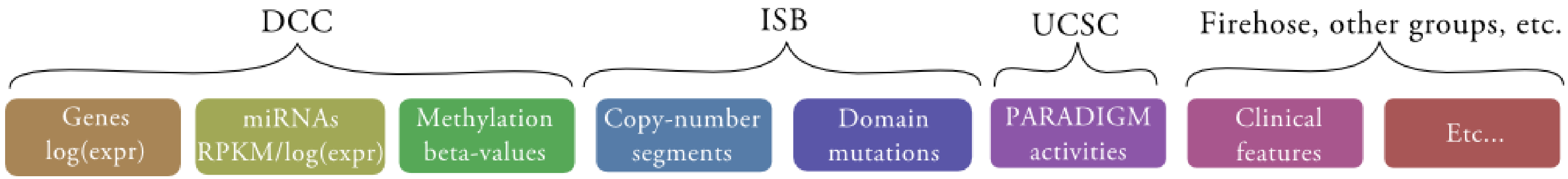
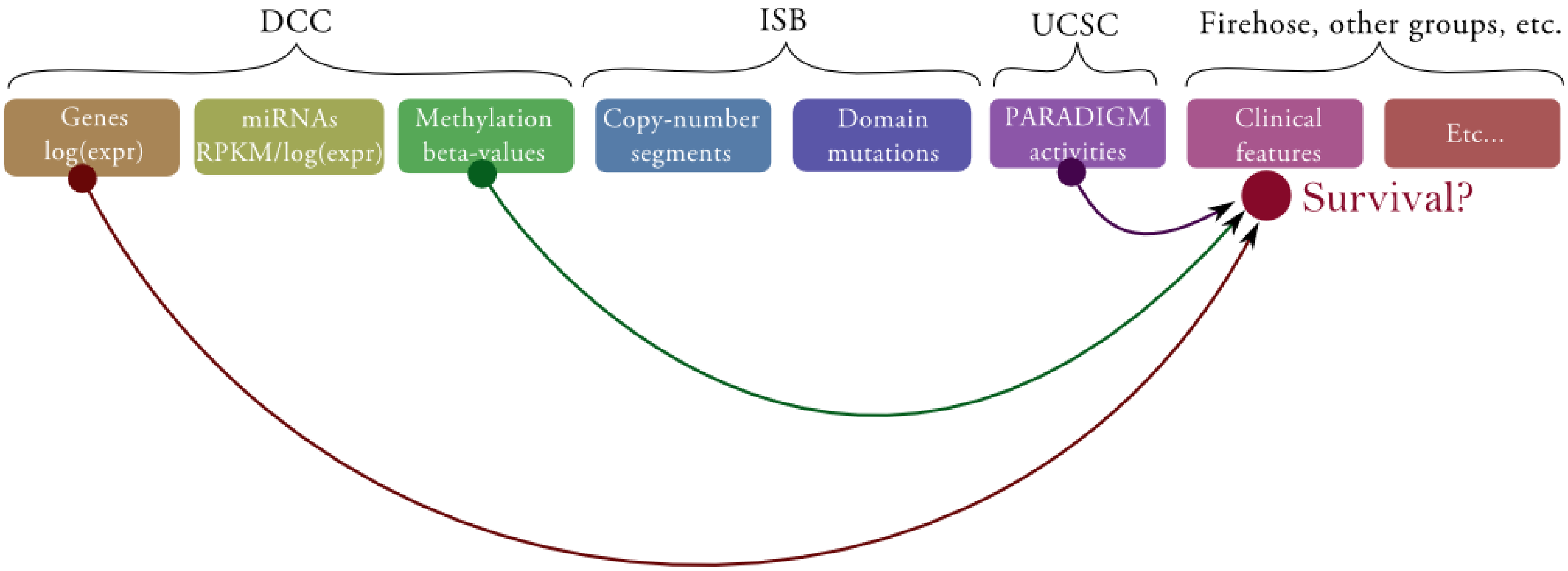
RF-ACE for uncovering nonlinear associations from heterogeneous cancer data

Timo Erkkilä
1st Annual TCGA symposium
National Harbor
Washington DC


DCC
ISB
UCSC
Firehose, other groups, etc.
Genes log(expr)
miRNAs RPKM/log(expr)
Methylation beta-values
Copy-number segments
Domain mutations
PARADIGM activities
Clinical features
Etc...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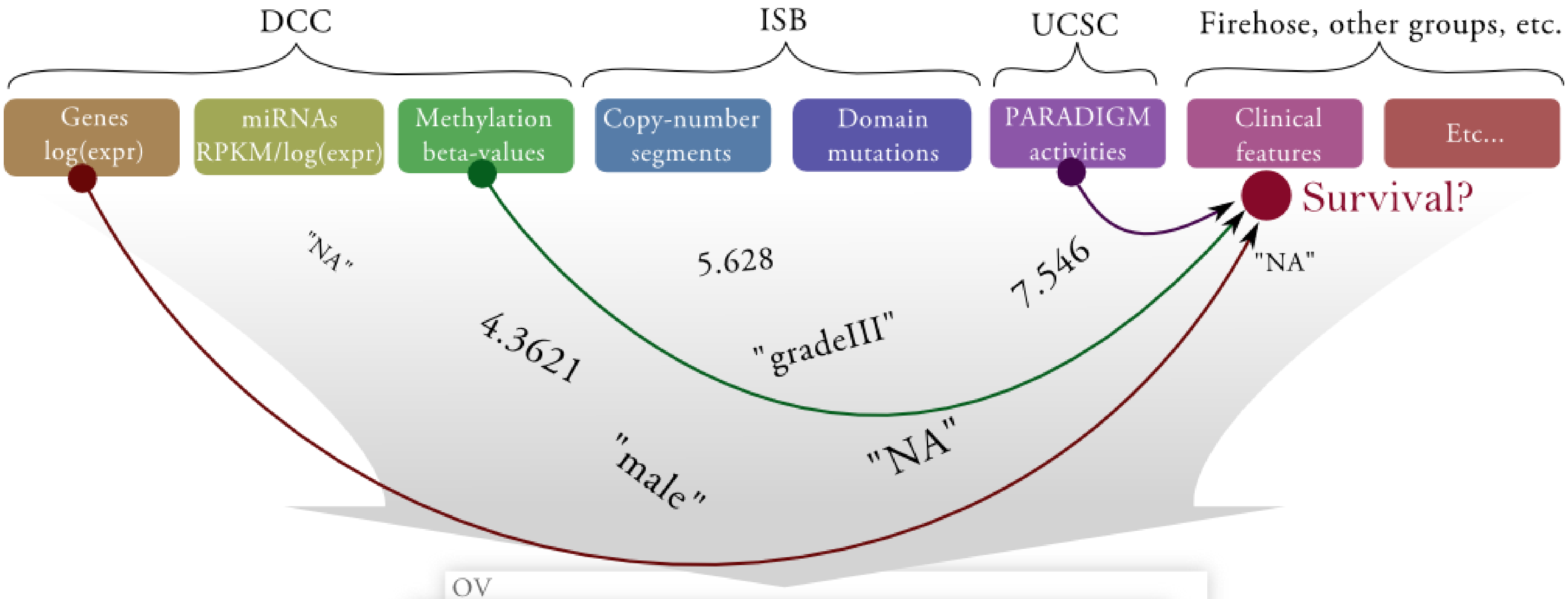
Survival?



OV

GBM

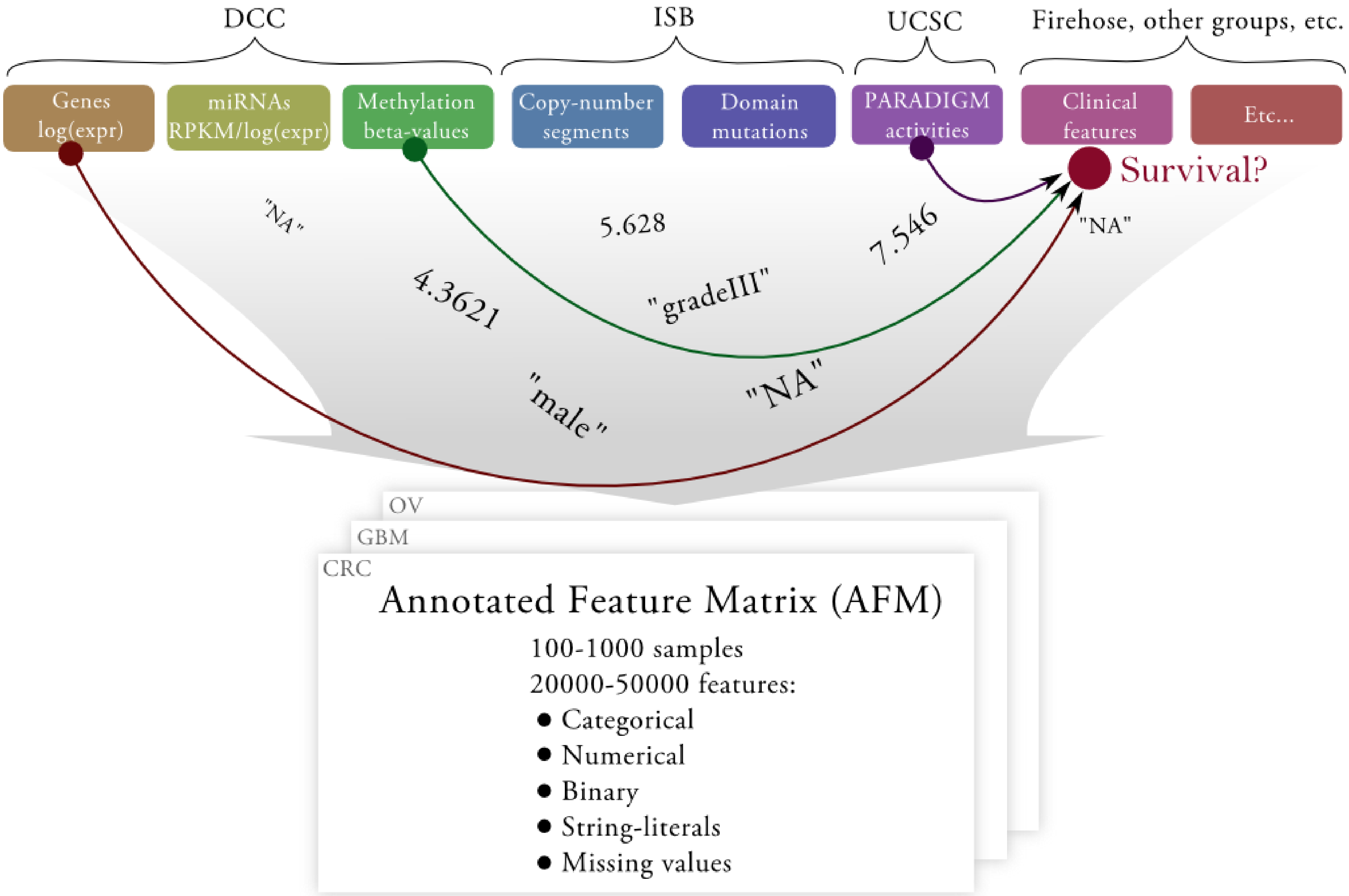
CRC

Annotated Feature Matrix (AFM)

100-1000 samples
20000-50000 features:

- Categorical
- Numerical
- Binary
- String-literals
- Missing values

Sheila Reynolds



Annotated Feature Matrix (AFM)

100-1000 samples
20000-50000 features:

- Categorical
- Numerical
- Binary
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- Missing values

Problem: need algorithm for feature selection with heterogeneous data

Sheila Reynolds

Random Forest (RF)

Pros:

+ supports mixed-type data and missing values
+ predicted target can be of any type
+ no data transformations necessary
+ supports multivariate & nonlinear associations

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Cons:

- importance score yields mere ranking of associations
- importance score is not normalized
- prediction performance could be better
- existing RF implementations often lack flexibility

RF-ACE

(Random Forests with Artificial Contrast Ensembles)

- RF implementation with added flexibility
  - support for string literals and various data formats
  - Easy interface with default parameter options

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- Inclusion of statistical testing framework
  - p-values for associations

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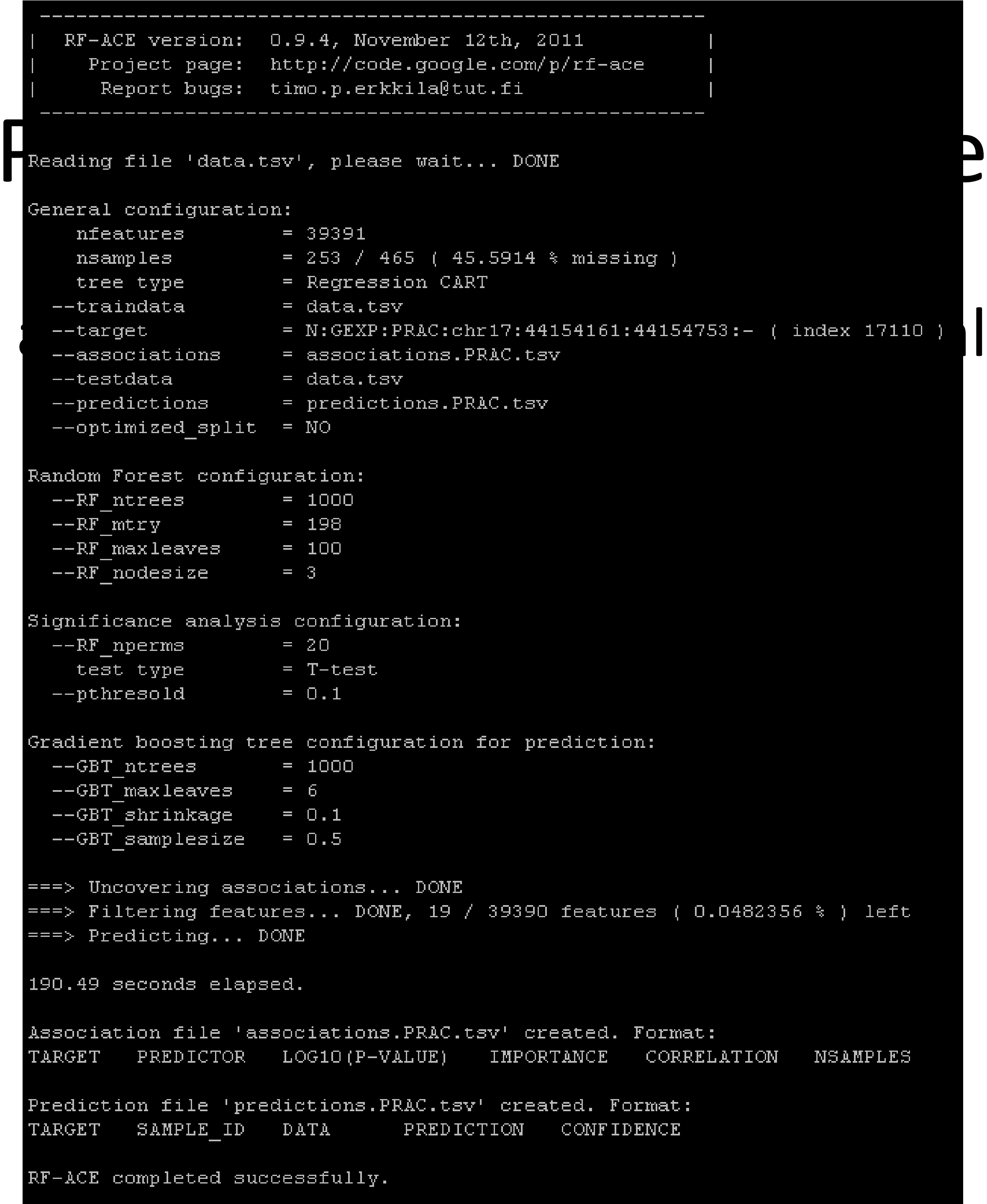
- Better predictive power with Gradient Boosting Trees

Pseudo-random example

- Find associations to PRAC in colorectal data

P e

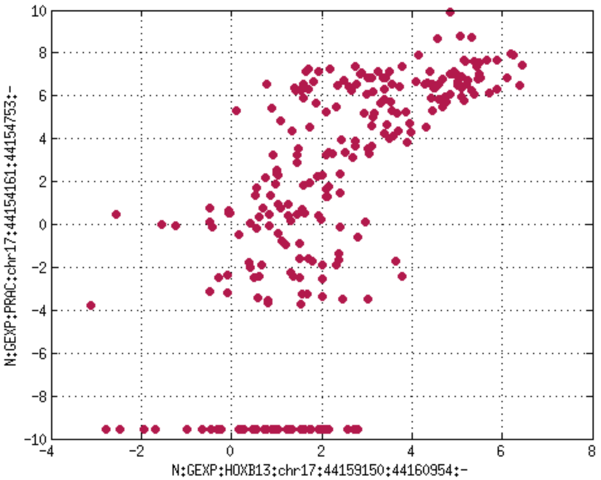
- Find a l data



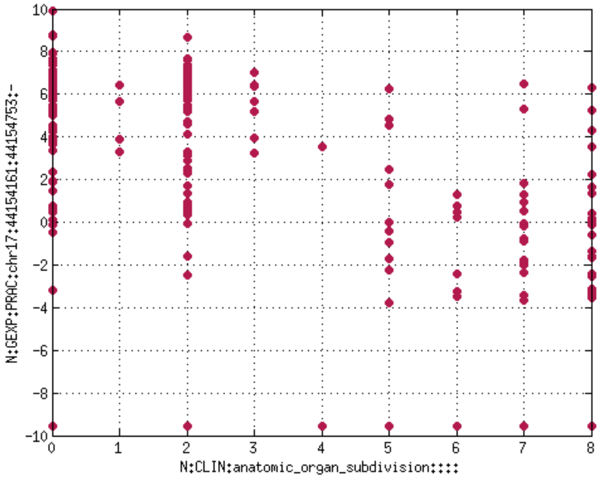
```
 ------------------------------------------------------
|  RF-ACE version:  0.9.4, November 12th, 2011          |
|    Project page:  http://code.google.com/p/rf-ace     |
|     Report bugs:  timo.p.erkkila@tut.fi               |
 ------------------------------------------------------

Reading file 'data.tsv', please wait... DONE

General configuration:
    nfeatures        = 39391
    nsamples         = 253 / 465 ( 45.5914 % missing )
    tree type        = Regression CART
  --traindata        = data.tsv
  --target           = N:GEXP:PRAC:chr17:44154161:44154753:- ( index 17110 )
  --associations     = associations.PRAC.tsv
  --testdata         = data.tsv
  --predictions      = predictions.PRAC.tsv
  --optimized_split  = NO

Random Forest configuration:
  --RF_ntrees        = 1000
  --RF_mtry          = 198
  --RF_maxleaves     = 100
  --RF_nodesize      = 3

Significance analysis configuration:
  --RF_nperms        = 20
    test type        = T-test
  --pthresold        = 0.1

Gradient boosting tree configuration for prediction:
  --GBT_ntrees       = 1000
  --GBT_maxleaves    = 6
  --GBT_shrinkage    = 0.1
  --GBT_samplesize   = 0.5

===> Uncovering associations... DONE
===> Filtering features... DONE, 19 / 39390 features ( 0.0482356 % ) left
===> Predicting... DONE

190.49 seconds elapsed.

Association file 'associations.PRAC.tsv' created. Format:
TARGET   PREDICTOR   LOG10(P-VALUE)   IMPORTANCE   CORRELATION   NSAMPLES

Prediction file 'predictions.PRAC.tsv' created. Format:
TARGET   SAMPLE_ID   DATA      PREDICTION   CONFIDENCE

RF-ACE completed successfully.
```

Top 3 associations for PRAC (out of 19 significant)

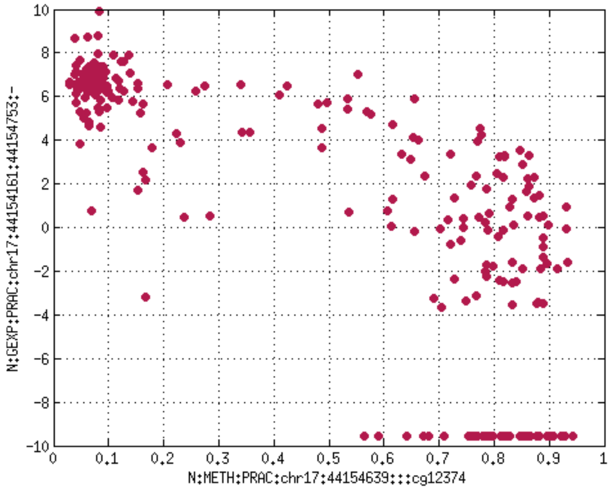
HOXB13



Anatomic organ subdivision



Promoter methylation



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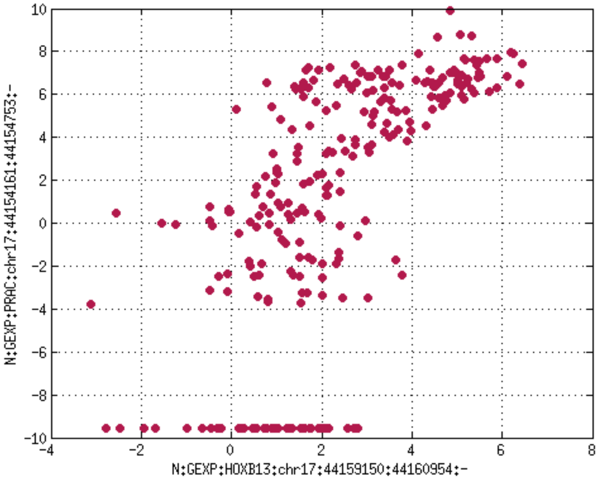

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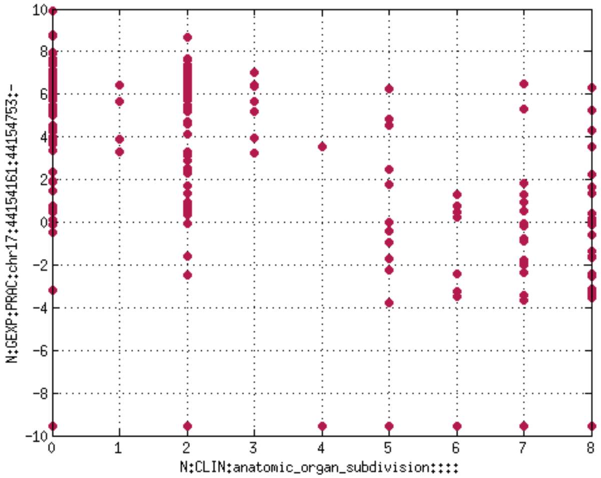

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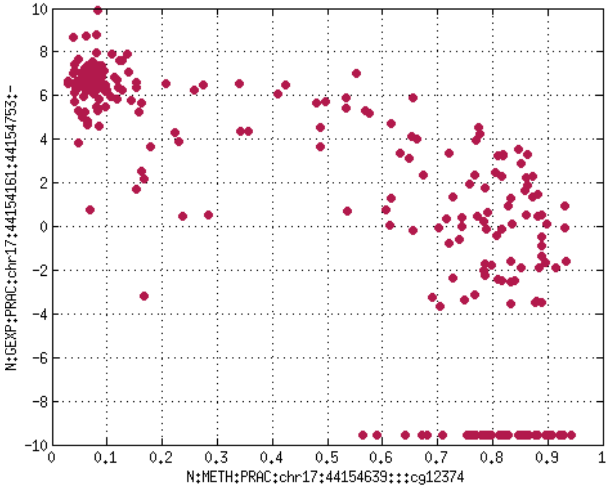
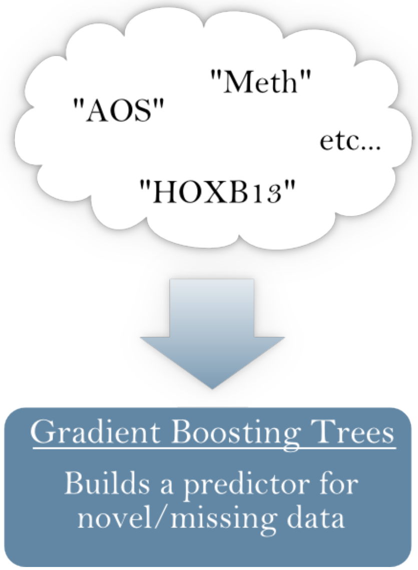
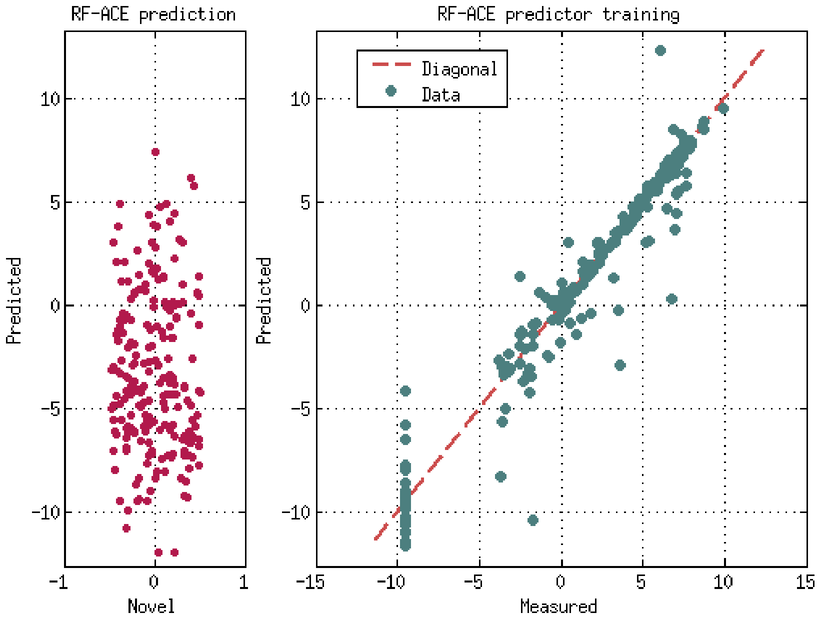


"Core" features associated to PRAC



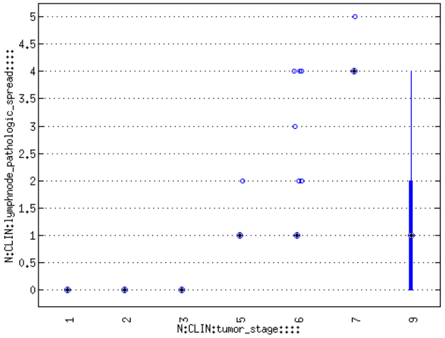
Gradient Boosting Trees

Builds a predictor for novel/missing data

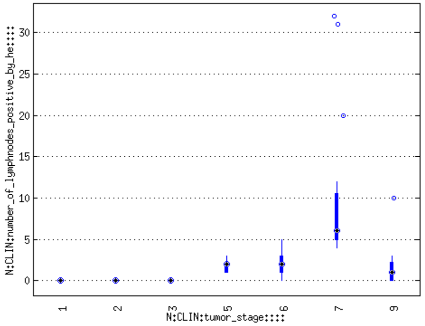


Repeat the analysis for Tumor Stage

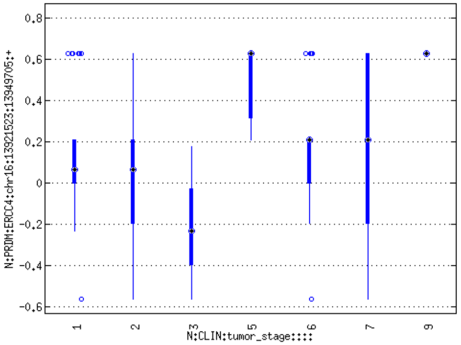
Lymphnode spread



Number of lymphnodes



PARADIGM ERCC4 act.



Etc.

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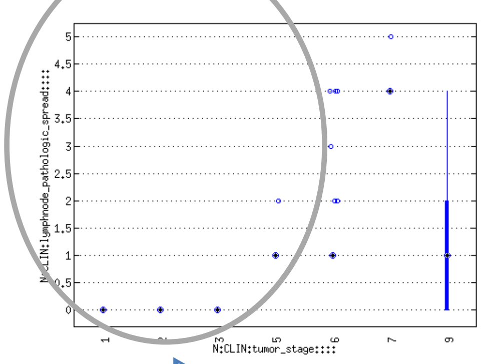

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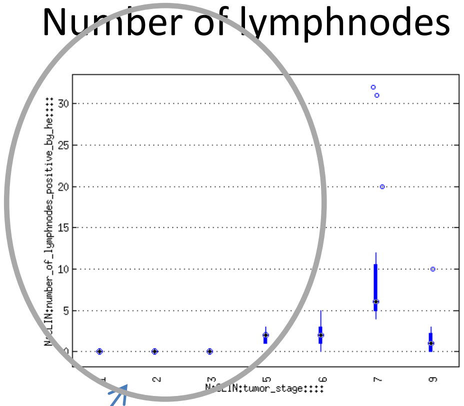

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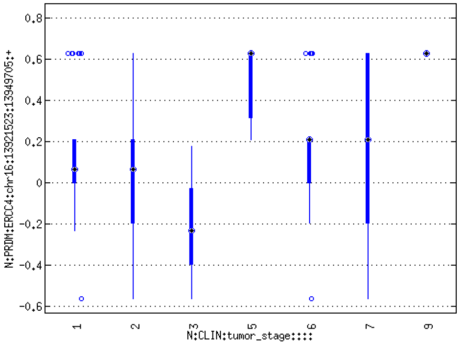
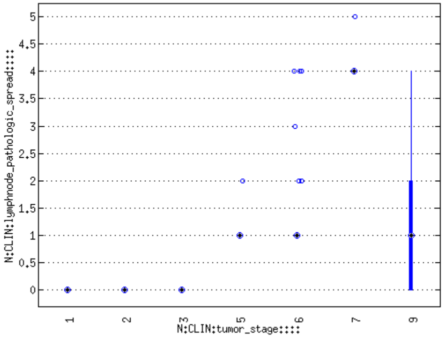


Etc.

Low predictive power in low tumor stages?

Repeat the analysis for Tumor Stage

Lymphnode spread



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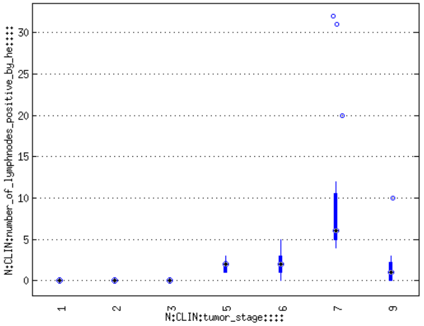

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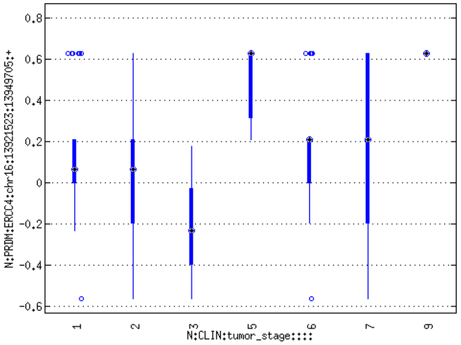
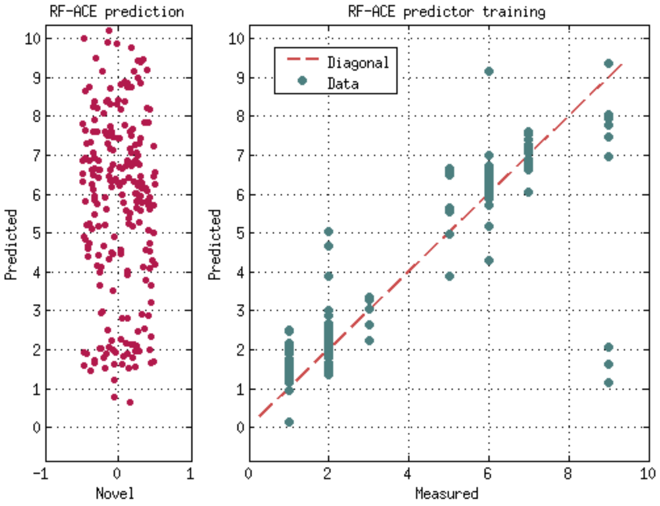
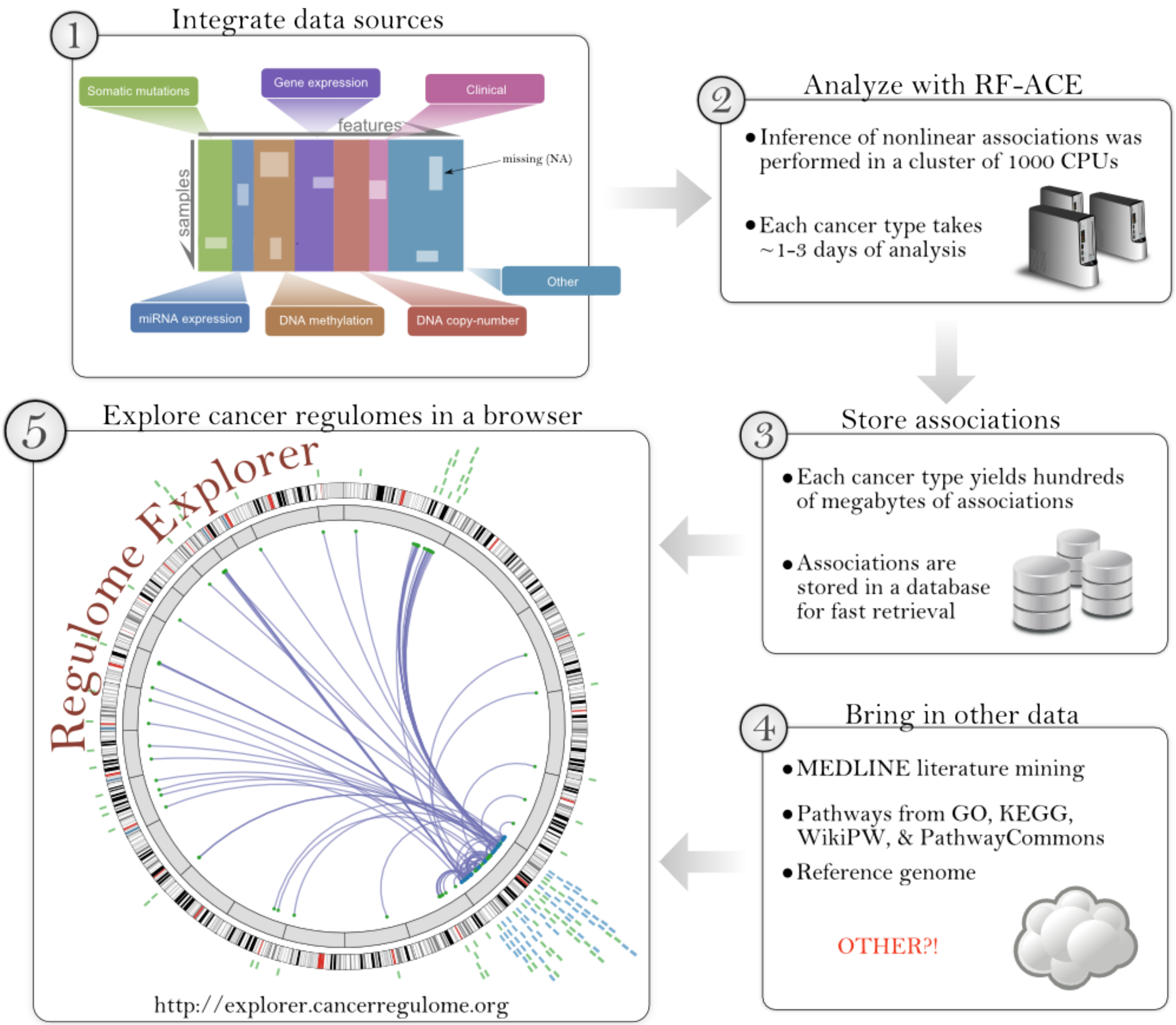


Etc.





1 Integrate data sources

2 Analyze with RF-ACE

- Inference of nonlinear associations was performed in a cluster of 1000 CPUs
- Each cancer type takes ~1-3 days of analysis

3 Store associations

- Each cancer type yields hundreds of megabytes of associations
- Associations are stored in a database for fast retrieval

4 Bring in other data

- MEDLINE literature mining
- Pathways from GO, KEGG, WikiPW, & PathwayCommons
- Reference genome

OTHER?!

5 Explore cancer regulomes in a browser

http://explorer.cancerregulome.org

Summary

- RF-ACE combines good parts from various established algorithms
  - RF, GBT, ACE (Tuv et al., 2009)
- Generic & fast implementation
  - Suits well to TCGA data
- Novel aspects
  - P-values for associations (not available in RF)
  - GBT for prediction

http://code.google.com/p/rf-ace

Many Thanks!

- Sheila Reynolds, Kari Torkkola, Jake Lin, Patrick May, Saija Sorsa, Brady Bernard, Adam Norberg, Thomas Robinson, Andrea Eakin, Ryan Bressler, Richard Kreisberg, Kalle Leinonen, Hector Rovira, Vesteinn Thorsson, Olli Yli-Harja, Harri Lähdesmäki, Ilya Shmulevich

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