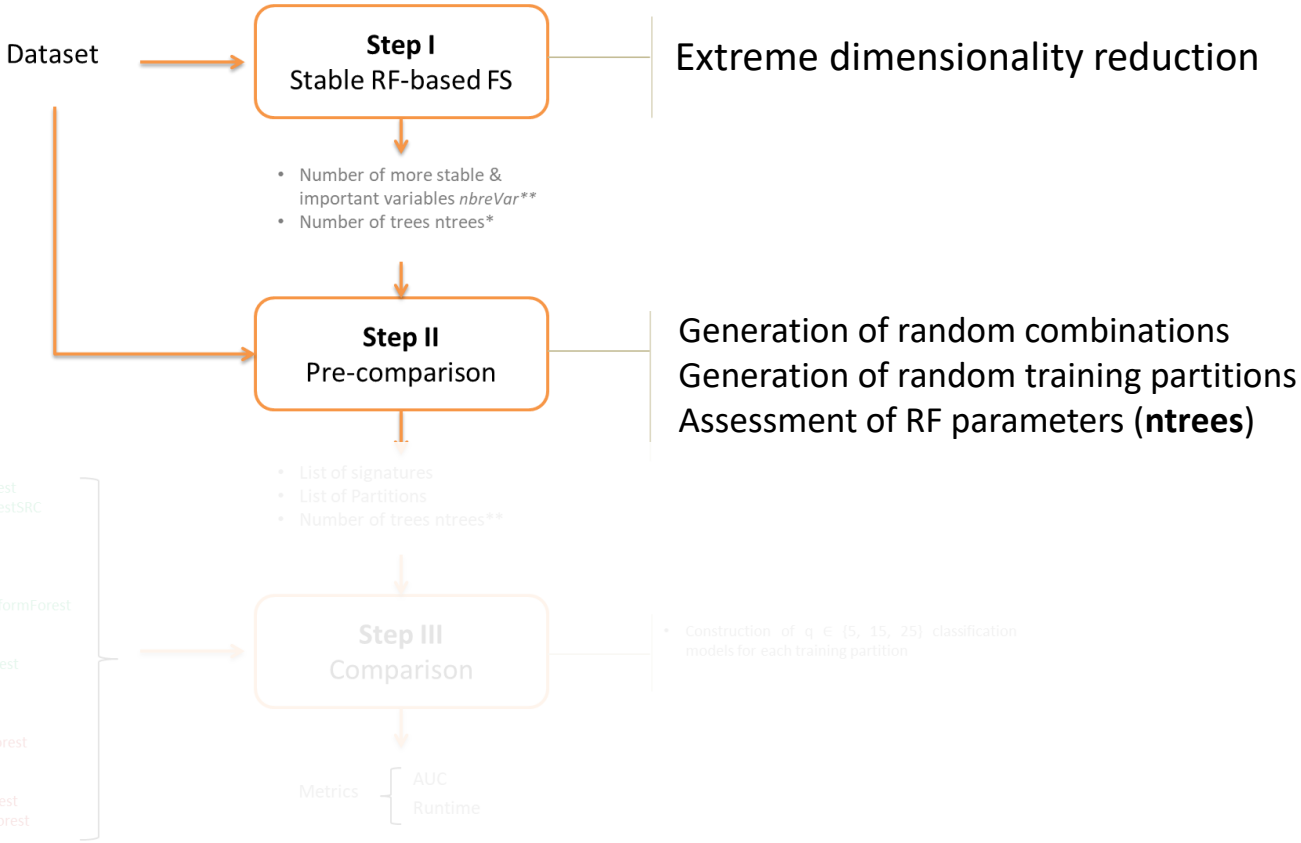

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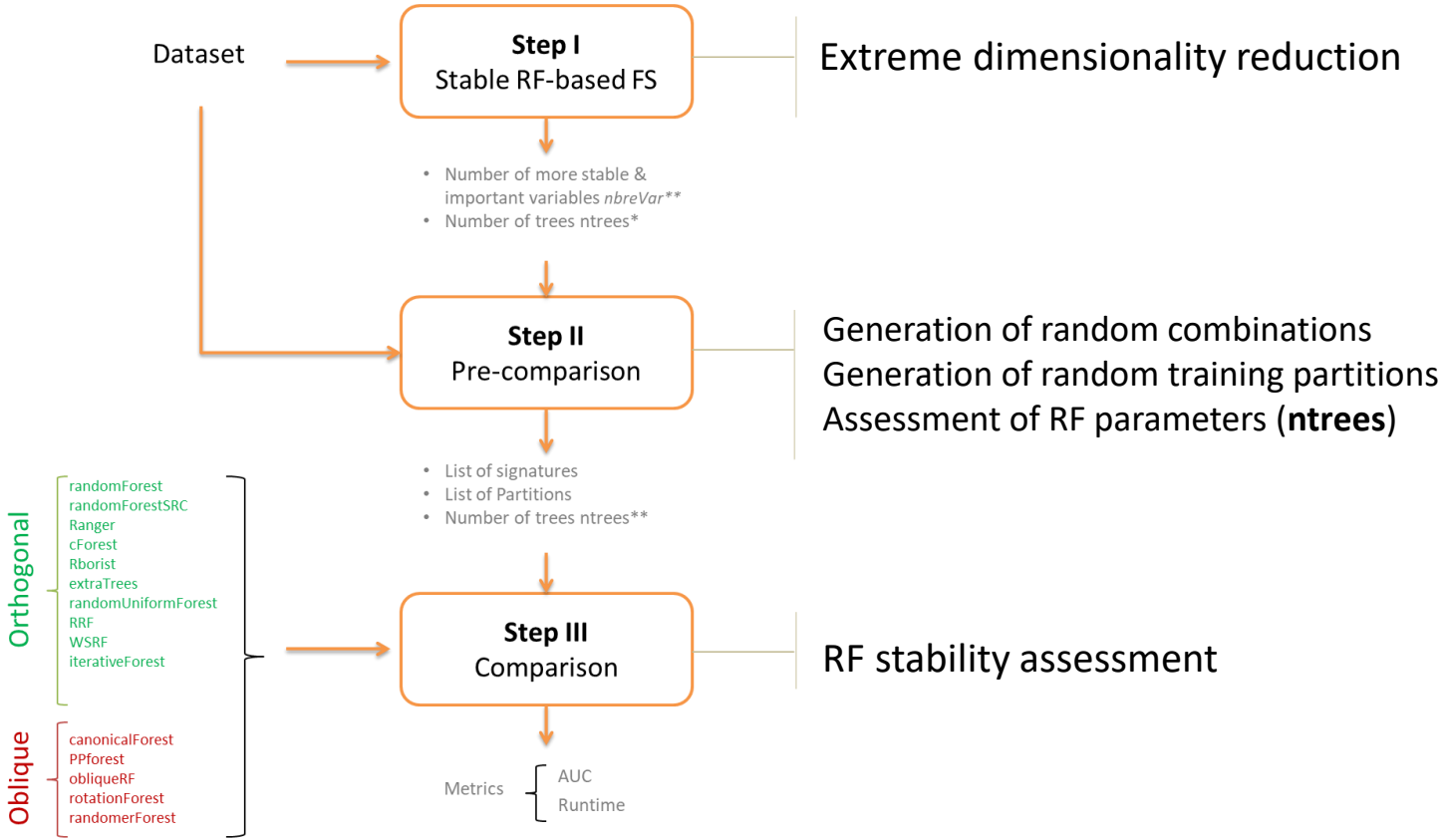
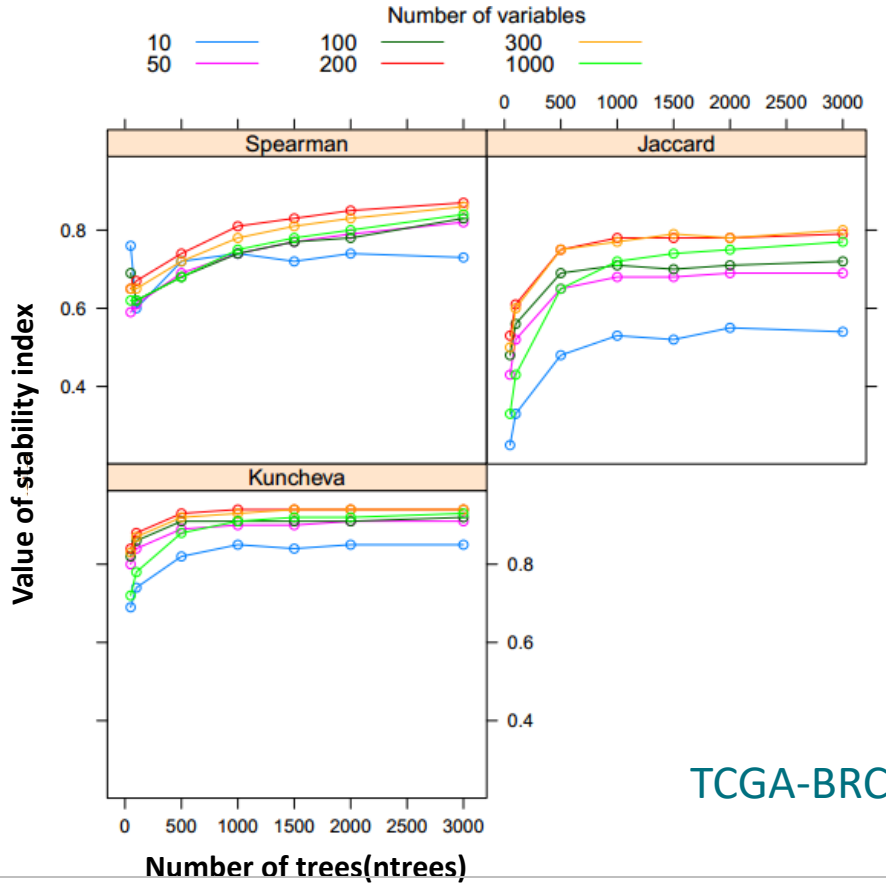


Stable Feature Selection

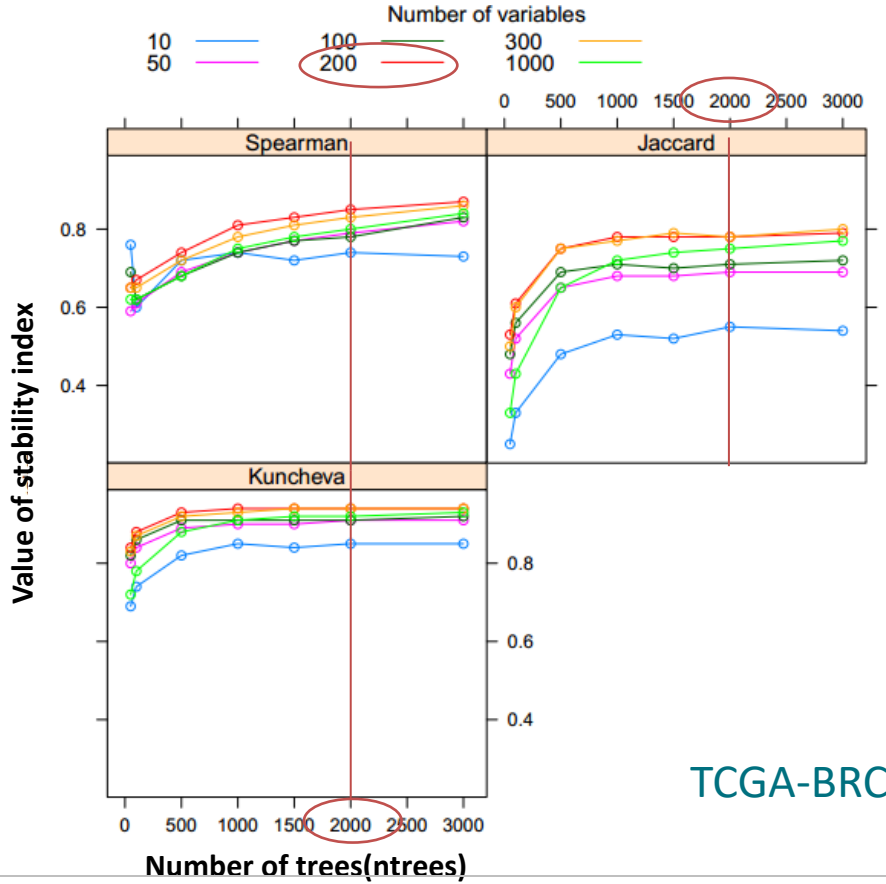
Extreme dimensionality reduction

First pass Feature Selection results



TCGA-BRCA dataset

First pass Feature Selection results

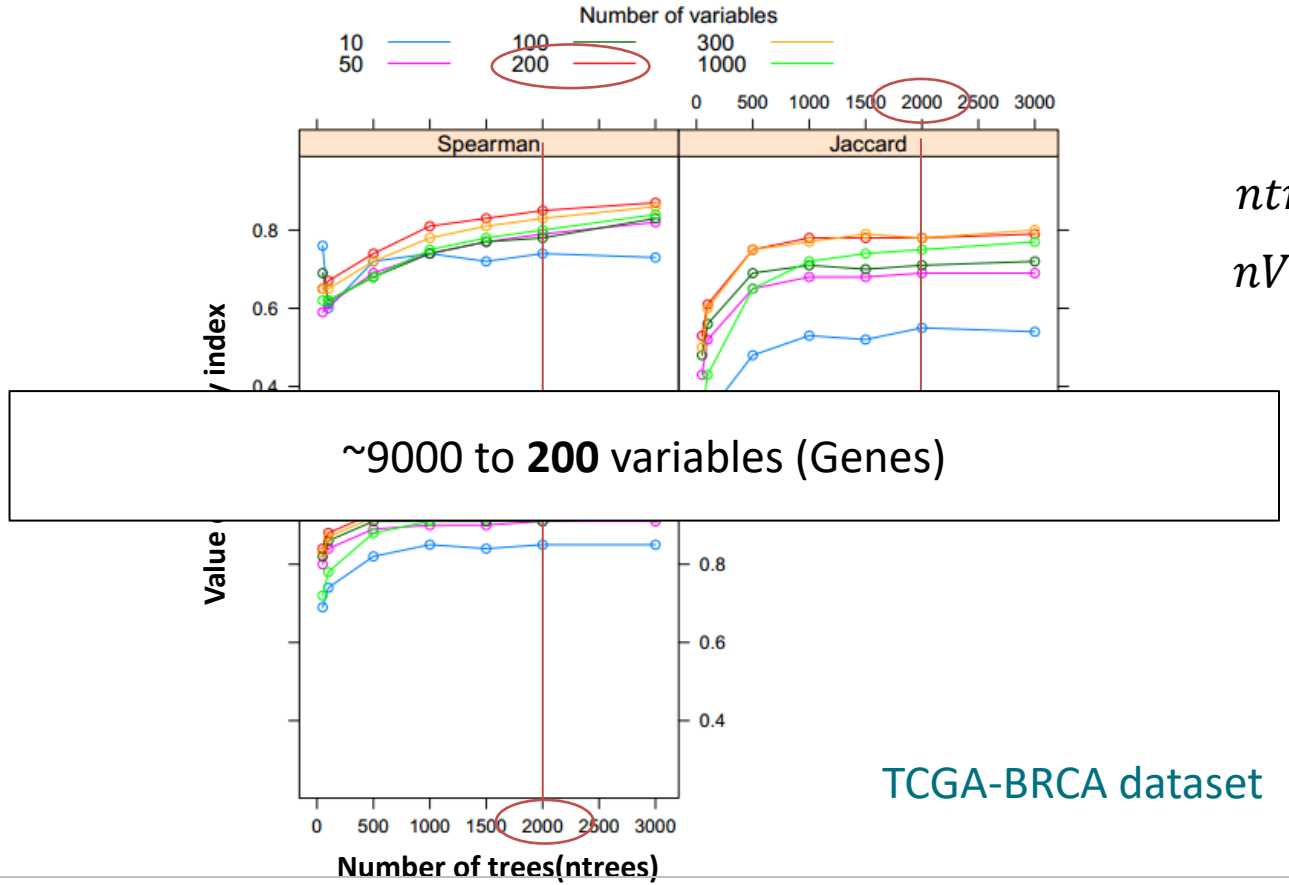


$ntrees^*$ = 2000

$nVar^*$ = 200

TCGA-BRCA dataset

First pass Feature Selection results



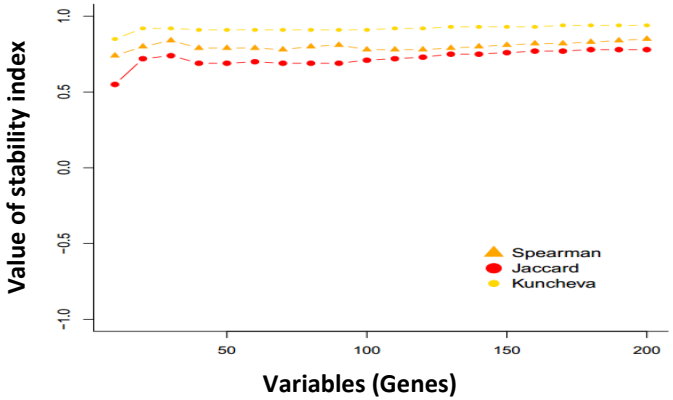
~9000 to **200** variables (Genes)

$ntrees^*$ = 2000

$nVar^*$ = 200

TCGA-BRCA dataset

Second pass Feature Selection results



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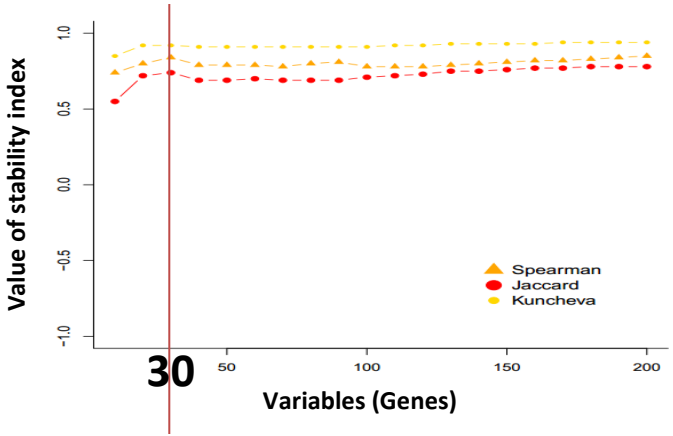
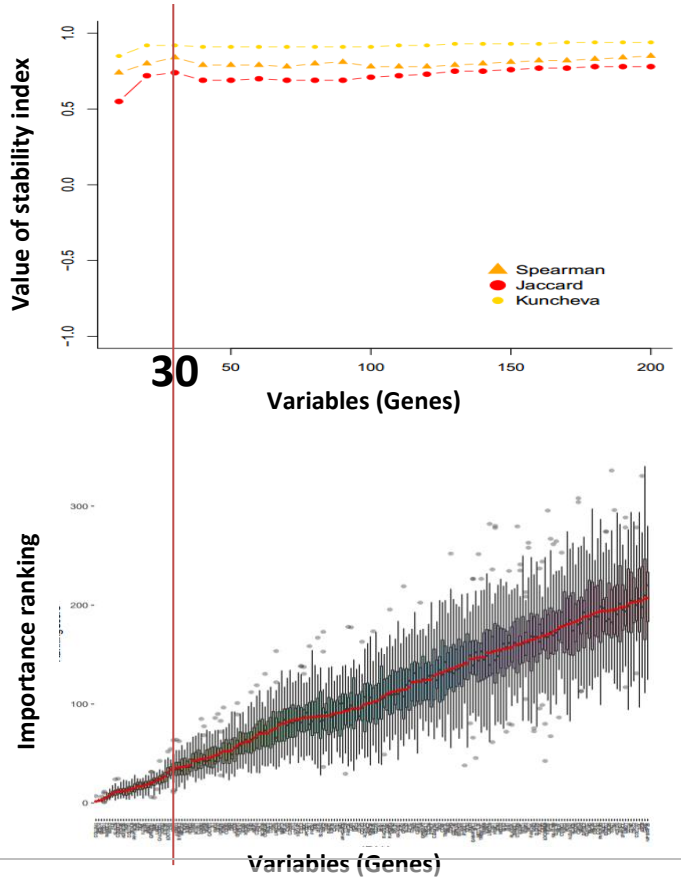


$$nVar^{**} = 30$$

TCGA-BRCA dataset

Second pass Feature Selection results



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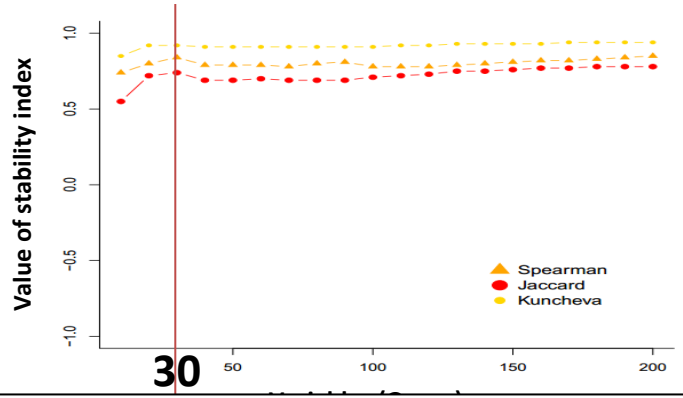
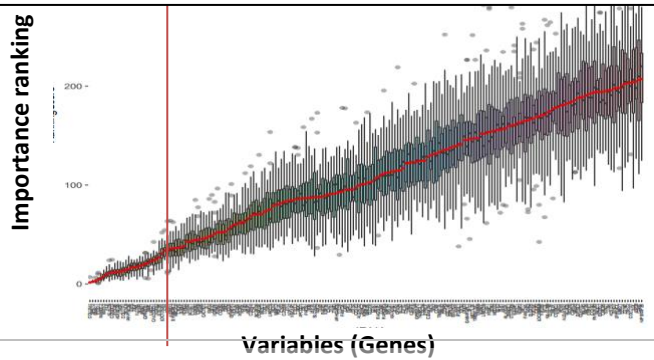


$nVar^{**} = 30$

~200 to **30** variables (Genes)



TCGA-BRCA dataset

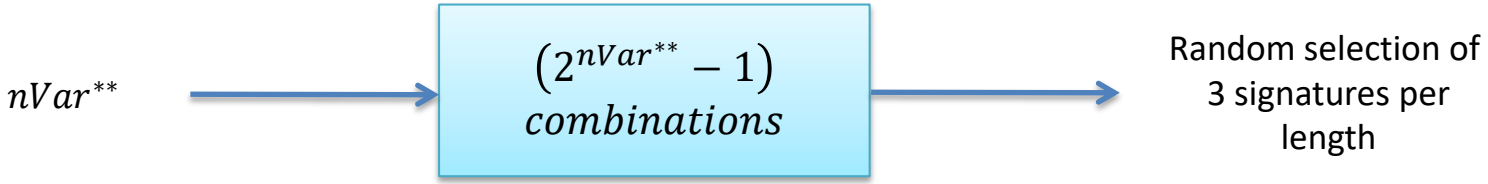
Pre-Comparison

Assessment of RF parameters & Generation of random combinations

Pre-comparison

I- Generation of random combinations (Cancer signatures)

- Multiple predictive models using combinations of different lengths



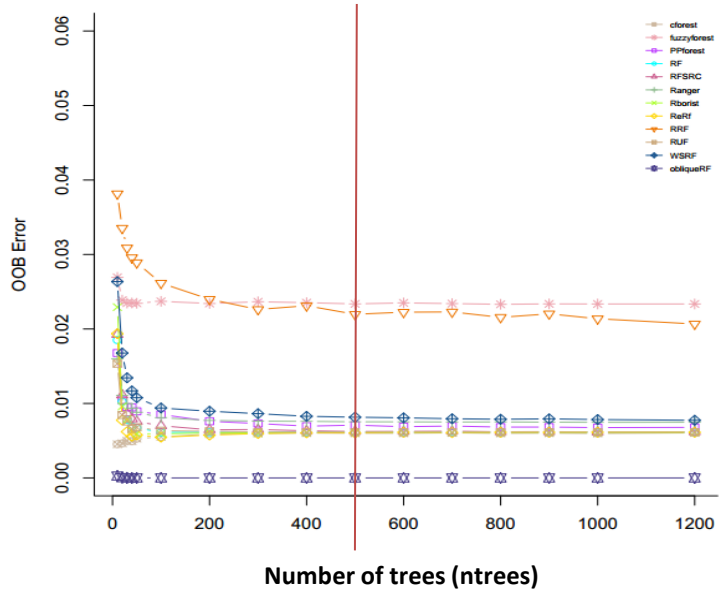
II- Generation of random training partitions

- 50 random training partitions

training partition = a set of samples used to construct a model

Pre-comparison

III- Tuning the parameter $ntrees$ for each RF method



TCGA-BRCA dataset

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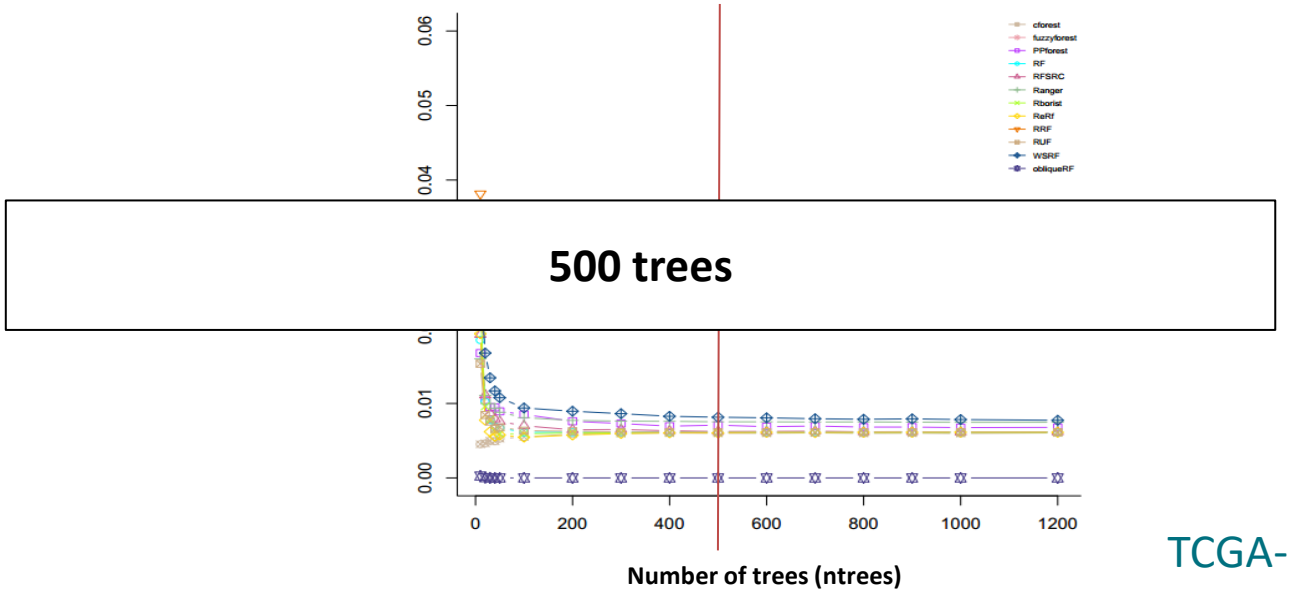


TCGA-BRCA dataset

Summary of step I + step II

Dataset	$nVar$	$nVar^{*}$	$nVar^{**}$	$ntrees^{*}$	$ntrees^{**}$	#Combinations
TCGA-BRCA	9560	200	30	2000	500	78
TCGA-LUSC	9262	200	10	2000	500	21

Comparison

Random Forest stability assessment

Random Forest Method Comparison

- **Same** conditions: **same** random training partitions, **same** signatures, computational nodes of **same** characteristics

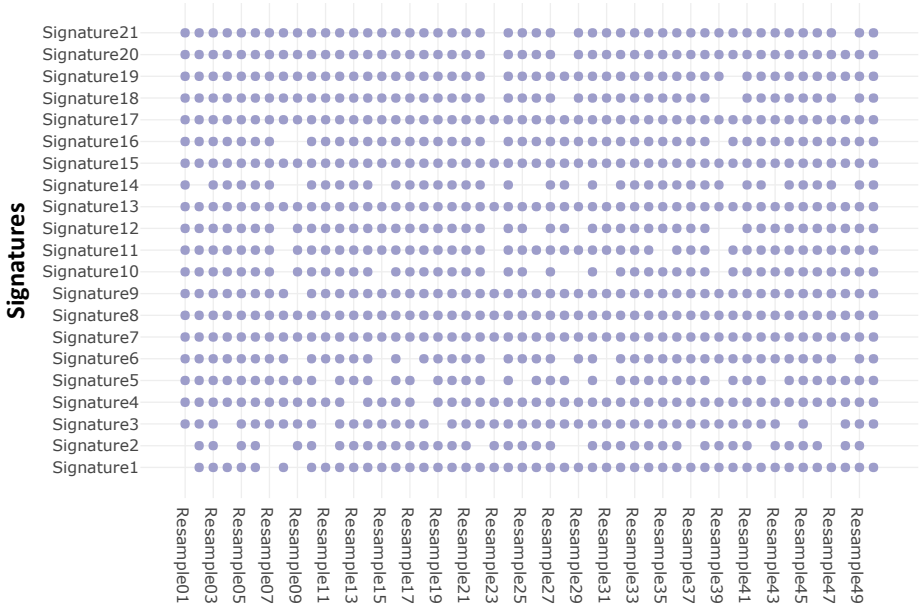
- For each signature, we'll focus on:
  - **50 resampling** to build the Training and the Validation set.
  - **25 modeling and validations.**

1,250 models & AUCs

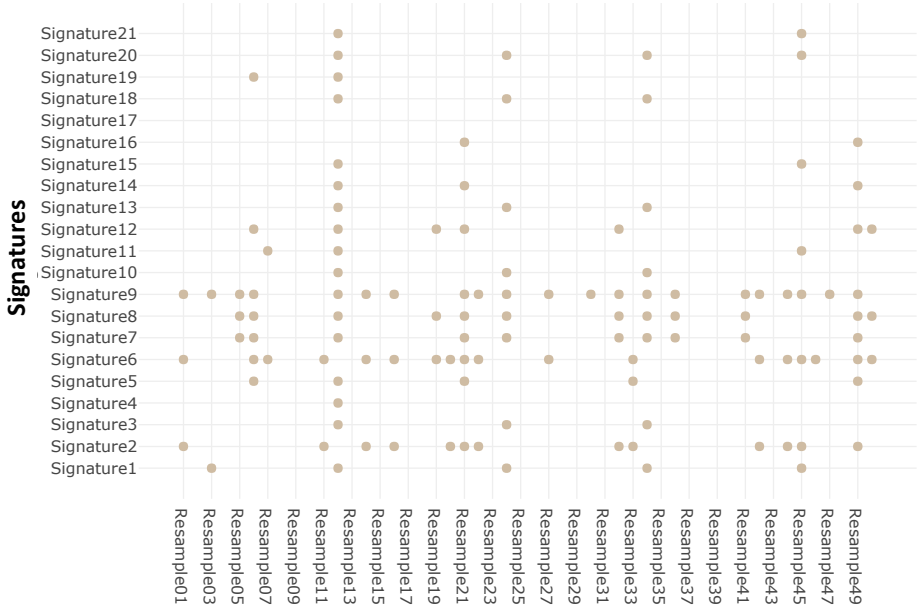
- Analysis of:
  - **Coefficient of Variation of 1,250 models & AUCs**

- **Hyper-stability (CV=0)**

Hyper Stability discriminates RF methods

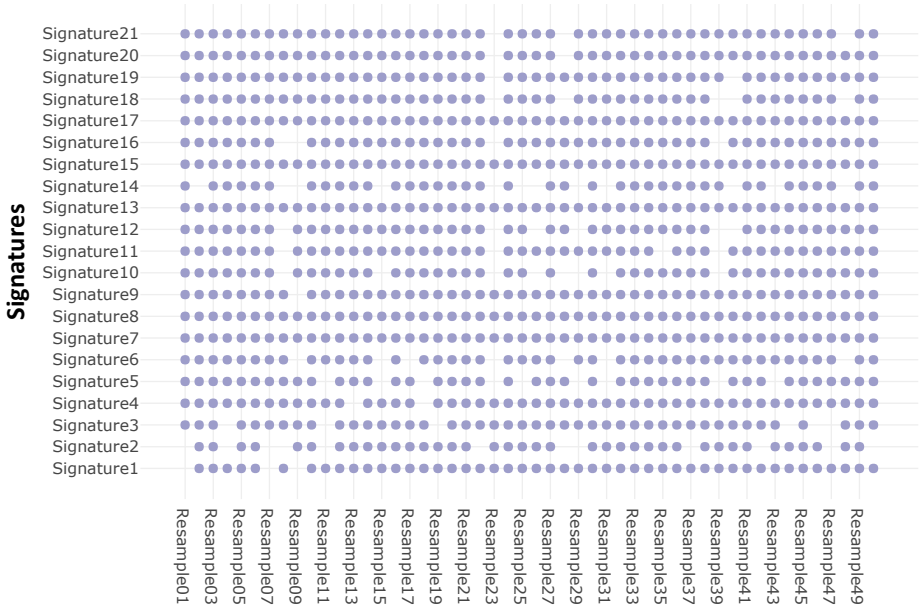


TCGA-LUSC dataset

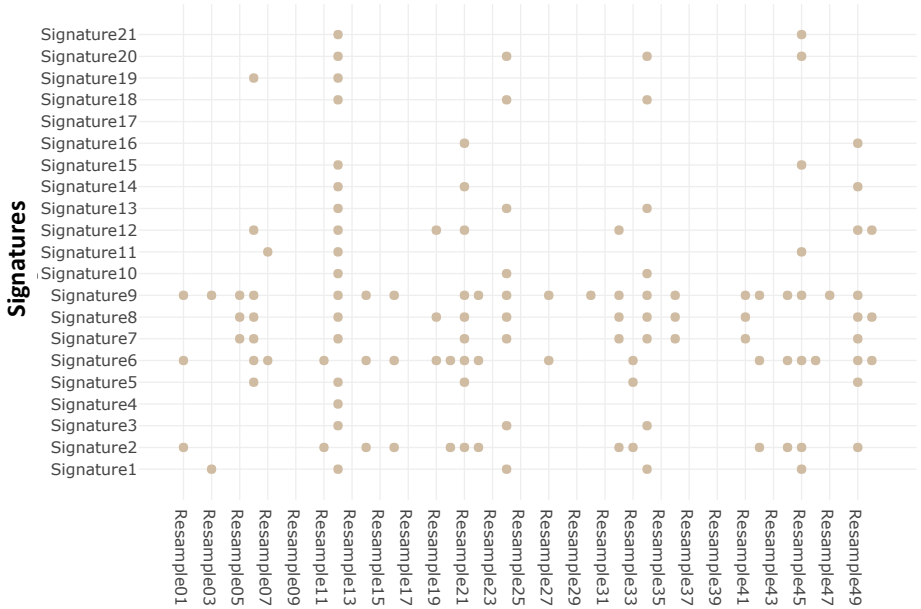


Hyper Stability discriminates RF methods

Best Methods

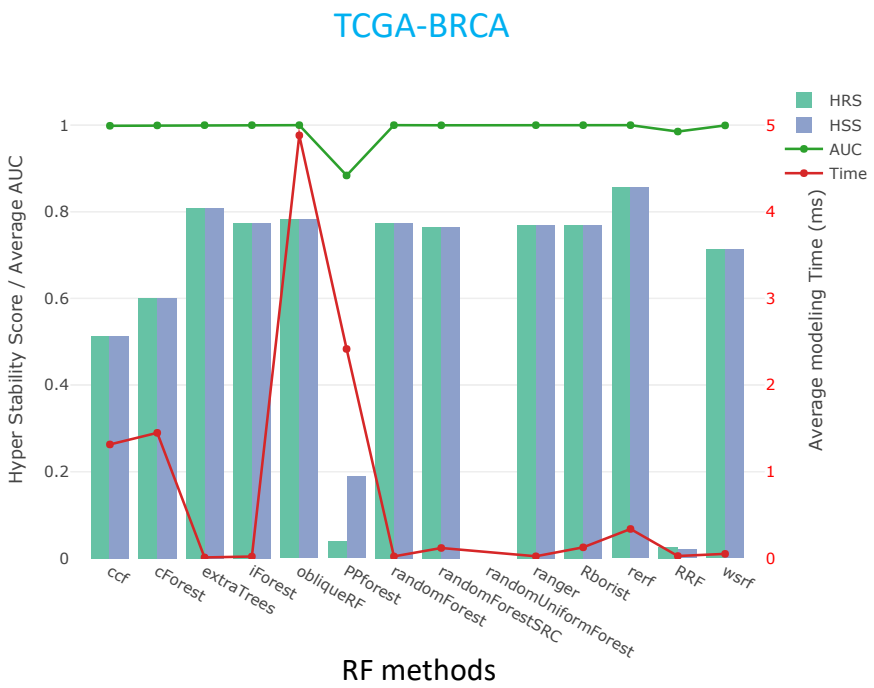


Worst Methods



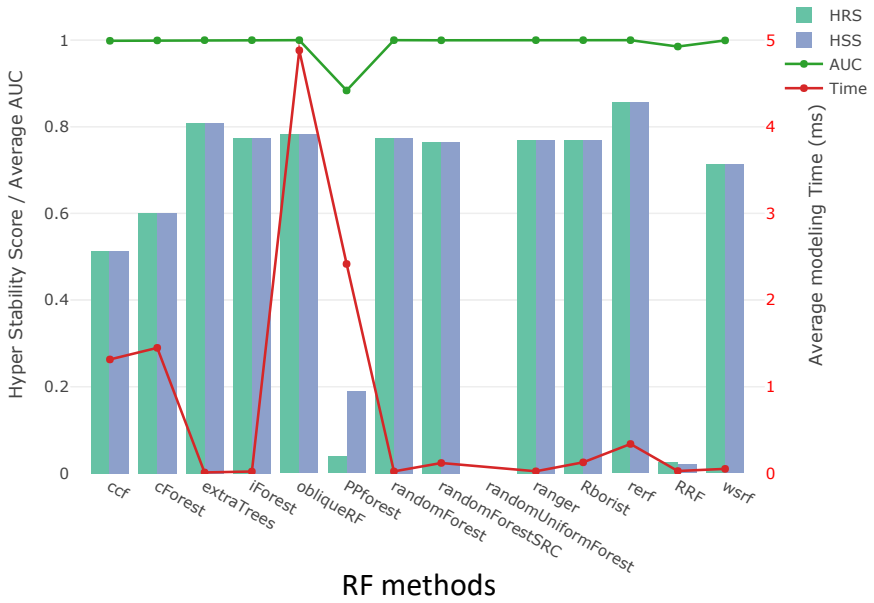
TCGA-LUSC dataset

Hyper Stability Score helps finding the best method(s)

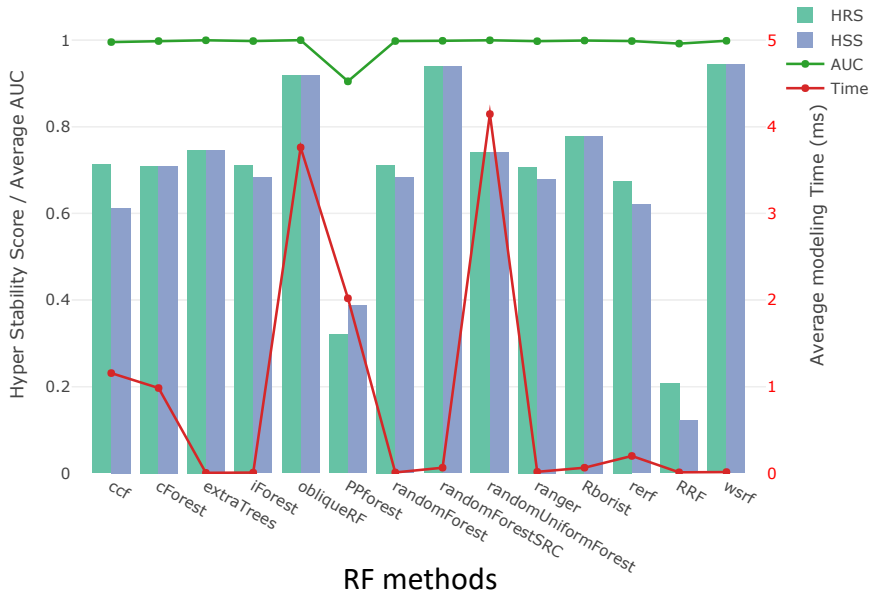


Hyper Stability Score is dataset dependent

TCGA-BRCA



TCGA-LUSC



Conclusions

- The AUC precision is dataset dependent
  - The Methods are dataset dependent.

- Trade-off:
  - AUC precision (hyper-stability)
  - Average AUC value
  - Modeling Time

} Classification of RF methods

Towards robust signatures and predictions

Perspectives

- Translation to the clinics: Ensemble of signatures
- Understanding differences in hyper-stability:
  - dimension,
  - platforms,
  - multicollinearity
- Including other ML methods
- Multi-Omics signatures

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