

# A comparison study of prediction approaches for multiple training data sets & test data with block-wise missing values

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*Master Thesis*

XX. August 2020

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# Block-Wise Missingness

**Block-wise missingness** is a special type of missingness that is common in practice, particular in the context of multi-omics data [1]

<i>weight</i>	<i>height</i>	<i>income</i>	<i>education</i>	$g_1$	...	$g_{100}$	<i>Y</i>	
65.4	187	2.536	<i>Upper</i>				1	<b>Fold1</b>
83.9	192	1.342	<i>Lower</i>				0	
67.4	167	5.332	<i>Upper</i>				1	
		743	<i>Lower</i>	-0.42	...	1.43	1	<b>Fold2</b>
		2.125	<i>Lower</i>	0.52	...	-1.37	0	
105.2	175			-1.53	...	2.01	0	<b>Fold3</b>
71.5	173			0.93	...	0.53	0	
73.0	169			0.31	...	-0.07	1	

Block 1      Block 2      Block 3

**Table:** A data set with block-wise missingness - consisting of three feature-blocks, three folds and a binary target variable 'Y'.

# Random Forest Model (RF)

- Introduced by Breiman in 2001 [2]
- Ensemble method that uses the decision tree as a base learner
- Modified bagging algorithm to construct decorrelated decision trees
- A prediction of a RF equals the average of the predictions from all its decision trees
- The RF can be evaluated internally with the OOB-error  
→ “almost identical to that obtained by N-fold cross-validation” [[3], p. 593]

# Complete-Case Approach

**Idea:** Process the training data - with regard to the test data -, such that it does not contain any missing values afterwards:

- ① Remove all folds from the training data that miss at least one feature-block from the test data
- ② Remove all feature-blocks from the training data that are not available for the test data  
→ On this data a RF can be trained regularly & create predictions for the test data then!

	<u>Test Set</u>	Y	Clinical	CNV	
		?	✓	✓	
<u>Processed Data</u>	HOSPITAL 1	✓	✓	✓	✗
	HOSPITAL 2	✓	✓	✗	✓
	HOSPITAL 3	✓	✗	✓	✗

**Figure:** The 'Complete-Case' processing of the training data according to the available feature-blocks in the test-set.

# Single-Block Approach

**Idea:** Use a single feature-block of the train data - that the train & test data have in common - to train a RF and create predictions on the test data then:

- ① Train a RF on the single feature-blocks that test and train data have in common (remove observations with missing values from the blocks)
- ② Each fitted RF can create predictions for the test data then  
→ can result in multiple predictions for the test data

	Test Set				
	Y	Clinical	CNV	RNA	miRNA
<u>Processed Data 1</u>	?	✓	✓		
	HOSPITAL 1	✓	✓	✓	✗
	HOSPITAL 2	✓	✓	✗	✓
<u>Processed Data 2</u>	HOSPITAL 3	✓	✗	✓	✗
	HOSPITAL 1	✓	✓	✓	✗
	HOSPITAL 2	✓	✓	✗	✓
	HOSPITAL 3	✓	✗	✓	✗

**Figure:** 'Single-Block' processing of the training data so a random forest model can be regularly trained with each of these processed data sets.

# Imputation Approach

**Idea:** Impute the missing values in the train data and fit a RF on the feature-blocks that the train & test data have in common:

- ① Impute missing values in the train data with the 'missForest' approach  
→ train data is completely observed then
- ② On the feature-blocks that the train & test data have in common a RF can be trained regularly and create predictions for the test data then!

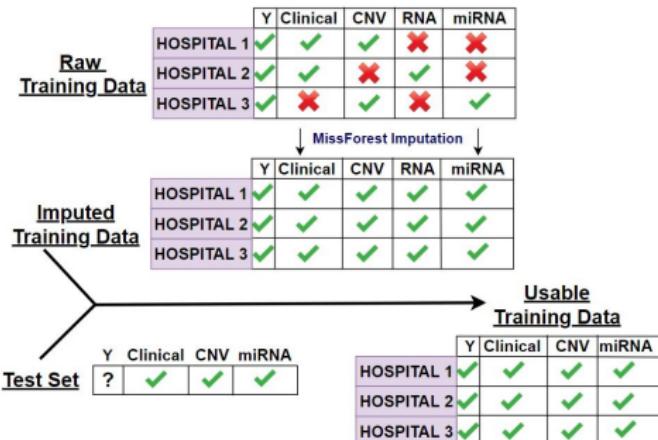
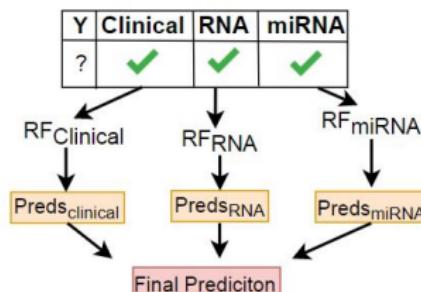
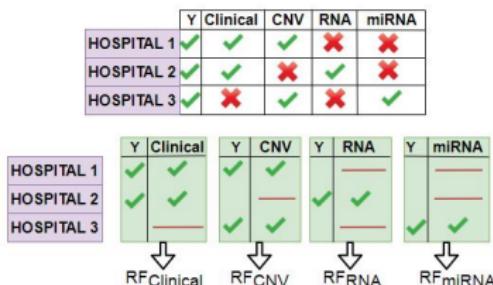


Figure: 'Imputation' approach to deal with block-wise missingness

# Block-Wise Approach

**Idea:** Fit a separate RF on each feature-block of the train data. To predict on the test data, the predictions of the block-wise fitted models are aggregated.

- ① Fit a separate RF on the observed parts of each feature-block in the training data
- ② To predict on the test data, each block-wise RF is asked for a prediction - only those RFs that were fitted on feature-block that is available for the test-set can do so
- ③ These block-wise predictions can be aggregated in a (un)weighted way



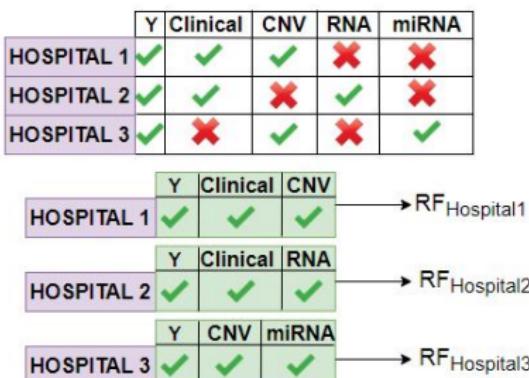
**Figure:** Training of random forest models with the 'Block-Wise' approach.

**Figure:** Prediction on test data with the 'Block-Wise' approach.

## Fold-Wise Approach

**Idea:** Fit a separate RF on the of each fold of the train data. To predict on the test data, the predictions of the fold-wise fitted models are aggregated.

- ① Fit a separate RF on the observed parts of each fold in the training data
- ② To predict on the test data, each fold-wise RF is asked for a prediction -  
The single decision trees of a RF might be pruned for this
- ③ The fold-wise predictions can be aggregated in a (un)weighted way



**Figure:** Training of random forest models with the 'Fold-Wise' approach.

# Fold-Wise Approach

**Idea:** Fit a separate RF on each fold of the train data. To predict on the test data, the predictions of the fold-wise fitted models are aggregated.

- Fit a separate RF on the observed parts of each fold in the training data
- To predict on the test data, each fold-wise RF is asked for a prediction -  
The single decision trees of a RF might be pruned for this
- The fold-wise predictions can be aggregated in a (un)weighted way

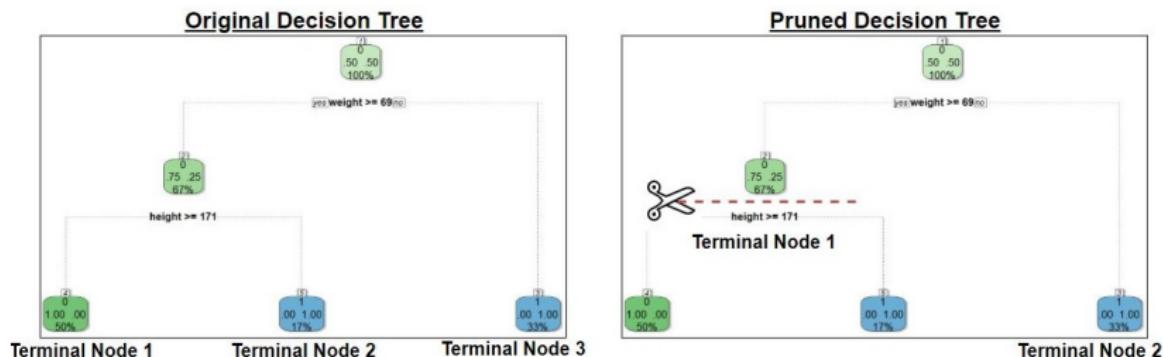


Figure: The pruning of a single decision tree.

## Fold-Wise Approach

**Idea:** Fit a separate RF on the observed parts of each fold of the train data. To predict on the test data, the predictions of the fold-wise fitted models are aggregated.

- ① Fit a separate RF on the observed parts of each fold in the training data
- ② To predict on the test data, each fold-wise RF is asked for a prediction -  
The single decision trees of a RF might be pruned for this
- ③ The fold-wise predictions can be aggregated in a (un)weighted way

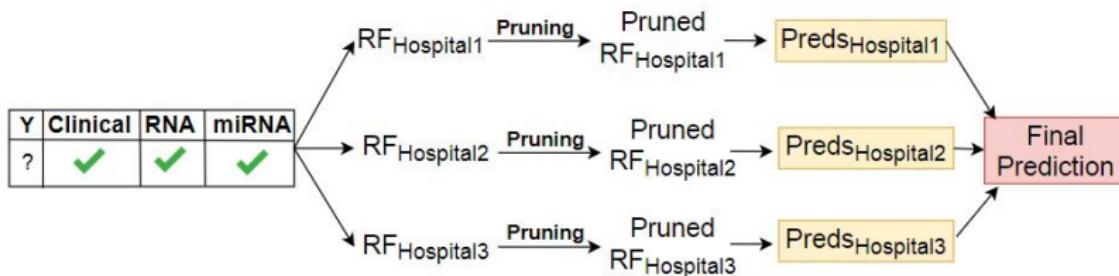


Figure: The prediction on test data with the 'Fold-Wise' approach.

# Metrics

Used to “evaluate the performance of a statistical learning method [...] - measure how well its predictions actually match the observed data” [[4], p. 29].

'F-1 Score' represents the harmonic mean of the precision and recall

$$\text{F-1 Score} = 2 * \frac{\left(\frac{\text{TP}}{\text{TP} + \text{FP}}\right) * \left(\frac{\text{TP}}{\text{TP} + \text{FN}}\right)}{\left(\frac{\text{TP}}{\text{TP} + \text{FP}}\right) + \left(\frac{\text{TP}}{\text{TP} + \text{FN}}\right)} \quad (1)$$

'Balanced Accuracy' represents the average of the class-wise accuracies

$$\text{Balanced Accuracy} = \frac{\frac{\text{TP}}{\text{TP} + \text{FN}} + \frac{\text{TN}}{\text{TN} + \text{FP}}}{2} \quad (2)$$

'Matthews correlation coefficient' can be seen as a “discretization of the Pearson correlation for binary variables” [[5], p. 1]

$$\text{MMC} = \frac{\text{TP} * \text{TN} - \text{FP} * \text{FN}}{\sqrt{(\text{TP} + \text{FP}) * (\text{TP} + \text{FN}) * (\text{TN} + \text{FP}) * (\text{TN} + \text{FN})}} \quad (3)$$

# TCGA data

- Received 21 processed data sets from Dr. Hornung
- The covariate 'gender' is used as a binary response variable
  - Even though it "is not a clinically meaningful outcome [...], it features major advantages for a purely methodological investigation" [[6], p. 5]
  - 7 data sets do not contain a 'gender' covariate and had to be removed  
→ A total of 14 data sets remained.
- Each of the 14 DFs contain the same five feature-blocks, whereby the dimensions were reduced to reduce the computational effort

Feature-Block	$\emptyset$ covariates in original	$\emptyset$ covariates in reduced
Clinical	3.5	3.5
miRNA	770	385
Mutation	16218	1616
CNV	57964	2898
RNA	23559	3555

Table: Average amount of covariates in each block over the 14 TCGA data sets.

# TCGA data

TCGA data sets are fully observed!!

→ Induce block-wise missingness so they can be used for the investigation of the approaches that can deal with block-wise missingness!

	Y	Clinical	CNV	RNA	Mutation	miRNA
Fold 1	✓	✓	✓	✗	✗	✗
Fold 2	✓	✓	✗	✓	✗	✗
Fold 3	✓	✓	✗	✗	✓	✗
Fold 4	✓	✓	✗	✗	✗	✓

	Y	Clinical	miRNA	RNA	Mutation	CNV
Fold 1	✓	✓	✓	✓	✓	✓
Fold 2	✓	✓	✗	✓	✓	✓
Fold 3	✓	✓	✗	✗	✓	✓
Fold 4	✓	✓	✗	✗	✗	✓

	Y	Clinical	CNV	RNA	Mutation	miRNA
Fold 1	✓	✓	✓	✓	✗	✓
Fold 2	✓	✓	✓	✓	✗	✗
Fold 3	✓	✓	✗	✓	✓	✓
Fold 4	✓	✓	✗	✓	✓	✓

	Y	Clinical	RNA & miRNA	Mutation & CNV
Fold 1	✓	✓	✓	✗
Fold 2	✓	✓	✗	✓

Table: The four various block-wise missingness patterns for the TCGA data sets.

# TCGA data

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## Algorithm 1: Evaluation of the approaches with the TCGA data

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**Input** :  $D \leftarrow$  TCGA data set with n observations & p features

$App \leftarrow$  Approach

$Patt \leftarrow$  Pattern of block-wise missingness

1. Split the fully observed data set D into five equally sized folds
  2. **for**  $k \leftarrow 1$  **to** 5 **do**
    - 2.1 Use fold  $k$  as test-set and the remaining four folds as train-set;
    - 2.2 Induce the block-wise missingness according to  $Patt$  into the train-set;
    - 2.3 Evaluate the predictive performance of the approach  $App$  for different combinations of observed feature-blocks in the test-set;
      - 2.3.1 Evaluation on the fully observed test-set;
      - 2.3.2 Evaluation on test-sets with one missing feature-block;
      - 2.3.3 Evaluation on test-sets with two missing feature-blocks;
      - 2.3.4 Evaluation on test-sets with three missing feature-blocks;
      - 2.3.5 Evaluation on test-sets with a single feature-block;
-

# Clinical asthma data

- The 'clinical asthma data' is a real-world data set with block-wise missingness
- It was provided by the group of Prof. Dr. med. Bianca Schaub at the 'paediatric clinic Dr. von Haunersches Kinderspital'
- Has a binary target variable that is defined as the presence of asthma (*521 observations: 265 with a negative & 256 with a positive response*)
- 5-fold CV to evaluate the approaches on this data
- Consists of six different blocks, whereby the amount of observations in the blocks inversely reflects the effort of generating the data

ID	Feature-Block	Number of observations	Number of variables
1	Questionnaire	521	44
2	Clinical routine diagnostics	385	16
3	Allergen sensitization	472	19
4	Cytokine expression data	149	29
5	Gene expression data I	66	82
6	Gene expression data II	46	84

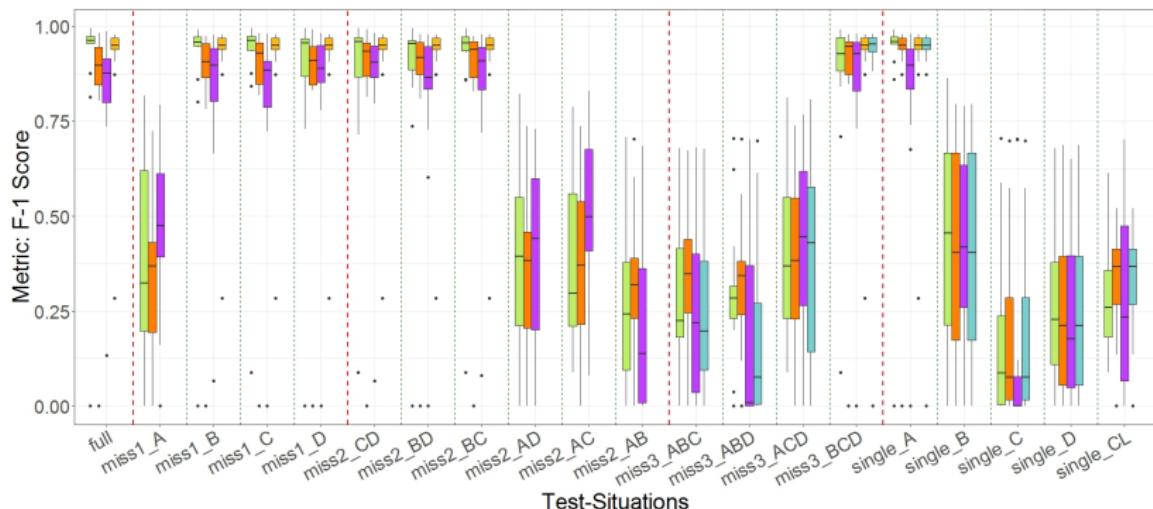
**Table:** The number of observations and variables for the different blocks in the clinical asthma data.

# TCGA data - Comparison - Pattern 1

## Comparison of all Approaches

TCGA - Pattern 1

Approach: ■ Fold-wise [F-1 Score] ■ Block-wise [F-1 Score] ■ Imputation ■ Single-Block [A'] ■ Complete-Case



**Figure:** Comparison of the different approaches on the TCGA data with induced block-wise missingness according to pattern 1.

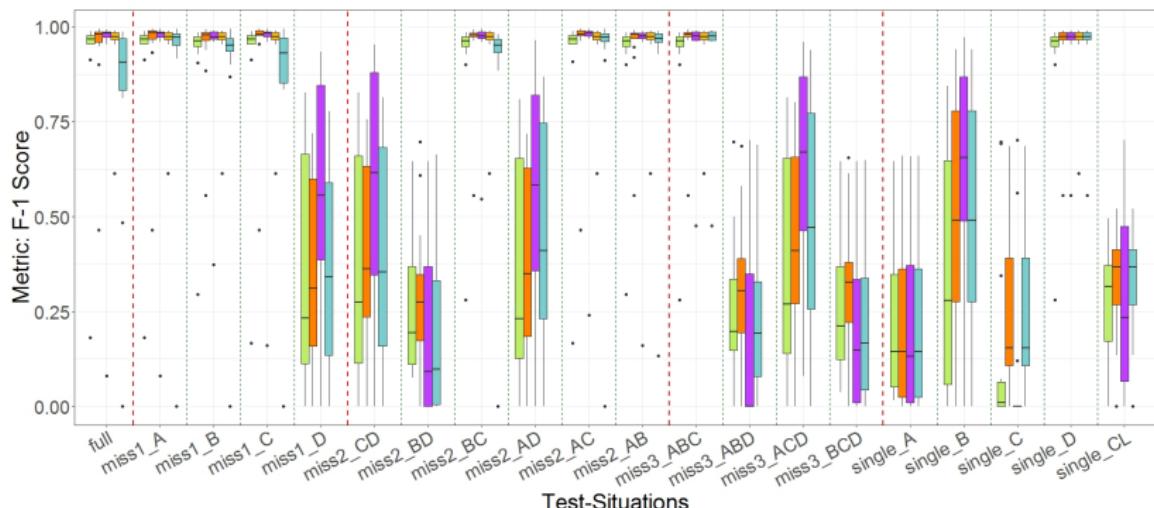
- Fold-Wise approach is the best in 11 test-situations
- Imputation approach is the best in 4 test-situations
- Block-Wise approach is the best in 3 test-situations

# TCGA data - Comparison - Pattern 2

## Comparison of all Approaches

TCGA - Pattern 2

Approach: ■ Fold-wise [F-1 Score] ■ Block-wise [F-1 Score] ■ Imputation ■ Single-Block [D] ■ Complete-Case



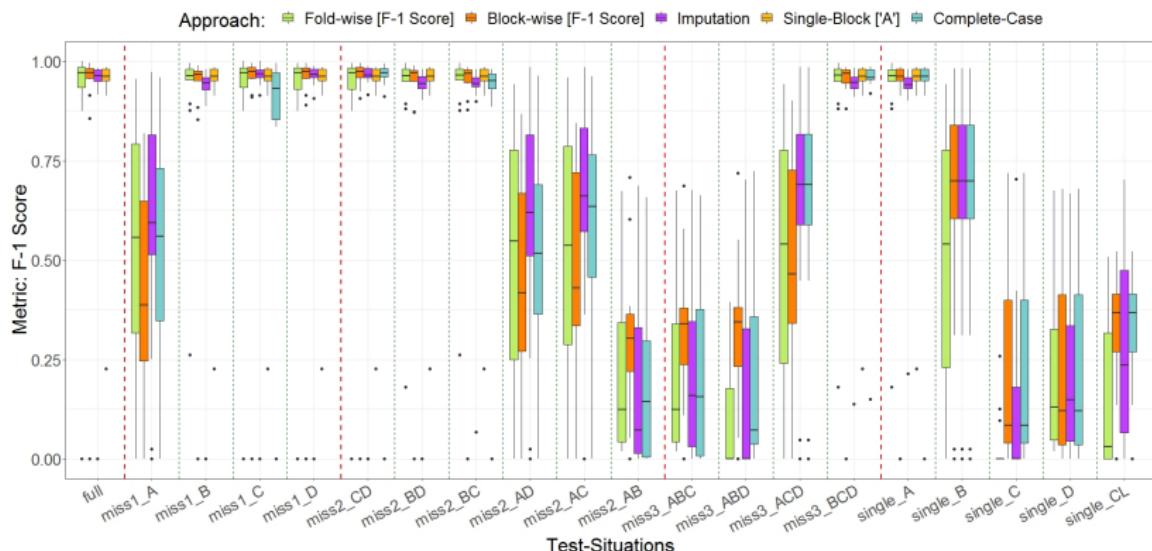
**Figure:** Comparison of the different approaches on the TCGA data with induced block-wise missingness according to pattern 2.

- Imputation approach is the best in 8 test-situations
- Block-Wise approach is the best in 8 test-situations

# TCGA data - Comparison - Pattern 3

## Comparison of all Approaches

TCGA - Pattern 3



**Figure:** Comparison of the different approaches on the TCGA data with induced block-wise missingness according to pattern 3.

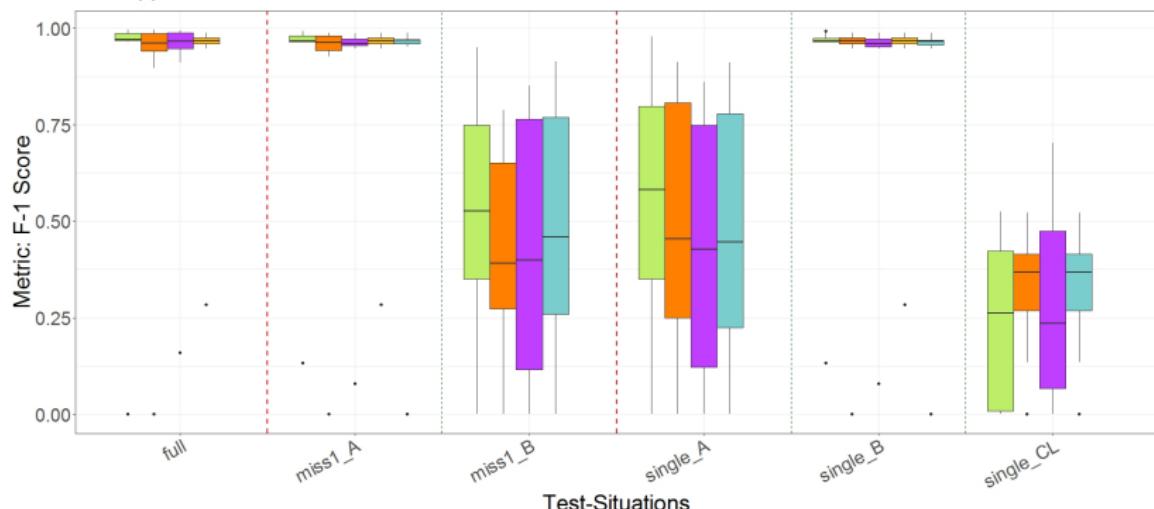
- Block-Wise approach is the best in 10 test-situations
- Imputation approach is the best in 4 test-situations
- Fold-Wise approach is the best in 2 test-situations

# TCGA data - Comparison - Pattern 4

## Comparison of all Approaches

TCGA - Pattern 4

Approach: ■ Fold-wise [F-1 Score] ■ Block-wise [F-1 Score] ■ Imputation ■ Single-Block [B] ■ Complete-Case



**Figure:** Comparison of the different approaches on the TCGA data with induced block-wise missingness according to pattern 4.

- Fold-Wise approach is the best in 4 test-situations
- Complete-Case approach in just a single case

## Clinical asthma data - Hagenberg's Methods

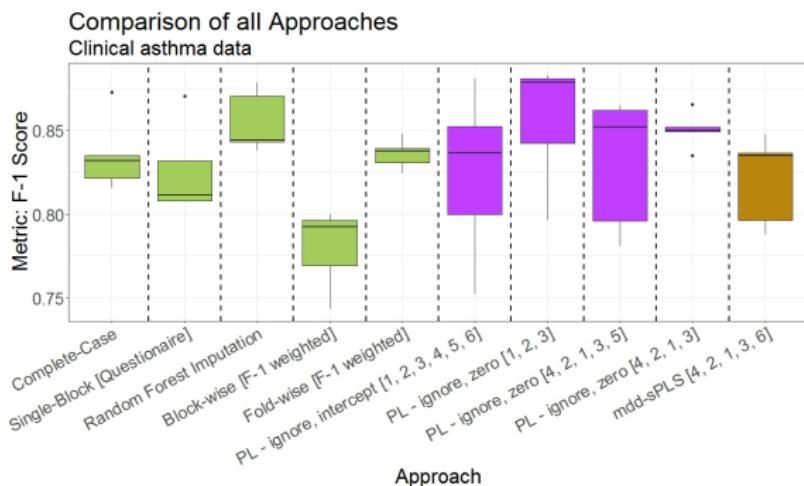
[1] The thesis from Hagenberg [7] introduced two adaptions of the priority-Lasso, such that it can directly deal with block-wise missingness.

- 'PL - ignore, intercept'
- 'PL - ignore, zero'
- 'PL - impute, max. n'
- 'PL - impute, max. blocks'

The diverse priority-Lasso approaches were evaluated with different priorities for the single feature-blocks in the training data and different subsets of blocks from test data used for the prediction

[2] Additionally, Hagenberg has used the mdd-sPLS method [8] as a reference approach

# Clinical asthma data - Results



**Figure:** Comparison of the random forest adaptions, the priority-Lasso adaptions and the mdd-sPLS method on the clinical asthma data.

→ Block-Wise < Single-Block < Complete-Case < mdd-sPLS <  
 'PL - ignore, intercept [1, 2, 3, 4, 5, 6]' < Fold-Wise < Imputation <  
 'PL - ignore, zero [4, 2, 1, 3]' < 'PL - ignore, zero [4, 2, 1, 3, 5]' <  
 'PL - ignore, zero [1, 2, 3]'

# Discussion and Conclusion

## Random Forest based approaches:

- Single-Block & Complete-Case are the simplest adaptions  
→ worst predictive performance among the RF approaches
- Block- & Fold-Wise approach have the best predictive performance with the 'F-1 Score' as weight metric
- Performance of the Block- & Fold-Wise approach is opposing  
→ in settings, where one performs good, the other performs bad
- Performance of the Imputation approach is comparable to the performance of the Block- & Fold-Wise approach
- The Imputation, Block- & Fold-Wise approach can be applied flexible to different test-sets
- The Imputation & Fold-Wise approach are extremely slow compared to the other RF approaches

## Discussion and Conclusion

### Comparison of the approaches:

- Comparison of the approaches based on the clinical asthma data
- Imputation & Fold-Wise are the best RF approaches on the clinical asthma data → outperform mdd-sPLS & 'PL-ignore, intercept' with the naive block-priority
- 'PL-ignore' with other block priorities and/ or only a subset of blocks for the prediction outperform the Imputation & Fold-Wise approach
- A 'selection bias' might have been introduced, as much more variants of the priority-Lasso have been tried out than with the RF approaches

⇒ **Choice of the approach depends on the prior knowledge of the data!**

- User knows which feature-blocks might be more important than others  
→ 'ignore' priority-Lasso adaptions can be recommended
- User does not know which feature-blocks might be more important than others  
→ random forest approaches seem to be the better choice  
(especially Fold- & Block-Wise, as these use an OOB metric to estimate the importance of the diverse folds/ feature-blocks)

# Discussion and Conclusion

## Outlook:

- Comparison of mdd-sPLS, PL & RF approaches on further data-sets for a better generalisation of the results
- Implementation of the Fold-Wise approach directly in 'C' / 'Java' for speed improvement
- Combining the idea of the 'Block Forest' article [9] with the Fold-Wise approach
  - Incorporation of the block structure for the split point selection

## References |

-  Roman Hornung et al. "Random forests for multiple training data sets with varying covariate sets". manuscript - unpublished yet. - in prep.
-  Leo Breiman. "Random forests". In: *Machine learning* 45.1 (2001), pp. 5–32.
-  Trevor Hastie, Robert Tibshirani, and Jerome Friedman. *The elements of statistical learning: data mining, inference, and prediction*. Springer Science & Business Media, 2009.
-  Gareth James et al. *An introduction to statistical learning*. Vol. 112. Springer, 2013.
-  Sabri Boughorbel, Fethi Jarray, and Mohammed El-Anbari. "Optimal classifier for imbalanced data using Matthews Correlation Coefficient metric". In: *PloS one* 12.6 (2017).
-  Nicole Schüller et al. "Improved outcome prediction across data sources through robust parameter tuning". In: (2019).

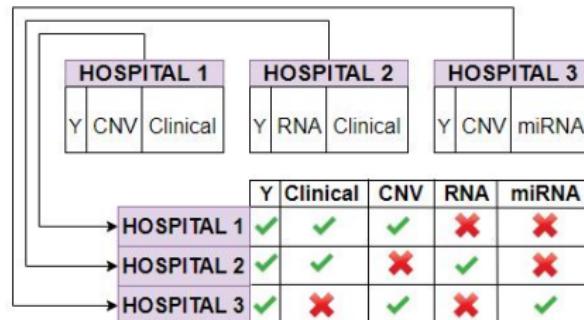
## References II

-  [Jonas Hagenberg](#). "Penalized regression approaches for prognostic modelling using multi-omics data with block-wise missing values". manuscript - unpublished yet. - in prep.
-  [Hadrien Lorenzo, Jérôme Saracco, and Rodolphe Thiébaut](#). "Supervised Learning for Multi-Block Incomplete Data". In: *arXiv preprint arXiv:1901.04380* (2019).
-  [Roman Hornung and Marvin N Wright](#). "Block Forests: random forests for blocks of clinical and omics covariate data". In: *BMC bioinformatics* 20.1 (2019), p. 358.

# Attachment I

There are two main reasons for block-wise missingness in 'Multi-Omics' data:

- ① Collection of omics data is more expensive and complex as for regular clinical data  
→ can not always be collected for all participants of a study
- ② Collection of data sets from different sources - e.g. various hospitals



**Figure:** Block-wise missingness, when concatenating data from diverse sources.

## Attachment II

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**Algorithm 2:** Growing a random forest model

---

**Input :**  $D \leftarrow$  data with  $n$  observations &  $p$  features  
 $M \leftarrow$  number of trees in the forest  
 $n_{min} \leftarrow$  'MinSplit' argument of a decision tree  
 $mtry \leftarrow$  number of variables to draw at each split

**for**  $m \leftarrow 1$  **to**  $M$  **do**

1. Draw a bootstrap sample  $Z^*$  of size ' $n$ ' from ' $D$ ';  
2. Based on  $Z^*$  grow a decision tree, by recursively repeating the following steps for each terminal node of the tree, until the minimum node size  $n_{min}$  is reached;
    - 2.1 Randomly draw ' $mtry$ ' of the ' $p$ ' available variables;
    - 2.2 Pick the best splitting point among the ' $mtry$ ' variables;
    - 2.3 Split the node into two daughter nodes;
-



## Attachment III

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### Algorithm 3: Evaluation of the approaches with the clinical asthma data

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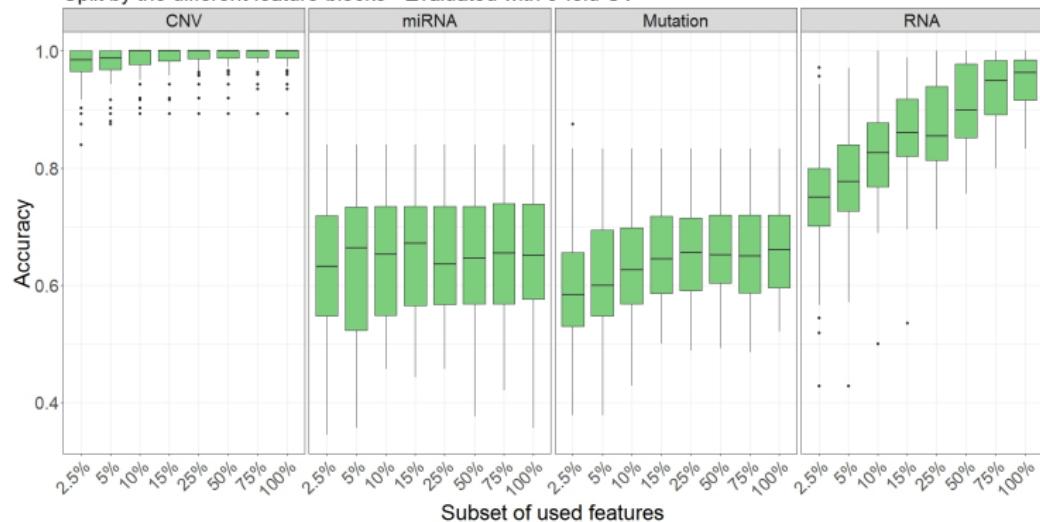
**Input** :  $D \leftarrow$  clinical asthma data with block-wise missingness  
 $App \leftarrow$  Approach

1. Split the clinical asthma data  $D$  into five equally sized folds
  2. **for**  $k \leftarrow 1$  **to** 5 **do**
    - 2.1 Use fold  $k$  as test-set and the remaining four folds as train-set;
    - 2.2 Extract the unique patterns of block-wise missingness in the test-set -  $test_{patterns}$ ;
    - 2.3 **for**  $pattern_{current} \in test_{patterns}$  **do**
      - 2.3.1 Fit  $App$  on the train-set, such that it can be used for the prediction on  $pattern_{current}$ ;
      - 2.3.2 Generate predictions for the test-observations with block-wise missingness according to  $current_{pattern}$
    - 2.4 Evaluate the predictive performance of the approach  $App$  by comparing the predicted classes with the true classes;
-



## Attachment IV

Single Block Performance of a random forest over all 14 TCGA data sets  
Split by the different feature-blocks - Evaluated with 5-fold CV

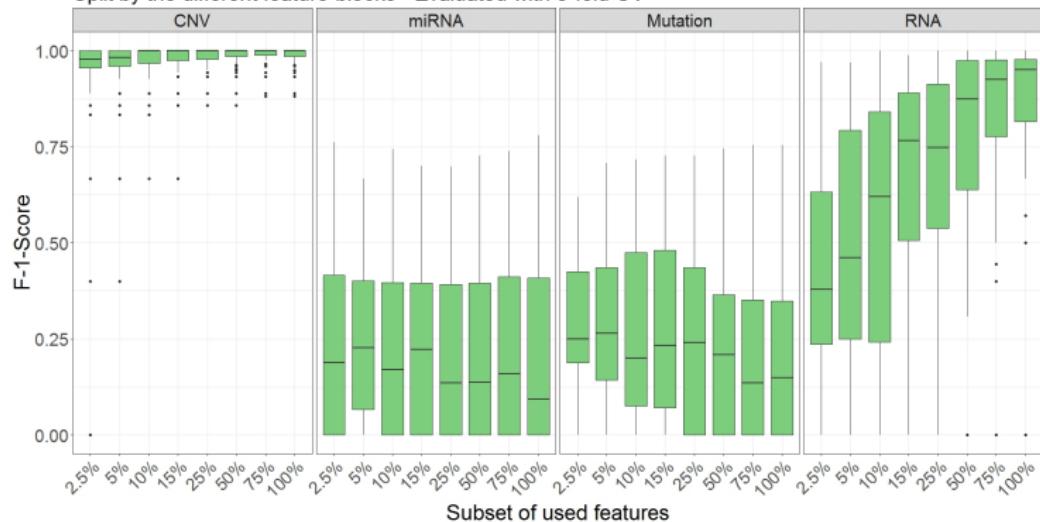


**Figure:** The accuracy of a random forest model evaluated on the single omics feature-blocks for a range of possible subsets on all 14 TCGA data sets.



## Attachment V

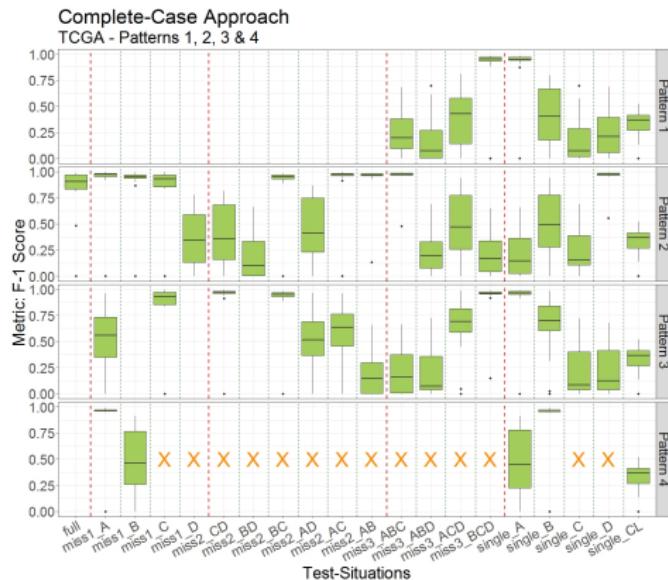
Single Block Performance of a random forest over all 14 TCGA data sets  
Split by the different feature-blocks - Evaluated with 5-fold CV



**Figure:** The F-1 score of a random forest model evaluated on the single omics feature-blocks for a range of possible subsets on all 14 TCGA data sets.



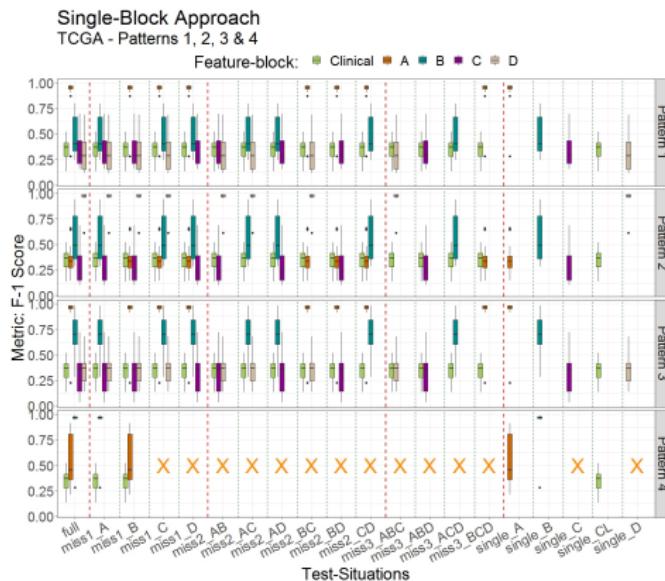
# Attachment VI



**Figure:** Results of the 'Complete-Case' approach on the TCGA data with induced block-wise missingness according to pattern 1, 2, 3 & 4. Test-Situations that are not available for 'Pattern 4' are marked with an orange cross.



## Attachment VII



**Figure:** Results of the 'Single-Block' approach on the TCGA data with induced block-wise missingness according to pattern 1, 2, 3 & 4. Test-Situations that are not available for 'Pattern 4' are marked with an orange cross.



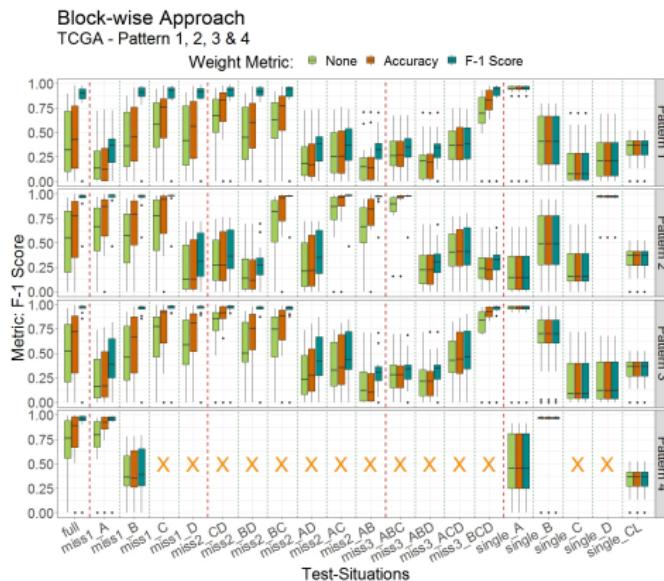
## Attachment VIII



**Figure:** Results of the 'Imputation' approach on the TCGA data with induced block-wise missingness according to pattern 1, 2, 3 & 4. Test-Situations that are not available for 'Pattern 4' are marked with an orange cross.



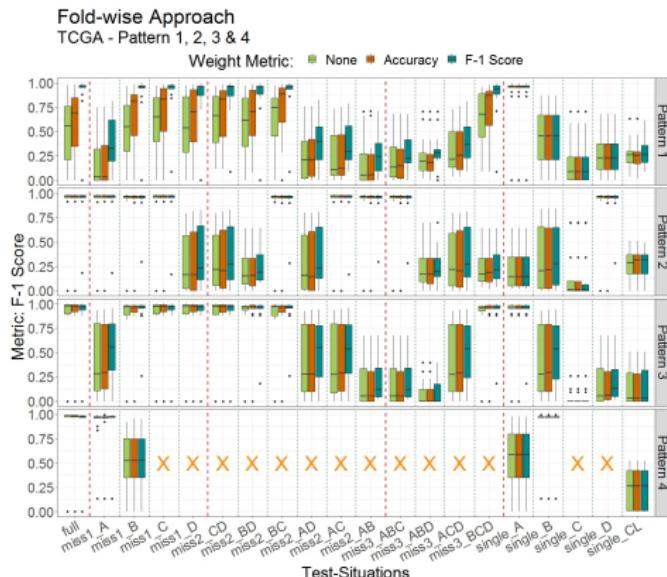
# Attachment IX



**Figure:** Results of the 'Block-Wise' approach on the TCGA data with induced block-wise missingness according to pattern 1, 2, 3 & 4. Test-Situations that are not available for 'Pattern 4' are marked with an orange cross.



# Attachment X

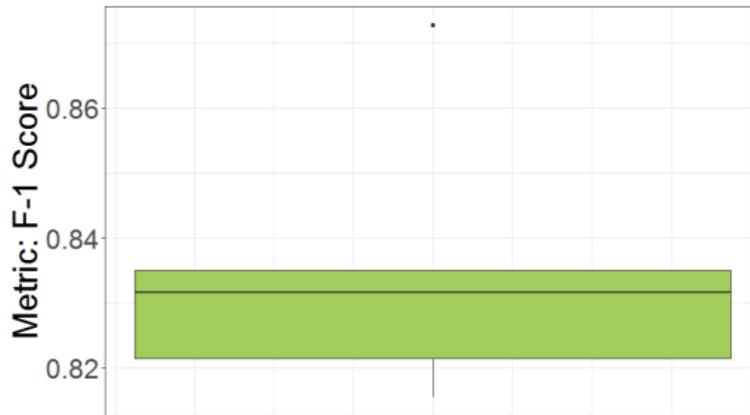


**Figure:** Results of the 'Fold-Wise' approach on the TCGA data with induced block-wise missingness according to pattern 1, 2, 3 & 4. Test-Situations that are not available for 'Pattern 4' are marked with an orange cross.



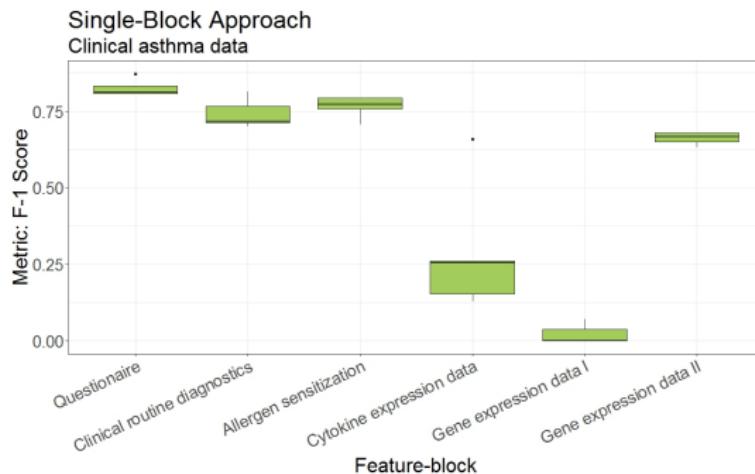
## Attachment XI

## Complete-Case Approach Clinical asthma data



**Figure:** Results of the 'Complete-Case' approach on the clinical asthma data

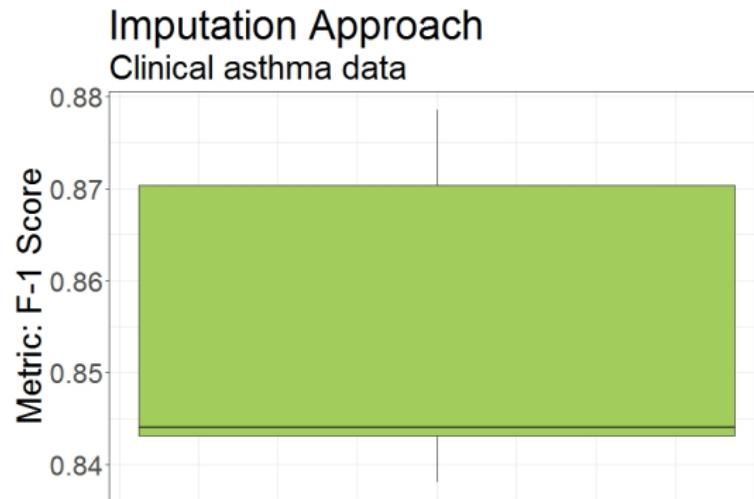
## Attachment XII



**Figure:** Results of the 'Single-Block' approach on the clinical asthma data



## Attachment XIII



**Figure:** Results of the 'Imputation' approach on the clinical asthma data



## Attachment XIV

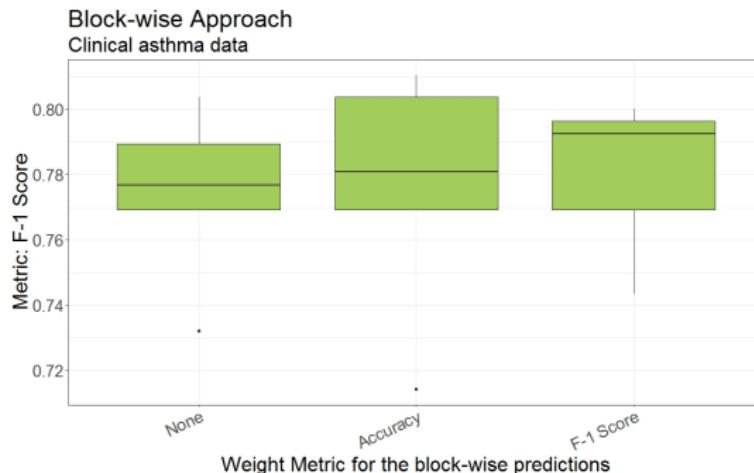


Figure: Results of the 'Block-Wise' approach on the clinical asthma data

# Attachment XV

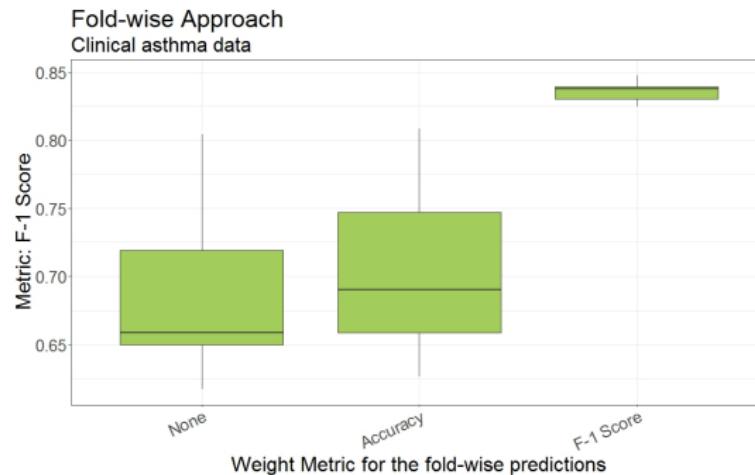
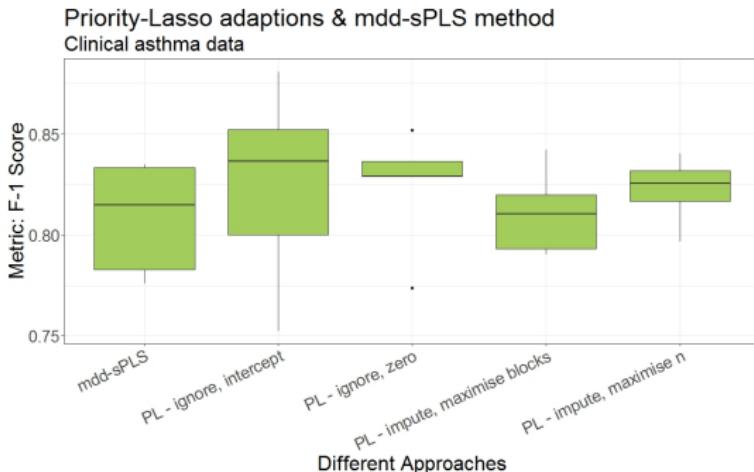


Figure: Results of the 'Fold-Wise' approach on the clinical asthma data

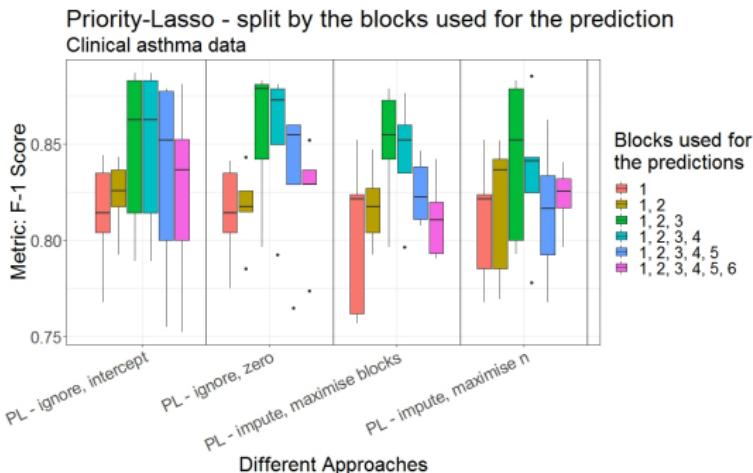
# Attachment XVI



**Figure:** Results of the priority-Lasso adaptions and mdd-sPLS with the naive block order on the clinical asthma data



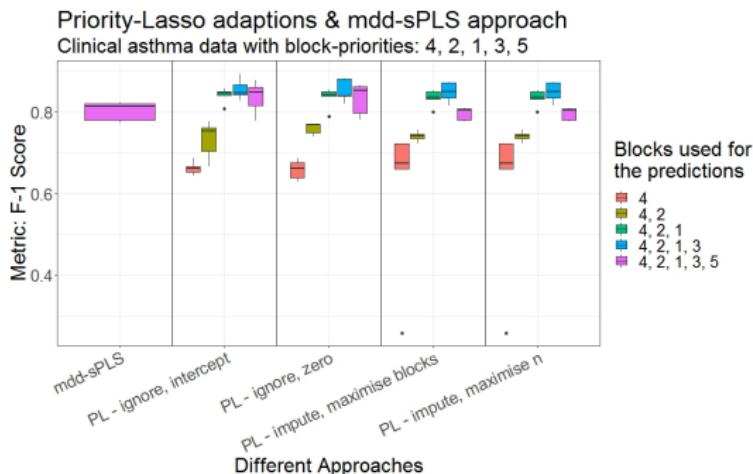
## Attachment XVII



**Figure:** Results of the priority-Lasso adaptions with the naive block order on the clinical asthma data - using only a subset of the blocks for the prediction

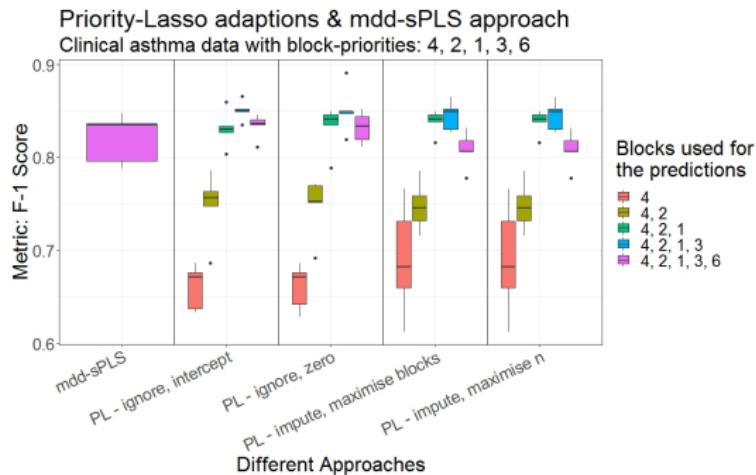


## Attachment XVIII



**Figure:** Results of the priority-Lasso adaptions with adjusted block order (4, 2, 3, 1, 5) on the clinical asthma data - using only a subset of the blocks for the prediction - and the mdd-sPLS method

## Attachment XIX



**Figure:** Results of the priority-Lasso adaptions with adjusted block order (4, 2, 3, 1, 6) on the clinical asthma data - using only a subset of the blocks for the prediction - and the mdd-sPLS method