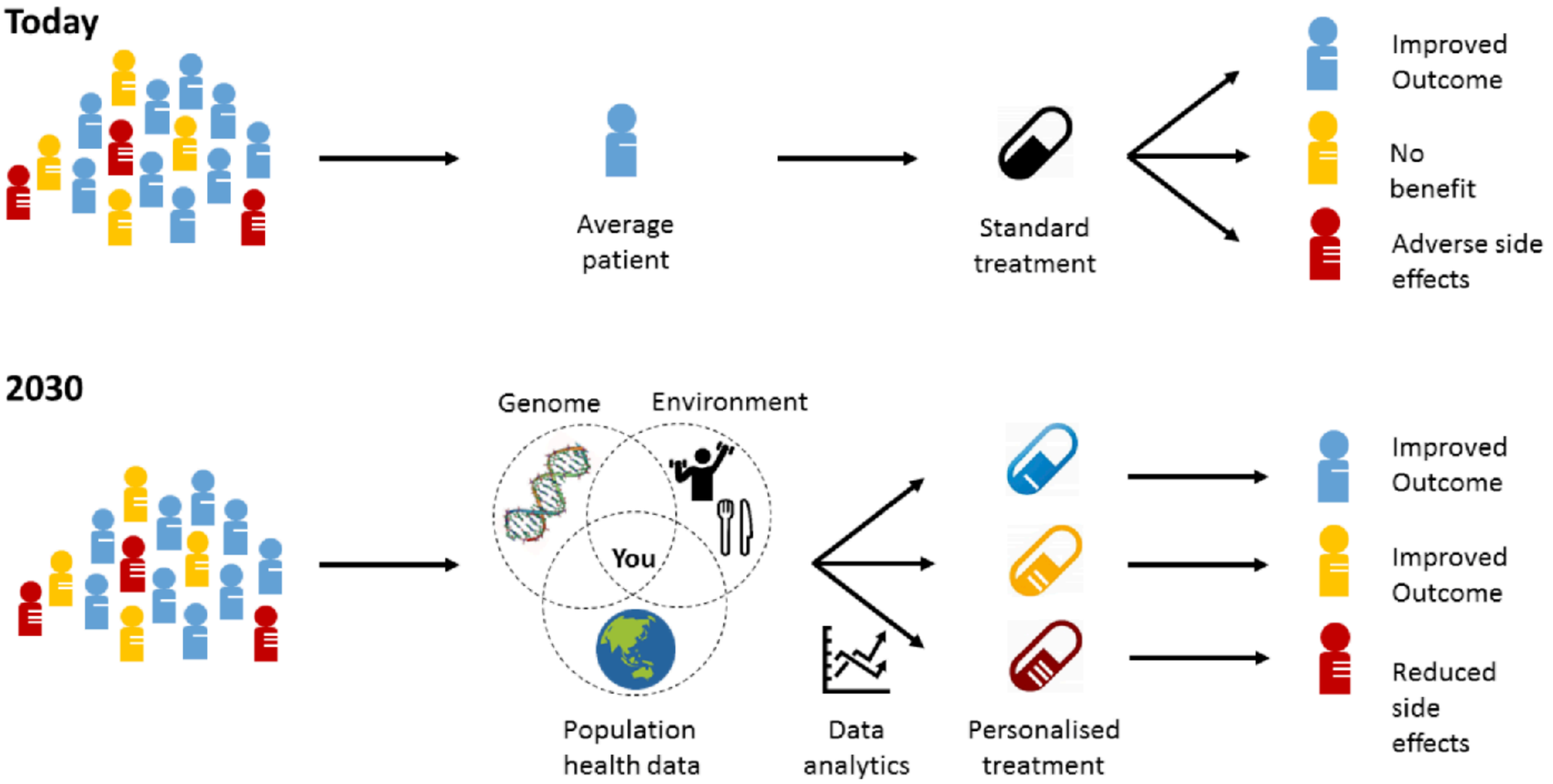
Kevin Wang

Cross-Platform Omics Prediction: a step towards precision medicine

Precision medicine: predicting best cause of action using omics data

https://www.chiefscientist.gov.au/wp-content/uploads/Precision-medicine-final.pdf

Precision medicine: predicting best cause of action using omics data



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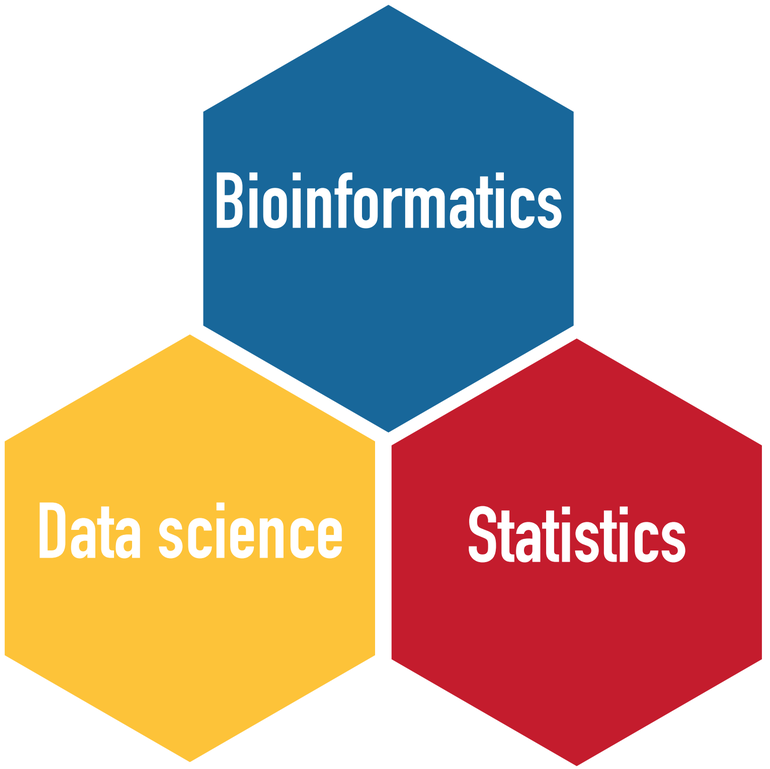
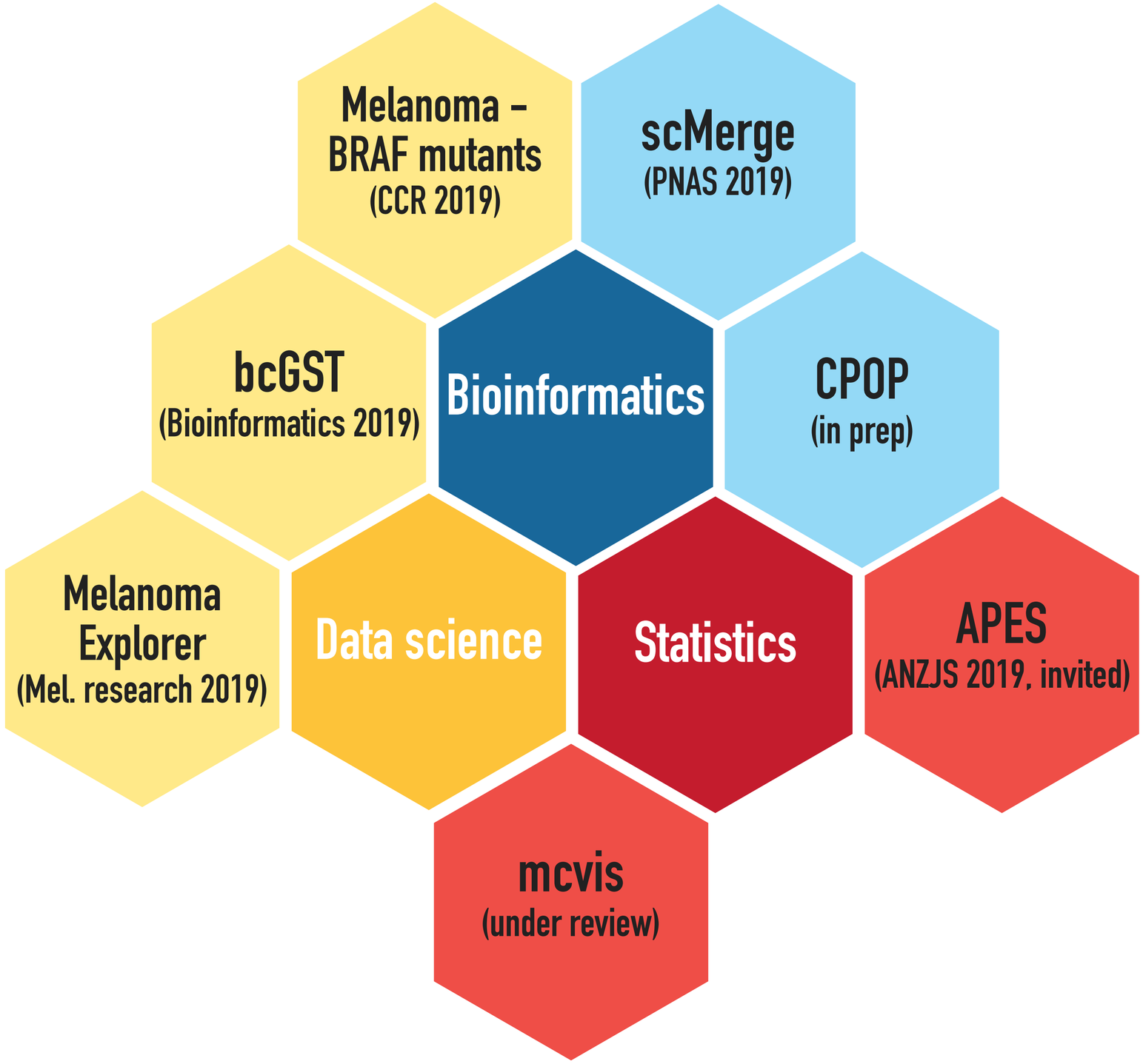
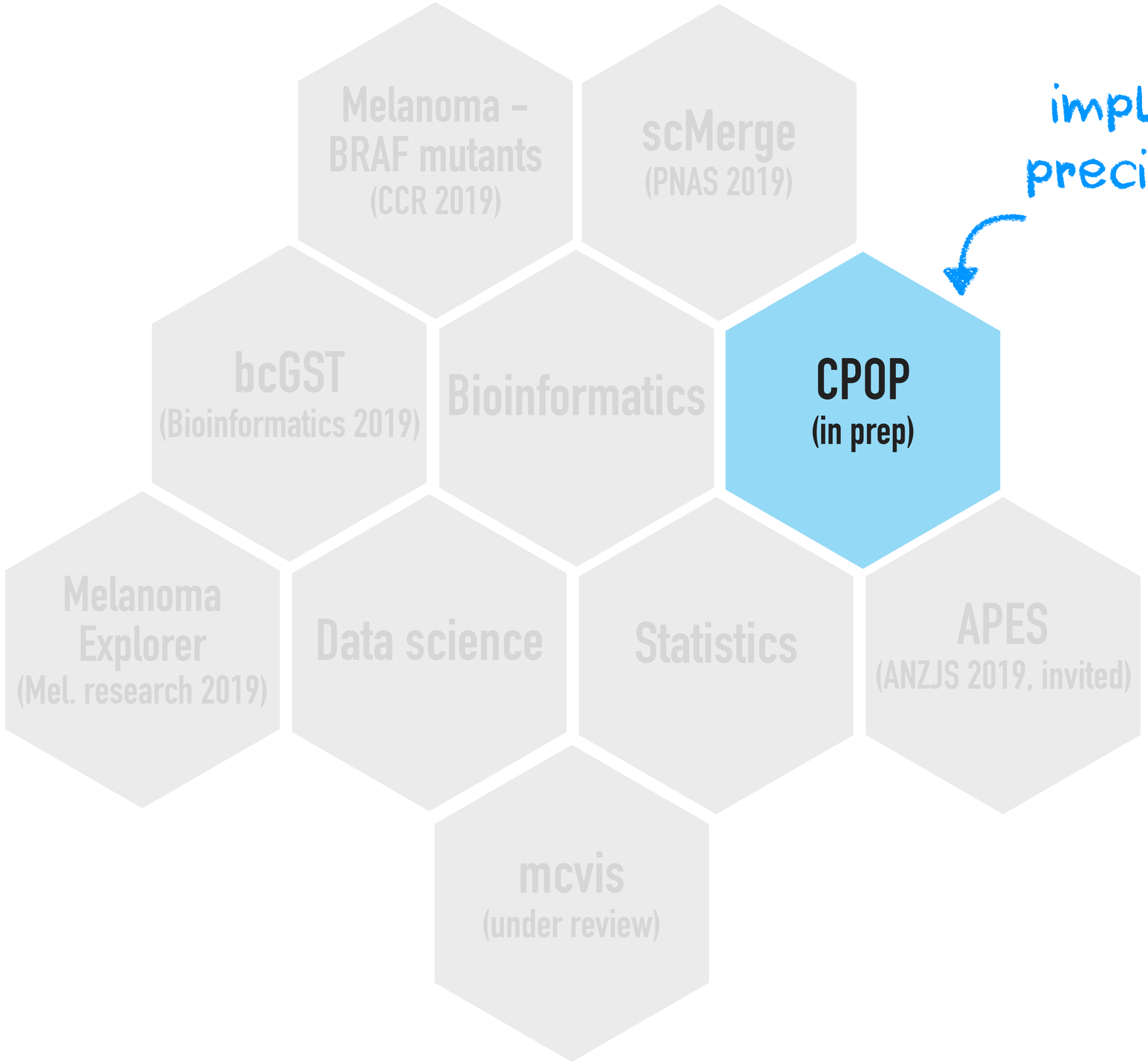

Bioinformatics
Data science
Statistics


Melanoma – BRAF mutants (CCR 2019)
scMerge (PNAS 2019)
bcGST (Bioinformatics 2019)
Bioinformatics
CPOP (in prep)
Melanoma Explorer (Mel. research 2019)
Data science
Statistics
APES (ANZJS 2019, invited)
mcvis (under review)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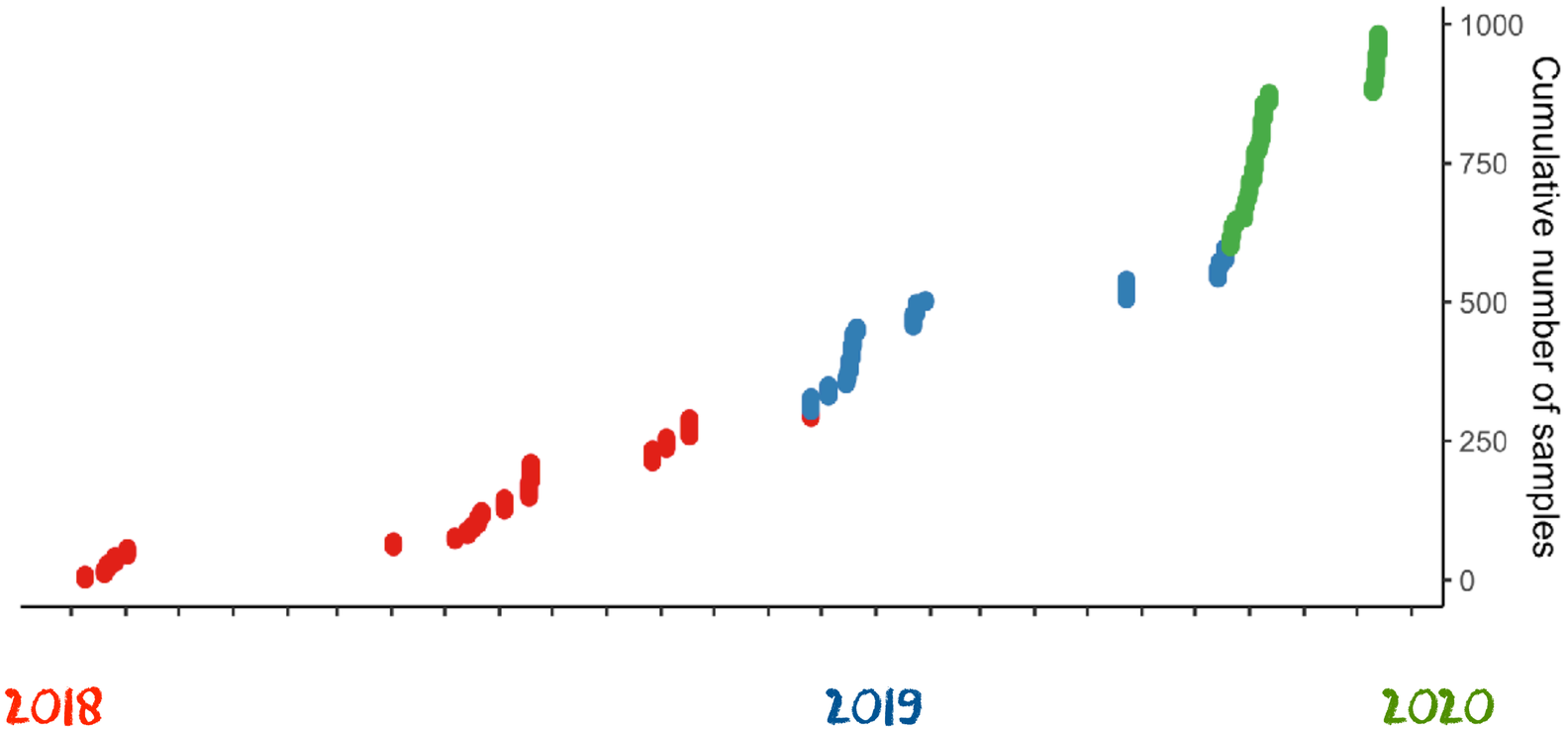
Towards implementation precision medicine

Melanoma Institute Australia

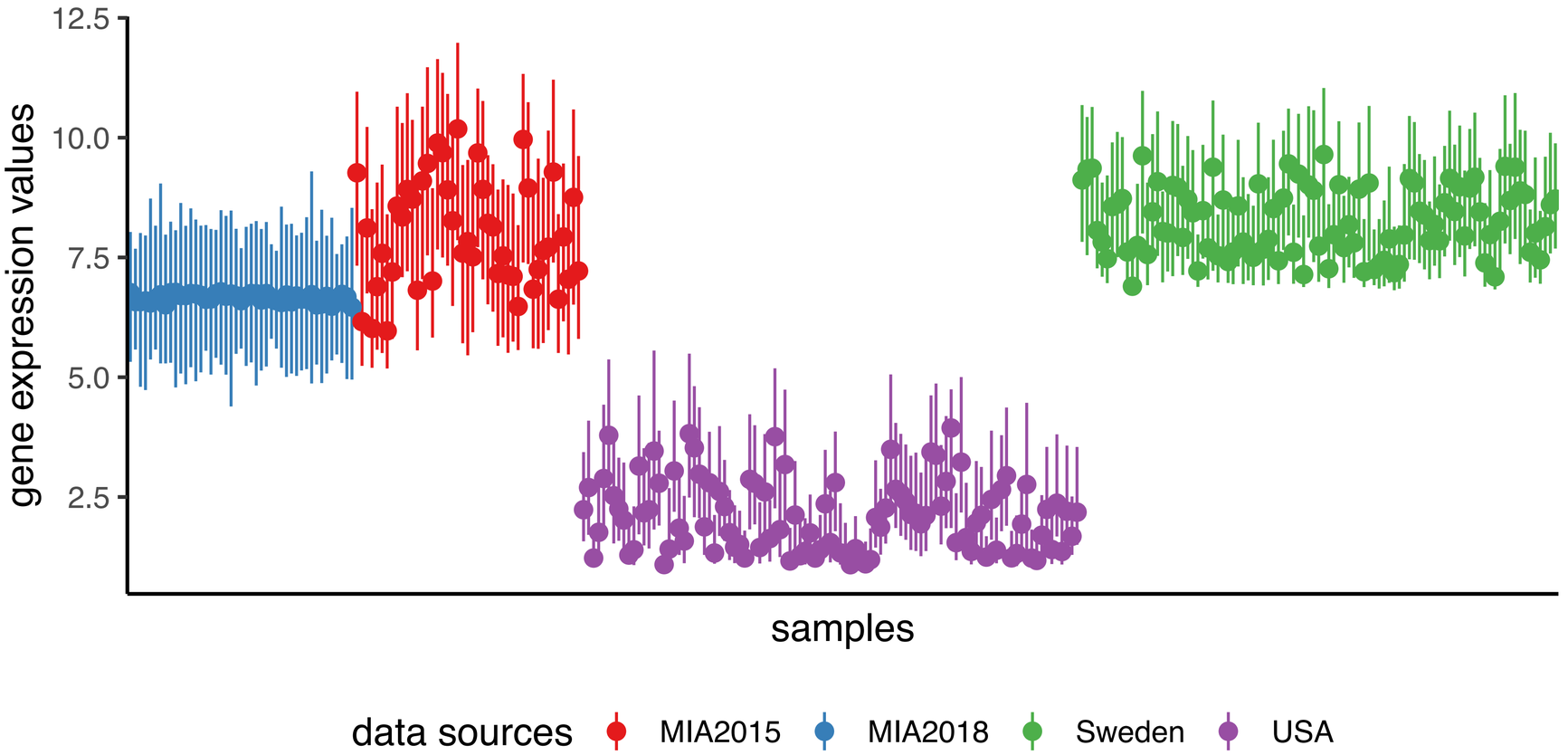
- Predict patient outcomes using gene expression:
  - prospectively



Melanoma Institute Australia

https://researchdata.ands.org.au/centre-research-excellence-outcomes-melanoma/1318231

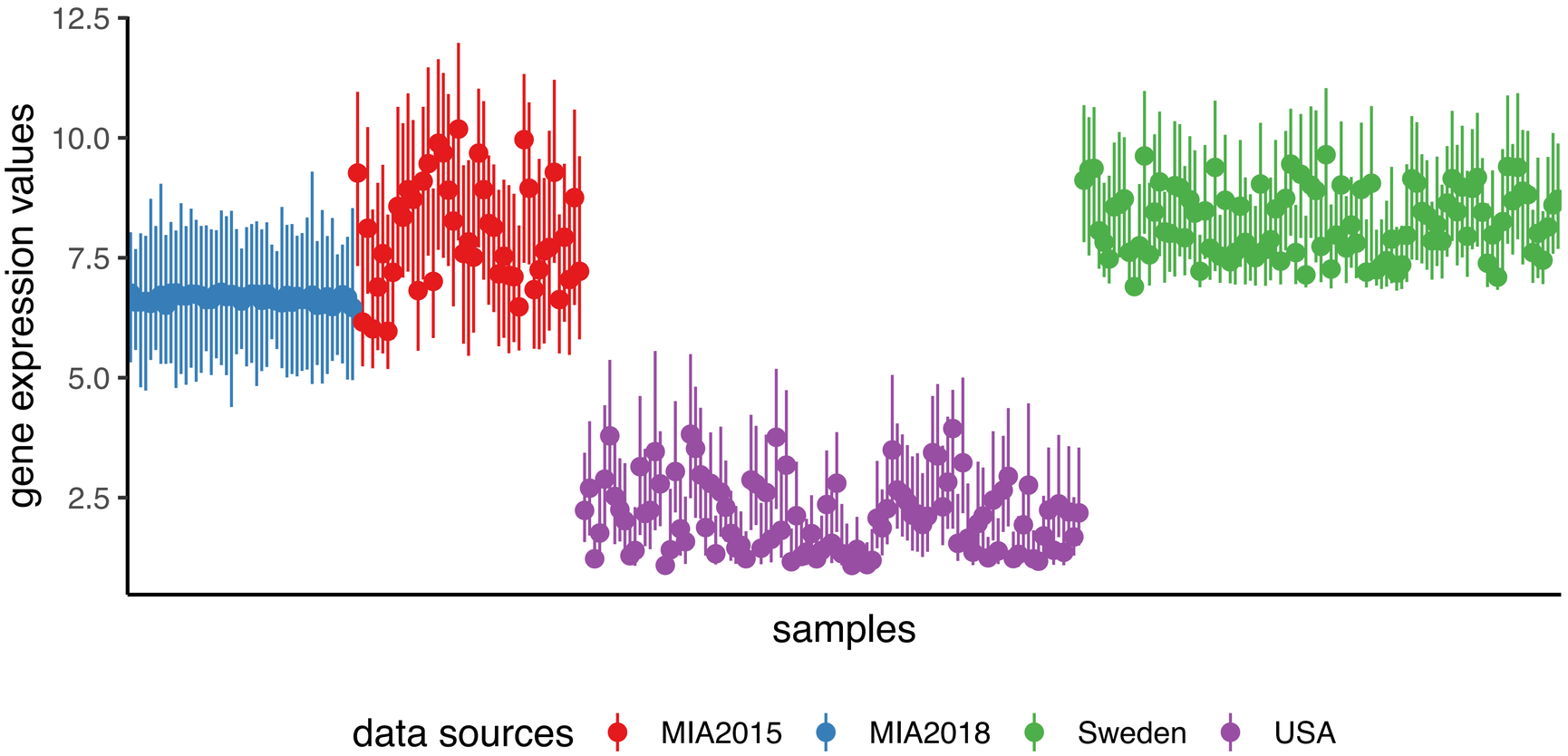
Melanoma Institute Australia



- Predict patient outcomes using gene expression:
  - prospectively
  - multi-centres
- CRE grant for implementation

https://researchdata.ands.org.au/centre-research-excellence-outcomes-melanoma/1318231

Vision of a risk score



$$\hat{y} = X\hat{\beta}$$

regression-based risk score

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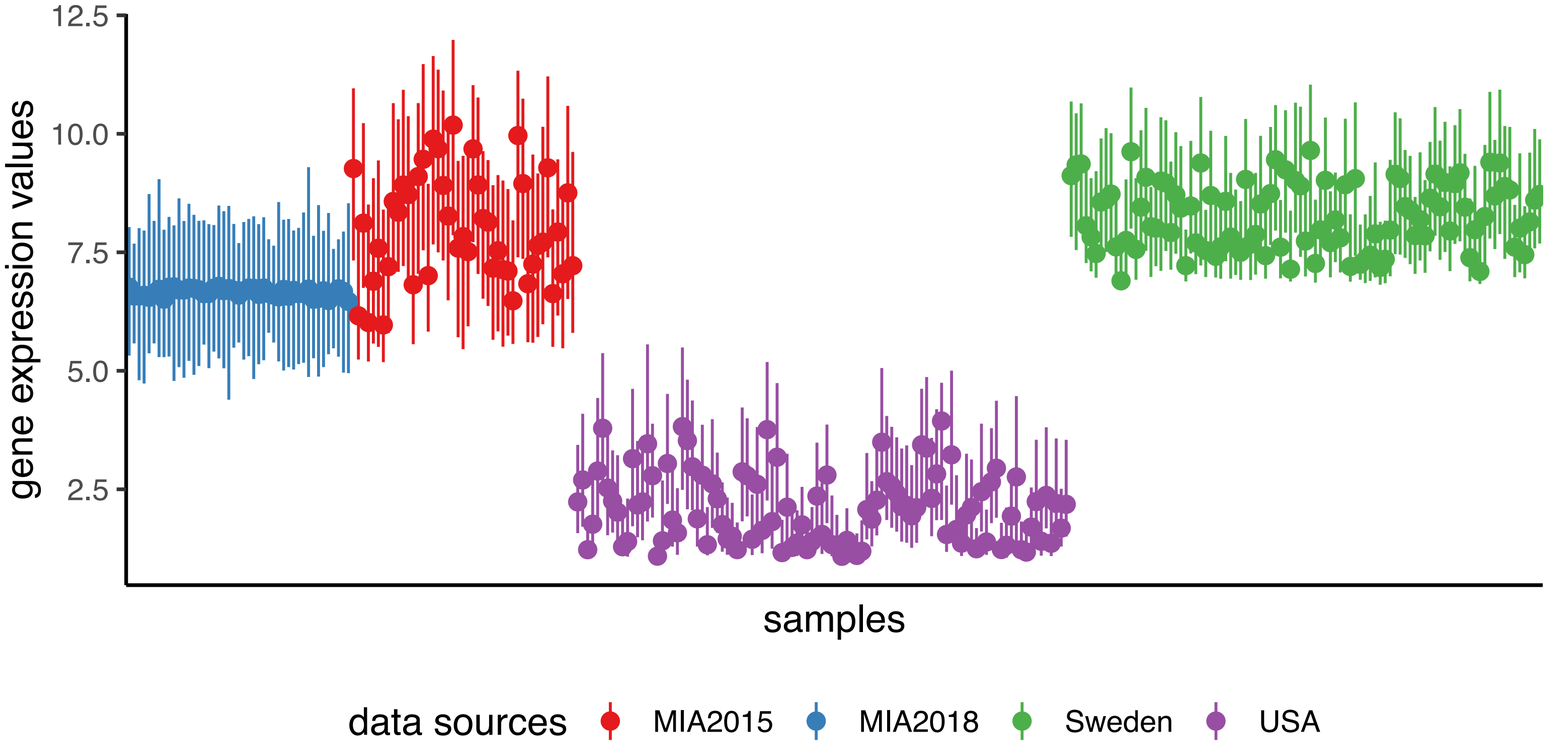
Omics-based risk score

Omics-based clinical risk score: what is so difficult?



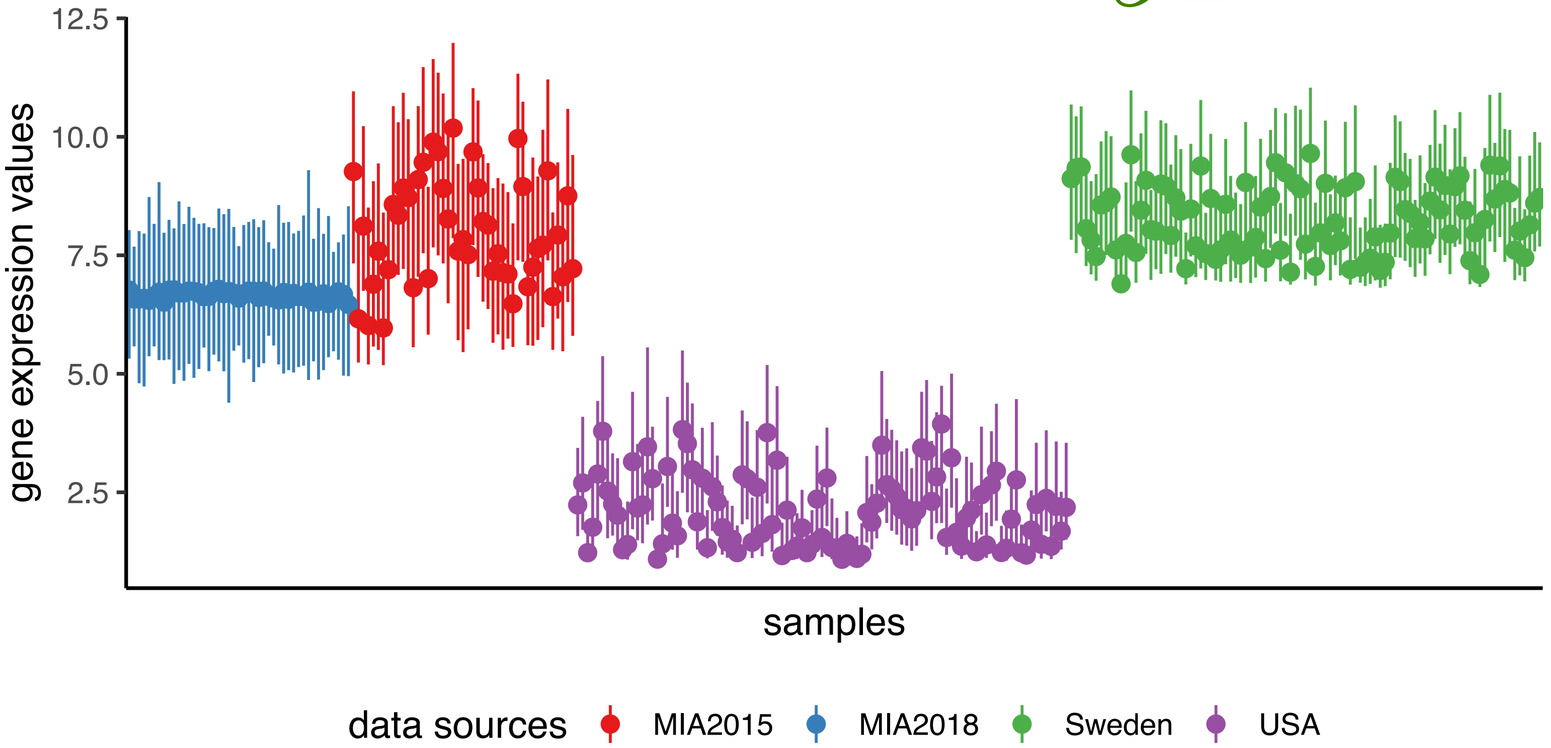
Transferability

For the same samples, the prediction from one gene expression platform should be equivalent to another platform

Omics-based clinical risk score: what is so difficult?

$$\hat{y}_1 = X_1\hat{\beta}_1$$

$$\hat{y}_2 = X_2\hat{\beta}_1$$



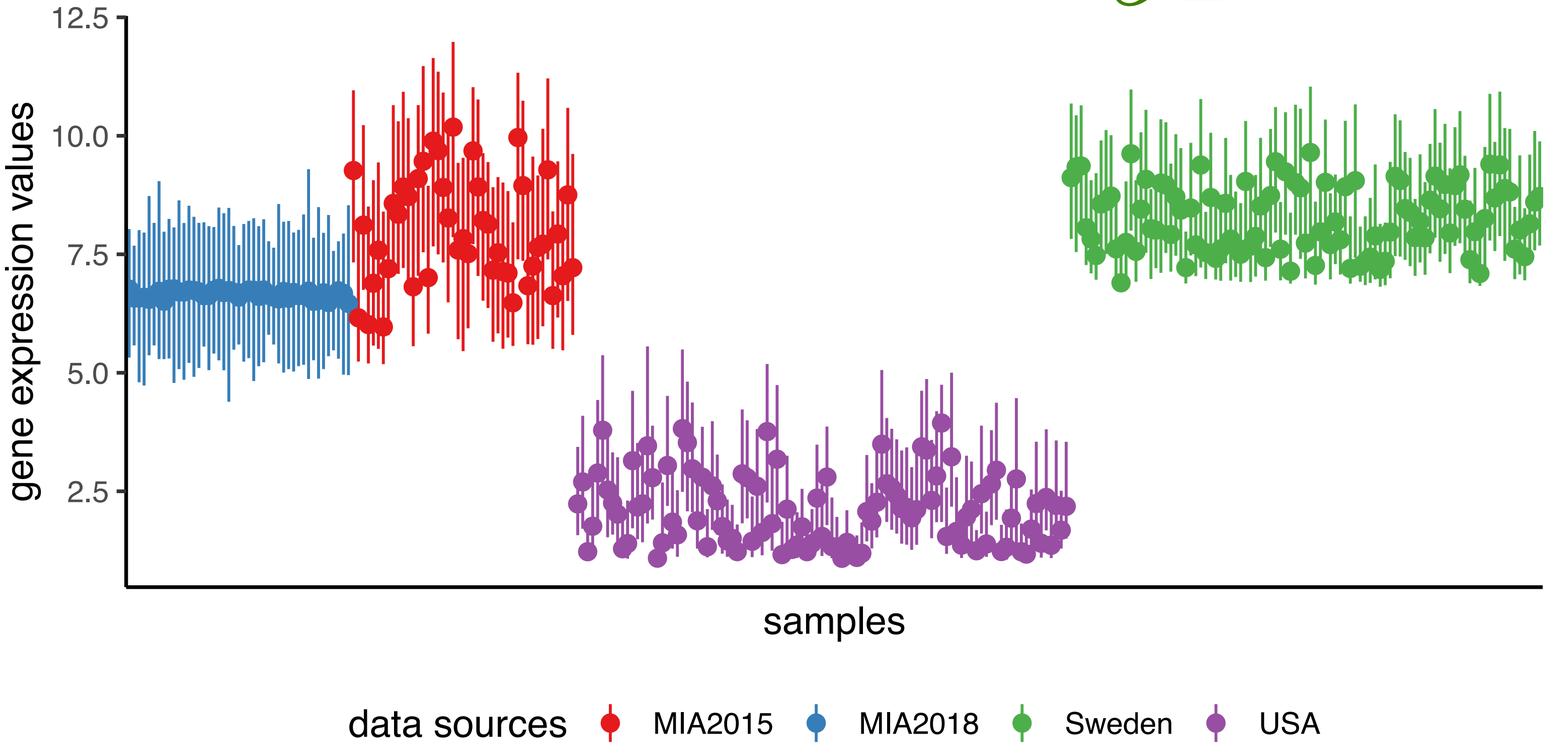
Omics features are on a relative and unit-less scale, a typical value in one data can be an impossible value on another

Omics-based clinical risk score: what is so difficult?

$$\hat{y}_1 = X_1\hat{\beta}_1$$

Assuming a noiseless shift

$$\hat{y}_2 = X_2\hat{\beta}_1 = (X_1 + \mathbf{1})\hat{\beta}_1$$



Omics features are on a relative and unit-less scale, a typical value in one data can be an impossible value on another

Components of a risk score

Data

$$(X_1, y_1)$$

$$(X_2, y_2)$$

Model

$$\hat{\beta}_1$$

Prediction

$$\hat{y}_1 = X_1 \hat{\beta}_1$$

$$\hat{y}_2 = X_2 \hat{\beta}_1$$

Components of a risk score

Data

$$(X_1, y_1)$$

$$(X_2, y_2)$$

Model

$$\hat{\beta}_1$$

Prediction

$$\hat{y}_1 = X_1 \hat{\beta}_1$$

$$\hat{y}_2 = X_2 \hat{\beta}_1$$

No renormalisation

No model retraining

Scale-equivalent prediction

Existing approach vs CPOP

Existing approach: data-harmonisation

Data

(X_1, y_1)

(X_2, y_2)

Harmonisation

Model

$\hat{\beta}_1$

Classical estimation methods

Prediction

$\hat{y}_1 = X_1\hat{\beta}_1$

$\hat{y}_2 = X_2\hat{\beta}_1$

Classical model prediction

1. Data-harmonisation: normalisation or standardisation

Data

(X_1, y_1)

(X_2, y_2)

Harmonisation

Introduces strong dependence between training samples and models

1. Prospective: re-normalisation upon new single-samples
2. Multi-centres: re-training of model upon new populations

2. Model-based approach: CPOP

Data

$$(X_1, y_1) \rightarrow (Z_1, y_1)$$

$$(X_2, y_2) \rightarrow (Z_2, y_2)$$

Feature transform

Model

$$\hat{\beta}_1 \approx \hat{\beta}_2$$

Stable estimation

Prediction

$$Z_1 \hat{\beta}_1 \approx Z_1 \hat{\beta}_2$$

$$Z_2 \hat{\beta}_1 \approx Z_2 \hat{\beta}_2$$

Stable prediction

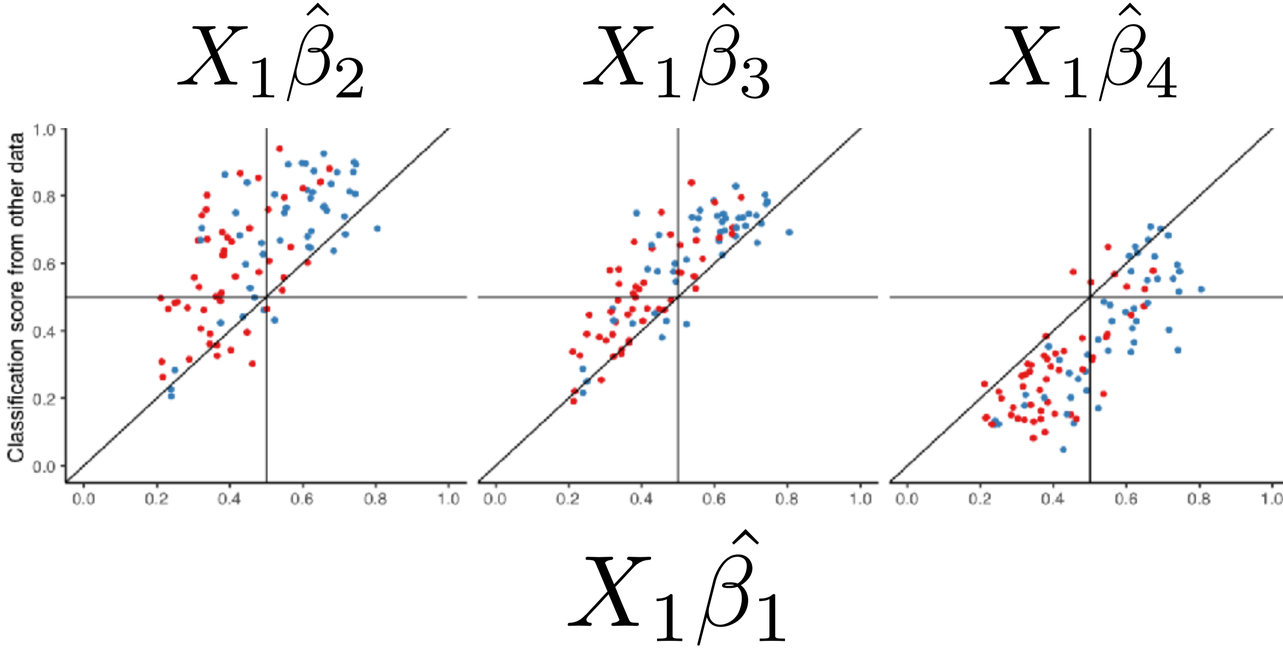
Statistical challenges

1. Concordance in features scaling across datasets

2. Concordance in feature selection and estimates

3. Single-patient prediction

Transferability implies that patients should be evenly scattered around the identity line



First component of CPOP: feature transform

就让我来吹透彻心扉的痛
都拿走 让我再次两手空空
只有奋奋一息过
那个真正的我
也才能够诞生

Log-ratio transformation

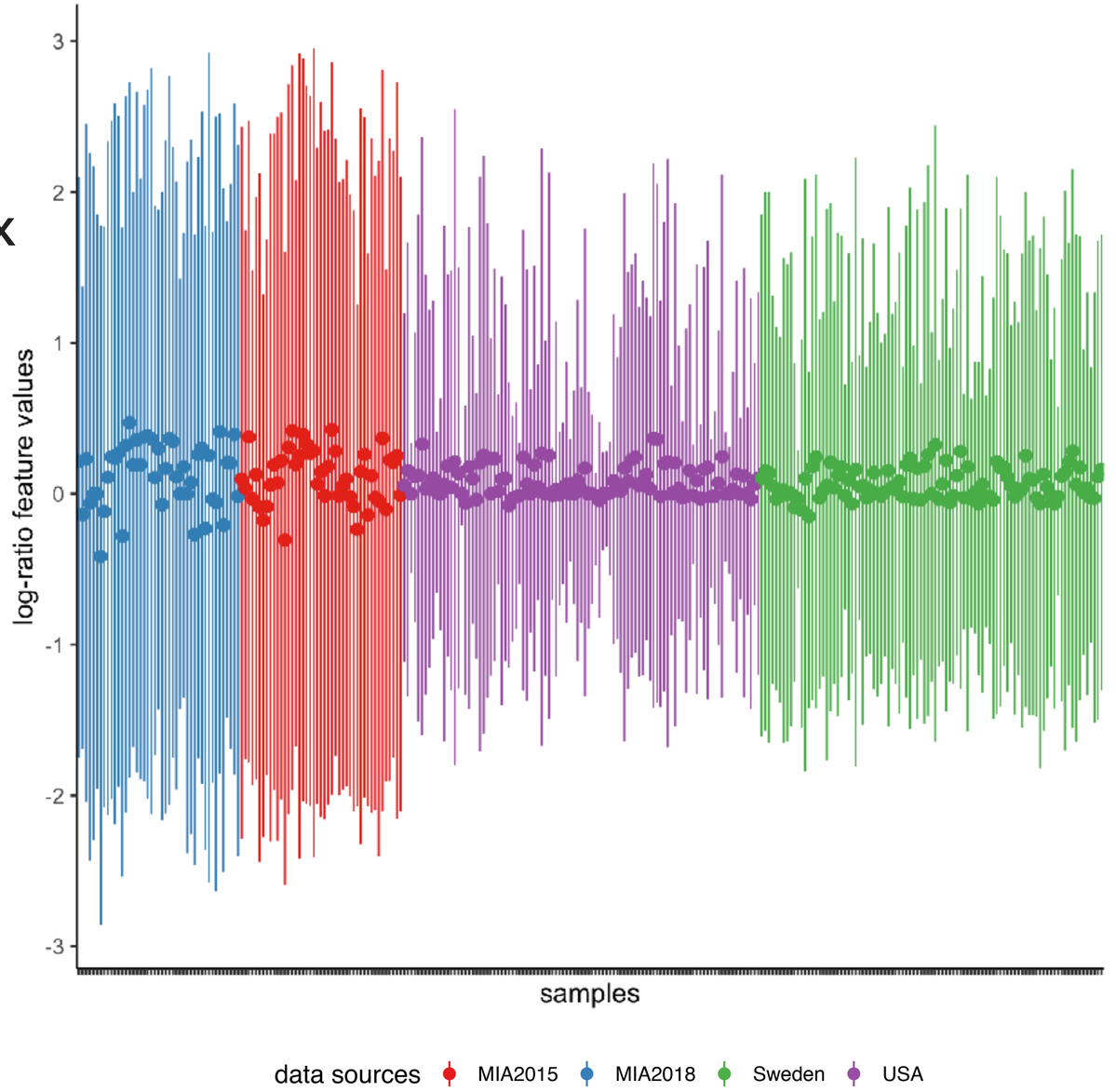
For each column in the gene expression matrix

$$X = \{\boldsymbol{x}_1, \ldots, \boldsymbol{x}_p\} \in \mathbb{R}^{n \times p}$$

Construct $Z \in \mathbb{R}^{n \times \binom{p}{2}}$ column-wise:

$$\boldsymbol{z}_j = \log\left(\frac{\boldsymbol{x}_l}{\boldsymbol{x}_m}\right)$$

$$\text{for } 1 \leq l < m \leq p$$



Why log-ratios?

- Within-sample standardisation avoids re-normalisation and model re-training
- Under-used in patient outcome prediction
- Potentials for further method developments

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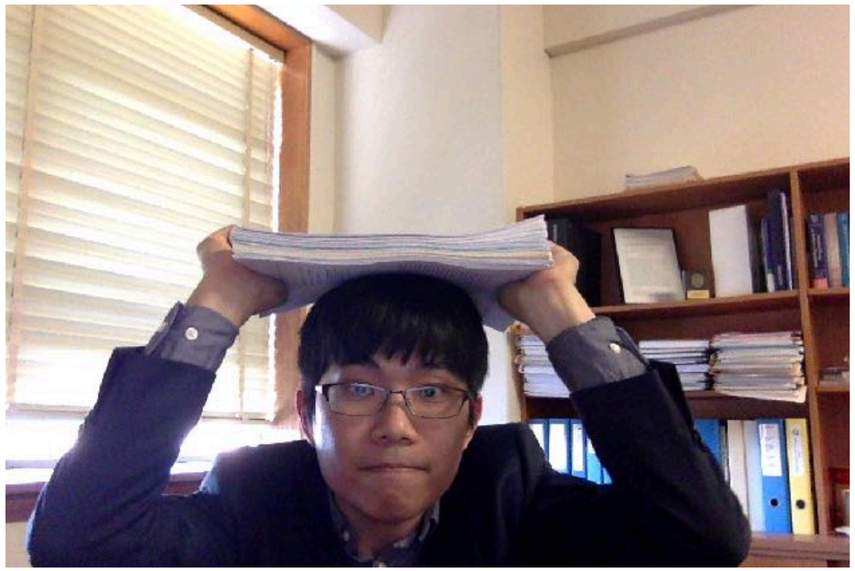

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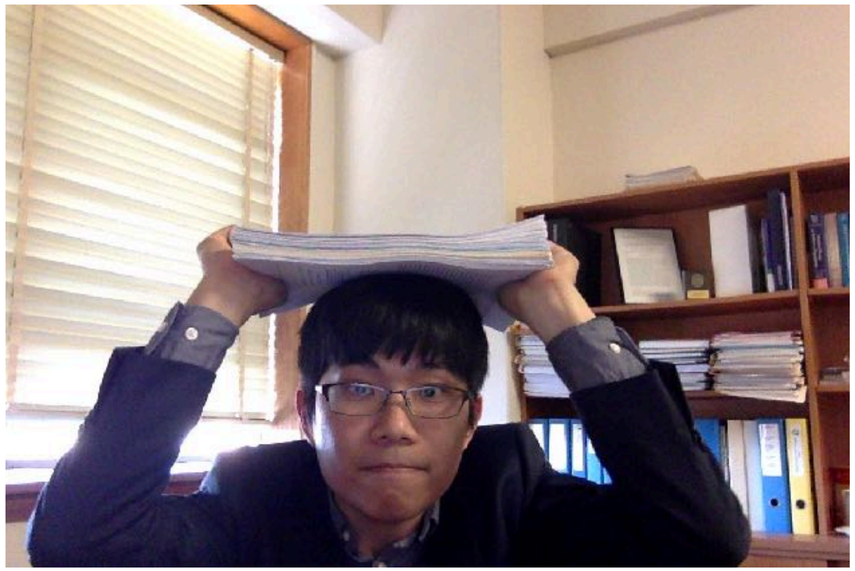
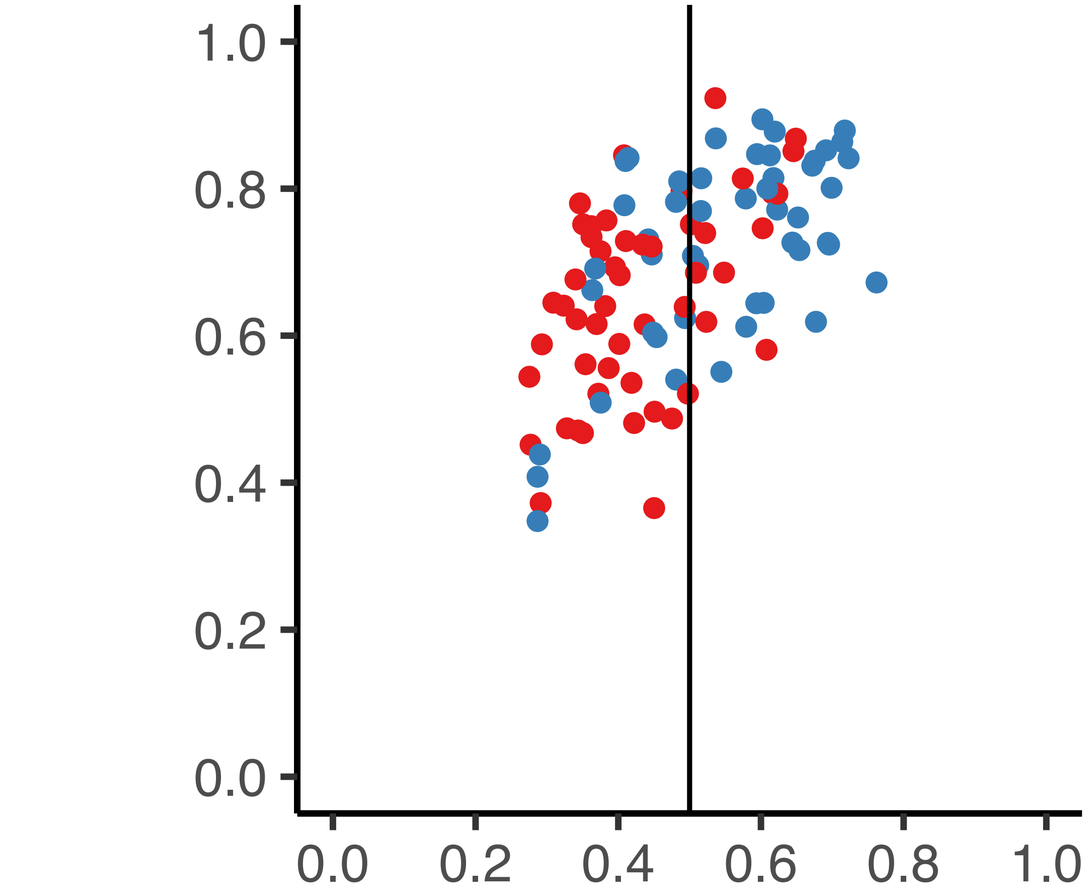
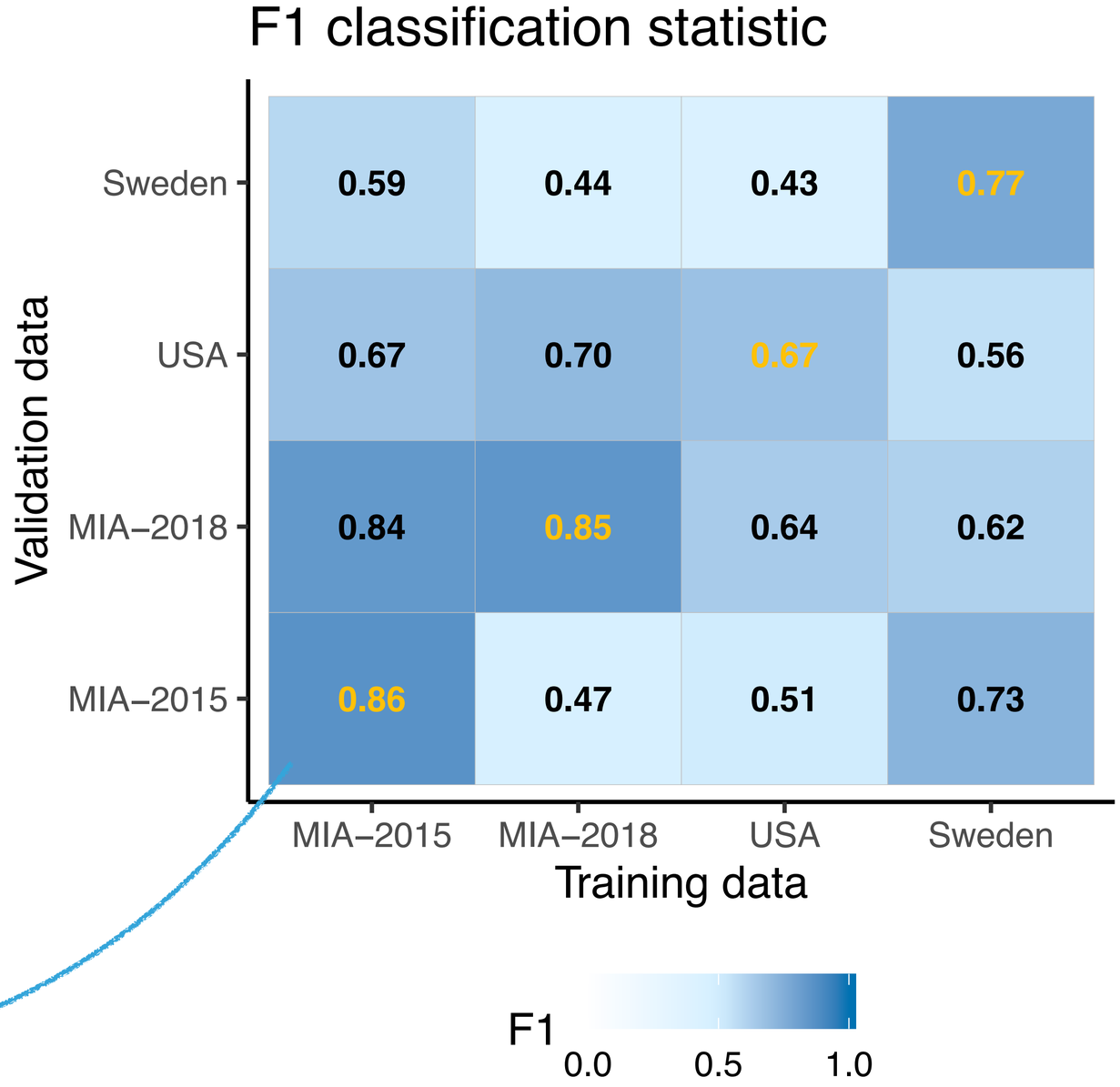


Is log-ratio enough?





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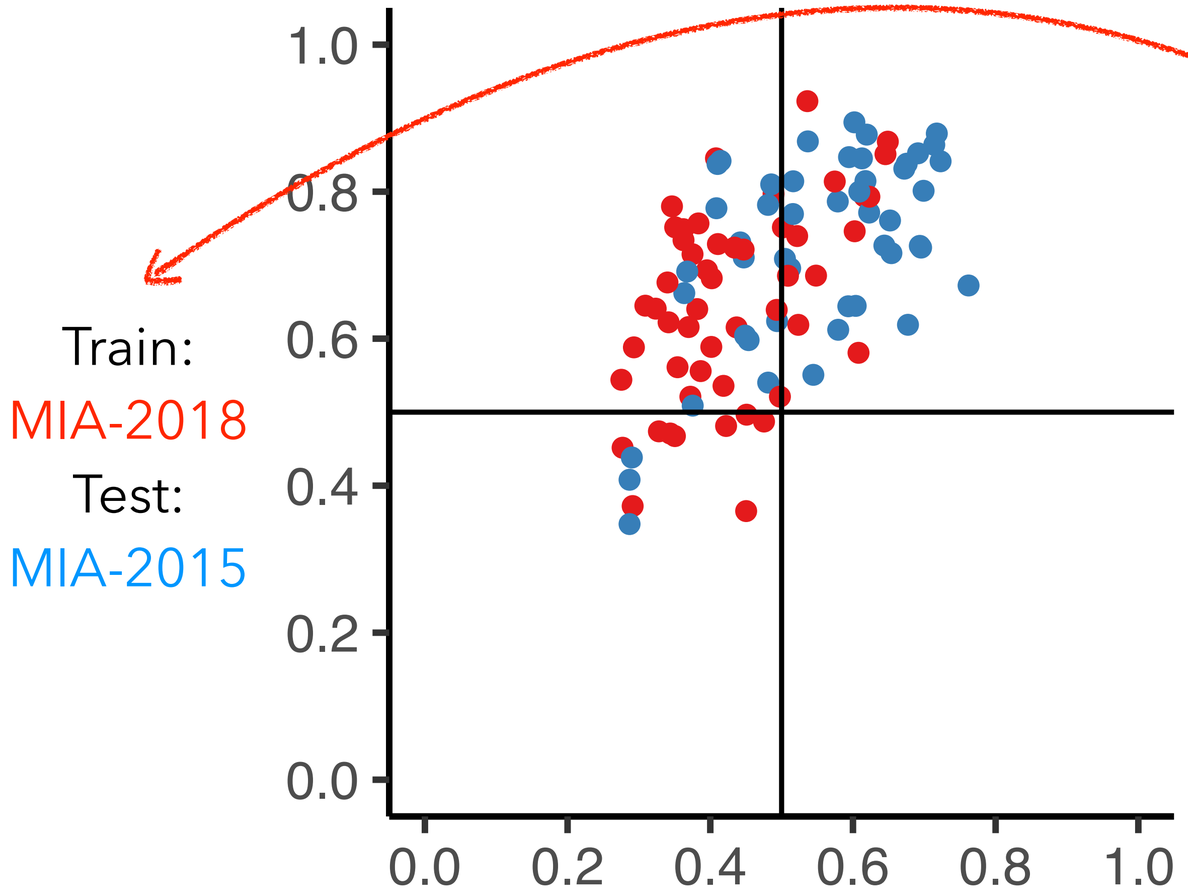

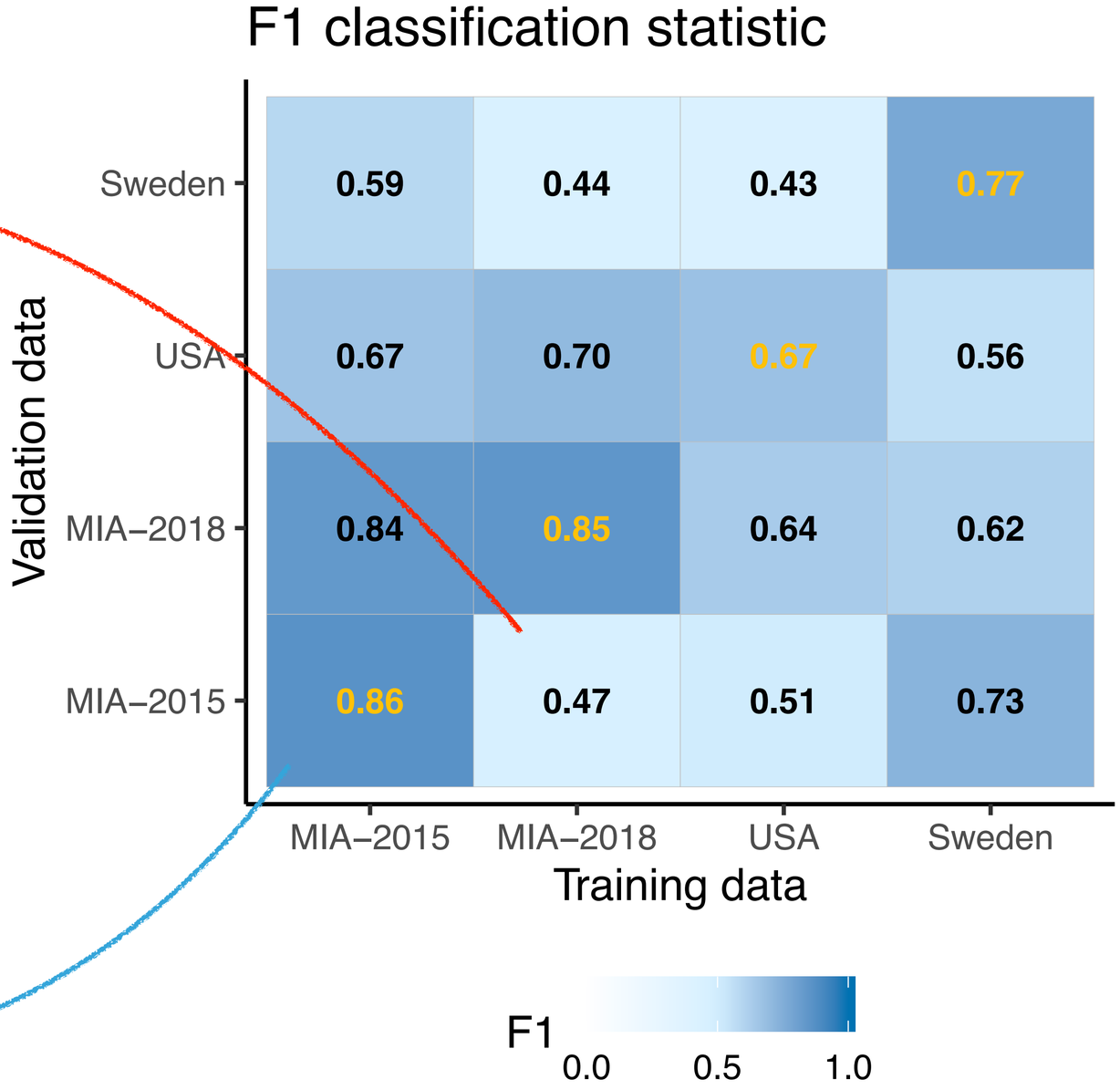

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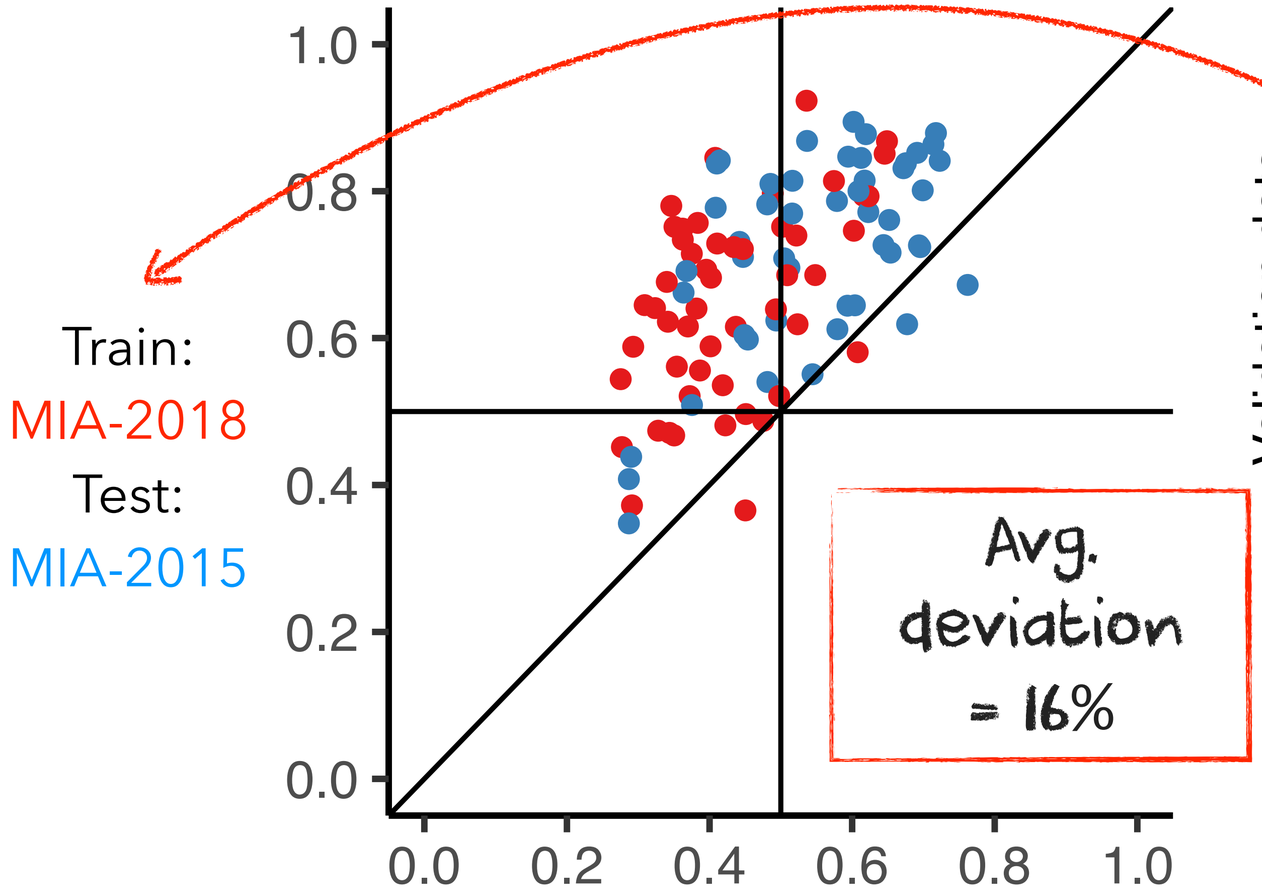
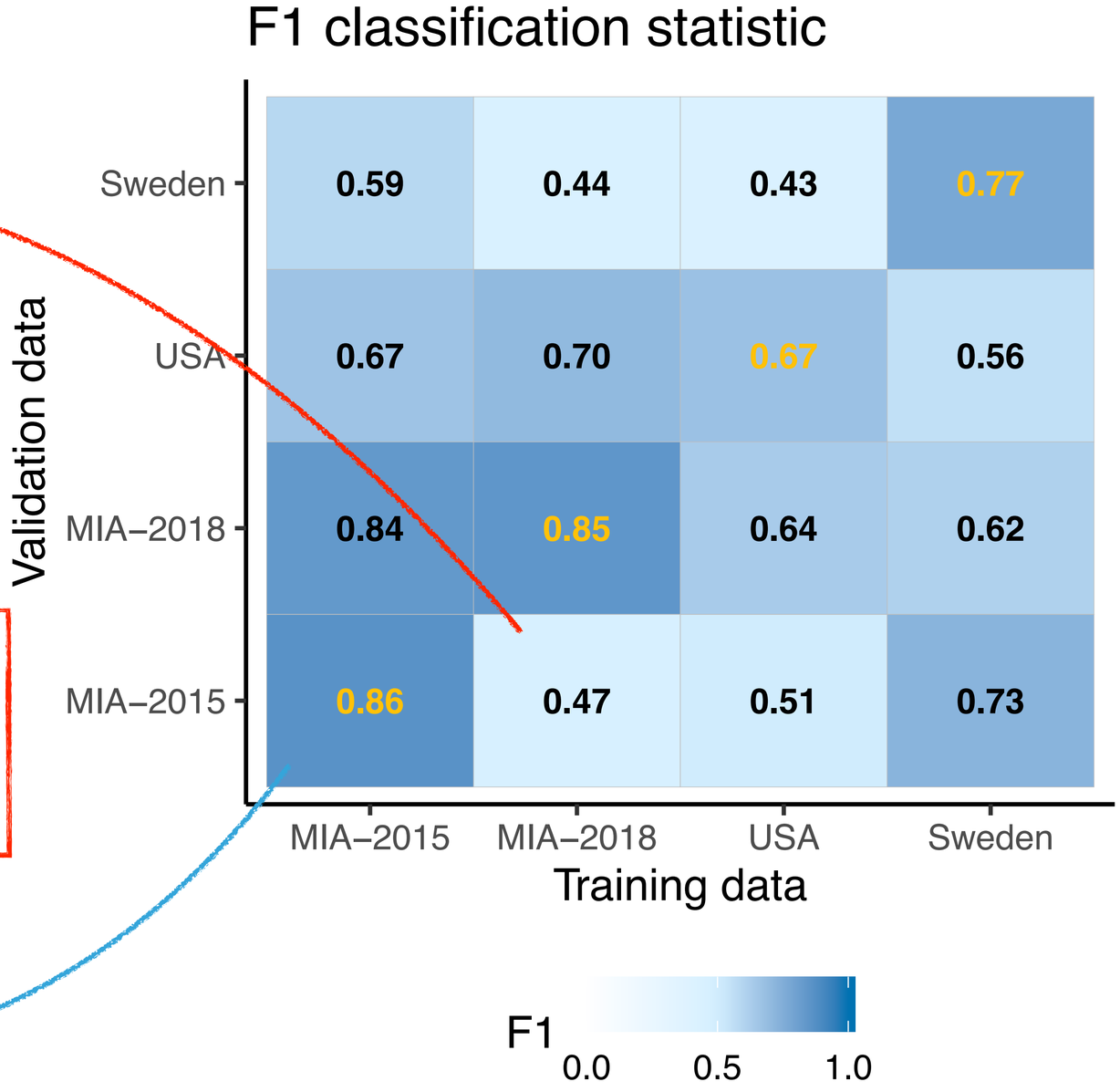
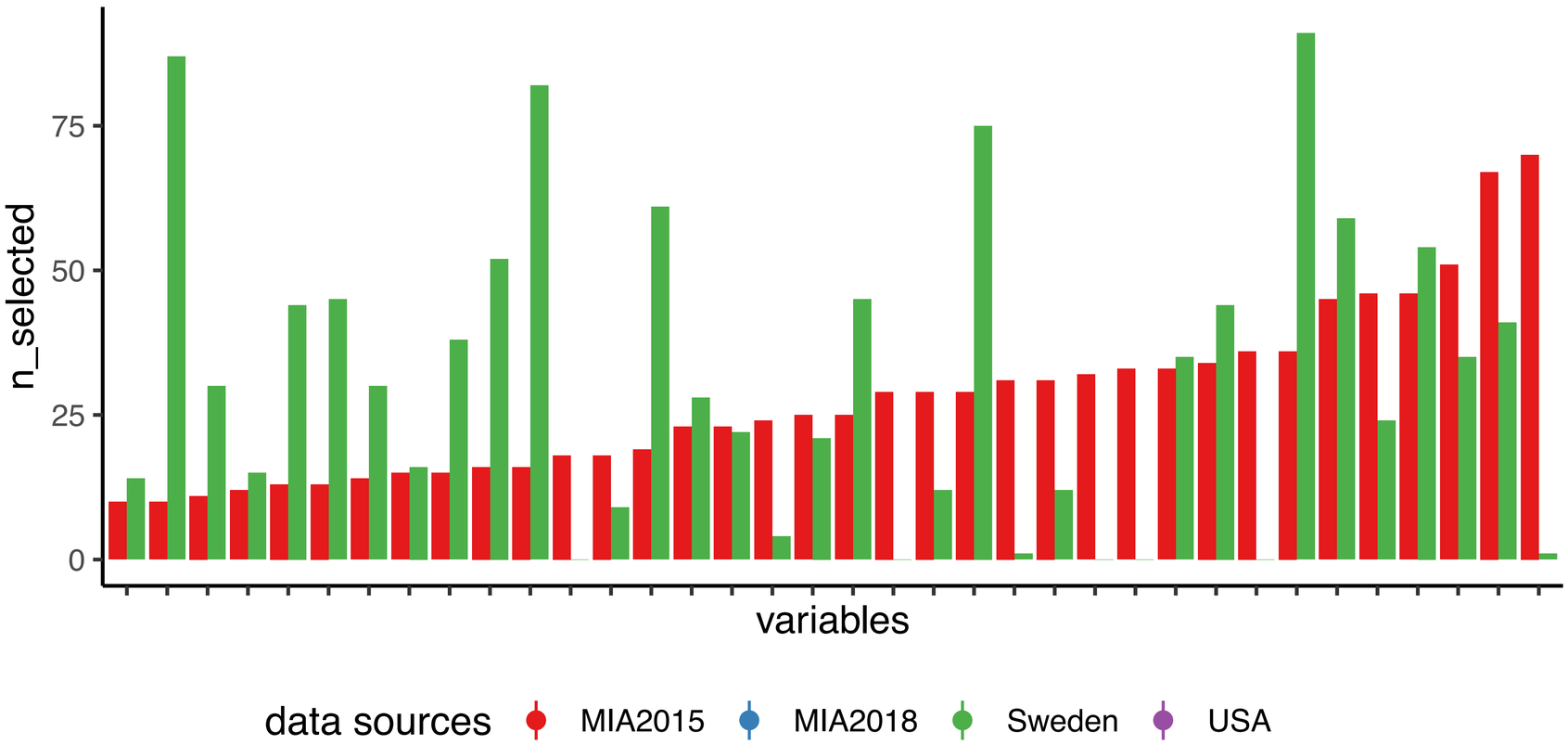




Lasso variable selection is not stable!

- Bach 2008
- Meinshausen & Bühlmann 2010
- Lim & Yu 2016

all pointed out that Lasso is unstable under cross-validation



Second component of CPOP: stable feature selection and estimation

我曾经毁了我的一切
只想永远地离开
我曾经陷入无边黑暗
想挣扎无法自拔
我曾经像你像他像那野草野花
绝望着也渴望着
也哭也笑也平凡着

CPOP flowchart

Data

$$(X_1, y_1) \rightarrow (Z_1, y_1)$$

$$(X_2, y_2) \rightarrow (Z_2, y_2)$$

Feature transform

Model

$$\hat{\beta}_1 \approx \hat{\beta}_2$$

Stable estimation

Prediction

$$Z_1\hat{\beta}_1 \approx Z_1\hat{\beta}_2$$

$$Z_2\hat{\beta}_1 \approx Z_2\hat{\beta}_2$$

Stable prediction

Weighted Elastic Net

Loss function, could be logistic or Cox

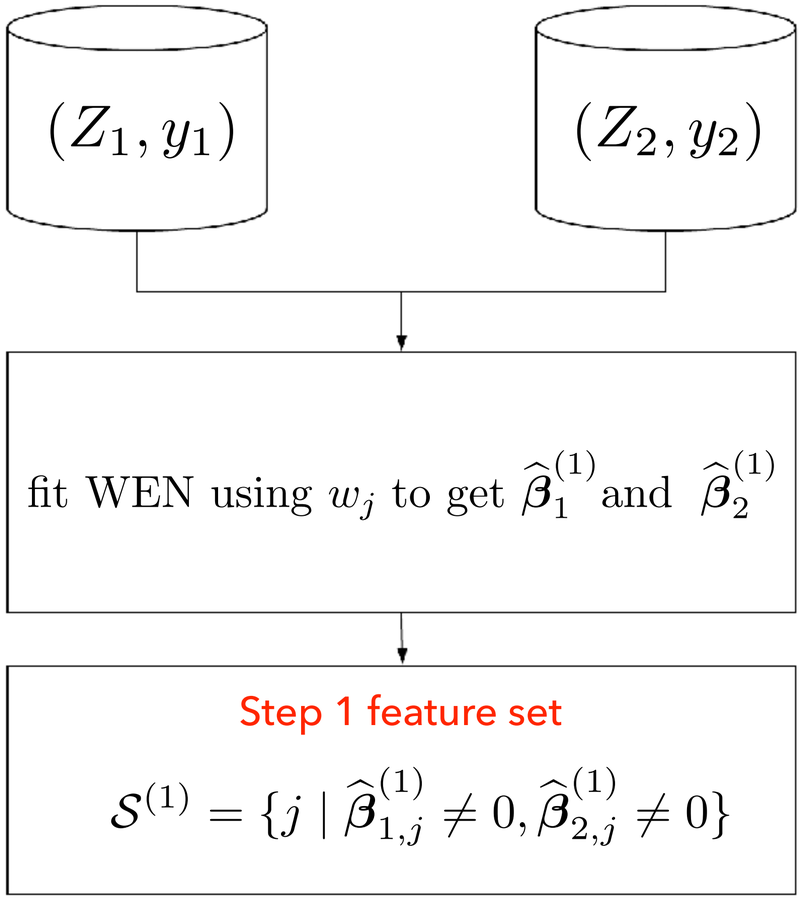
A mix of L1 and L2 penalties

$$\widehat{\boldsymbol{\beta}}(\boldsymbol{y}, \boldsymbol{Z}) = \underset{\boldsymbol{\beta} \in \mathbb{R}^{\binom{p}{2}}}{\operatorname{argmin}} \sum_{i=1}^{n} (y_i - \boldsymbol{z}_i^\top \boldsymbol{\beta})^2 + \lambda \sum_{j=1}^{q} w_j \left[\frac{(1-\alpha)}{2} \beta_j^2 + \alpha |\beta_j| \right]$$

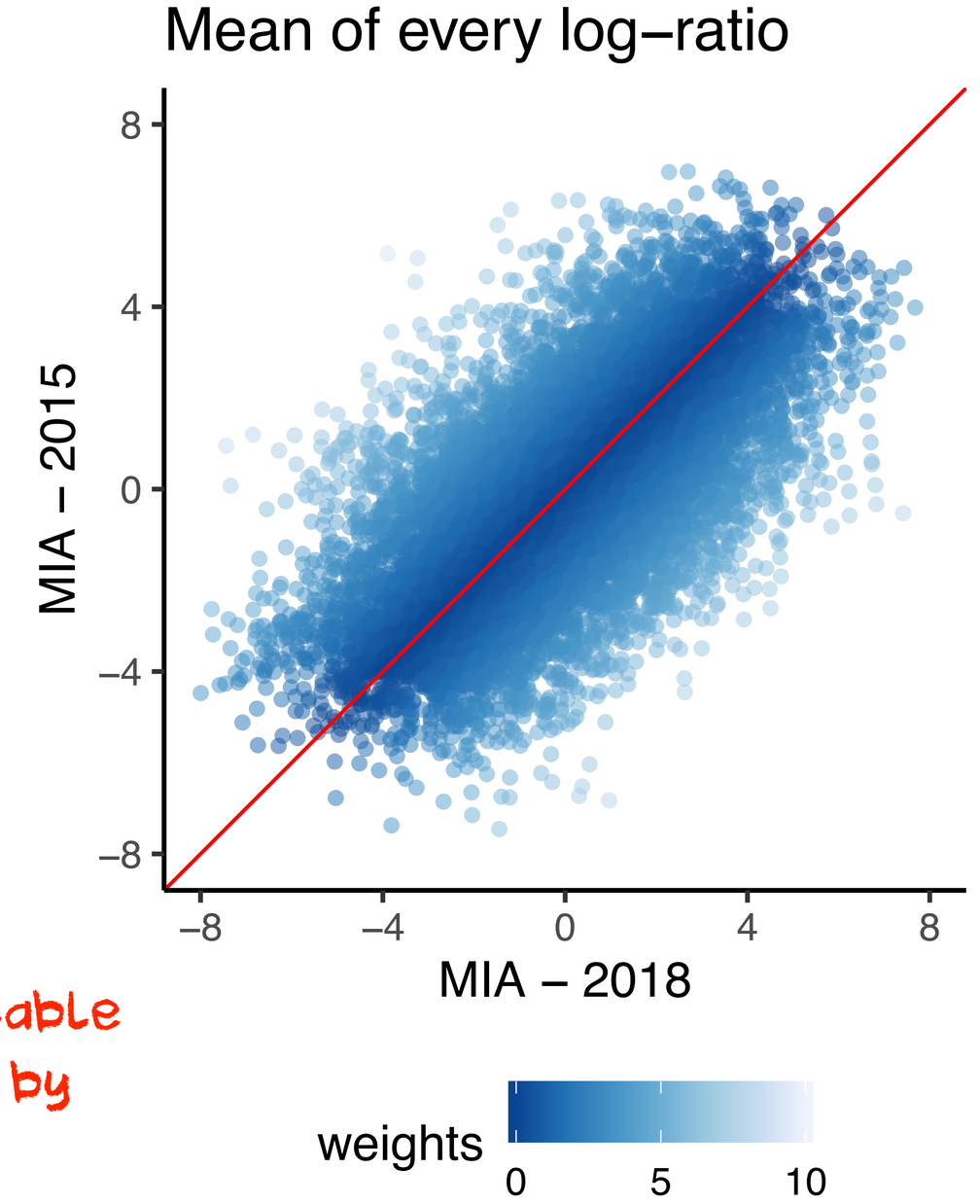
Modelling on log-ratio

Weights on each feature, proportional to the stability of features

Step 1: feature selection stability



informative and stable features agreed by both data



Step 2: feature estimation stability

Step 1 feature set

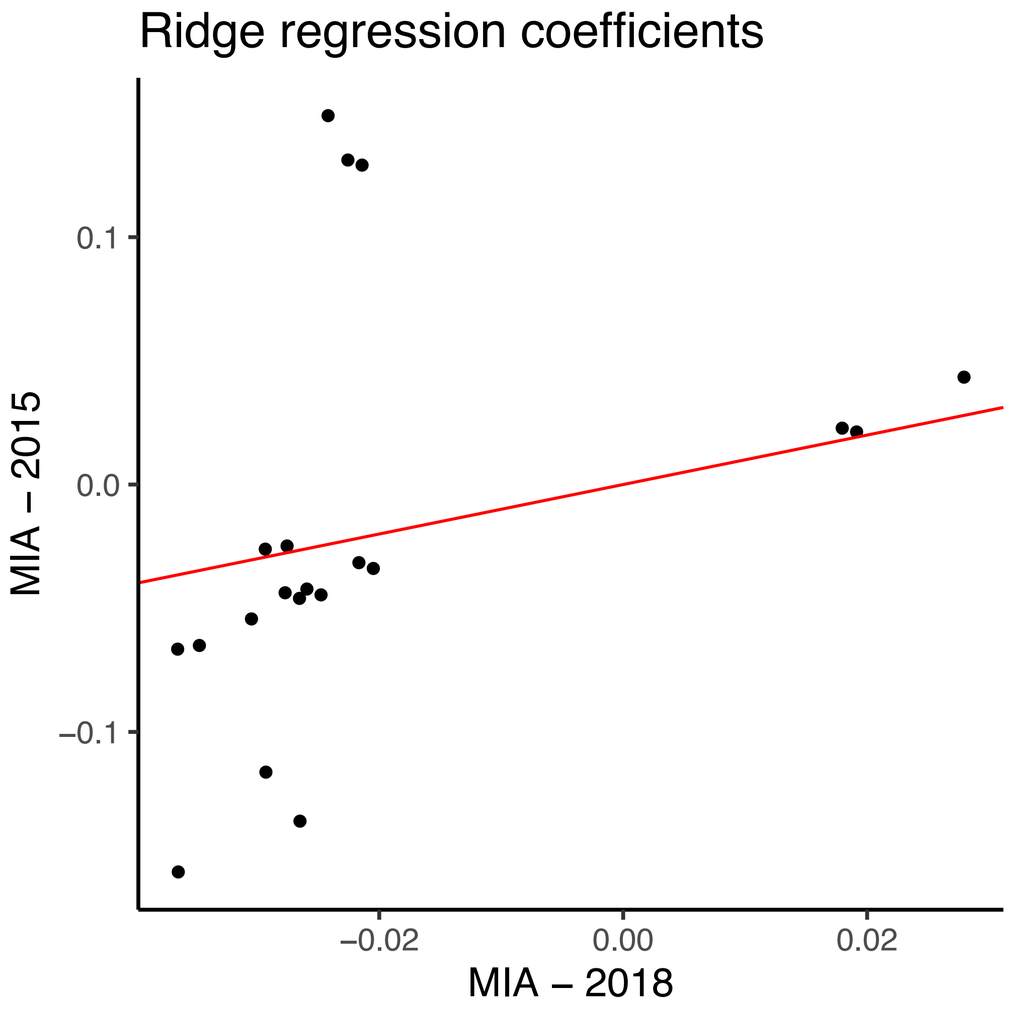
$$\mathcal{S}^{(1)} = \{j \mid \widehat{\boldsymbol{\beta}}^{(1)}_{1,j} \neq 0, \widehat{\boldsymbol{\beta}}^{(1)}_{2,j} \neq 0\}$$

$(\boldsymbol{Z}_{1,\mathcal{S}^{(1)}}, \boldsymbol{y}_1)$ $(\boldsymbol{Z}_{2,\mathcal{S}^{(1)}}, \boldsymbol{y}_2)$

fit Ridge to get $\widehat{\boldsymbol{\beta}}^{(2)}_1$ and $\widehat{\boldsymbol{\beta}}^{(2)}_2$

Step 2 feature set

$$\mathcal{S}^{(2)} = \{j \mid \text{sign}(\widehat{\boldsymbol{\beta}}^{(2)}_{1,j}) = \text{sign}(\widehat{\boldsymbol{\beta}}^{(2)}_{2,j})\}$$



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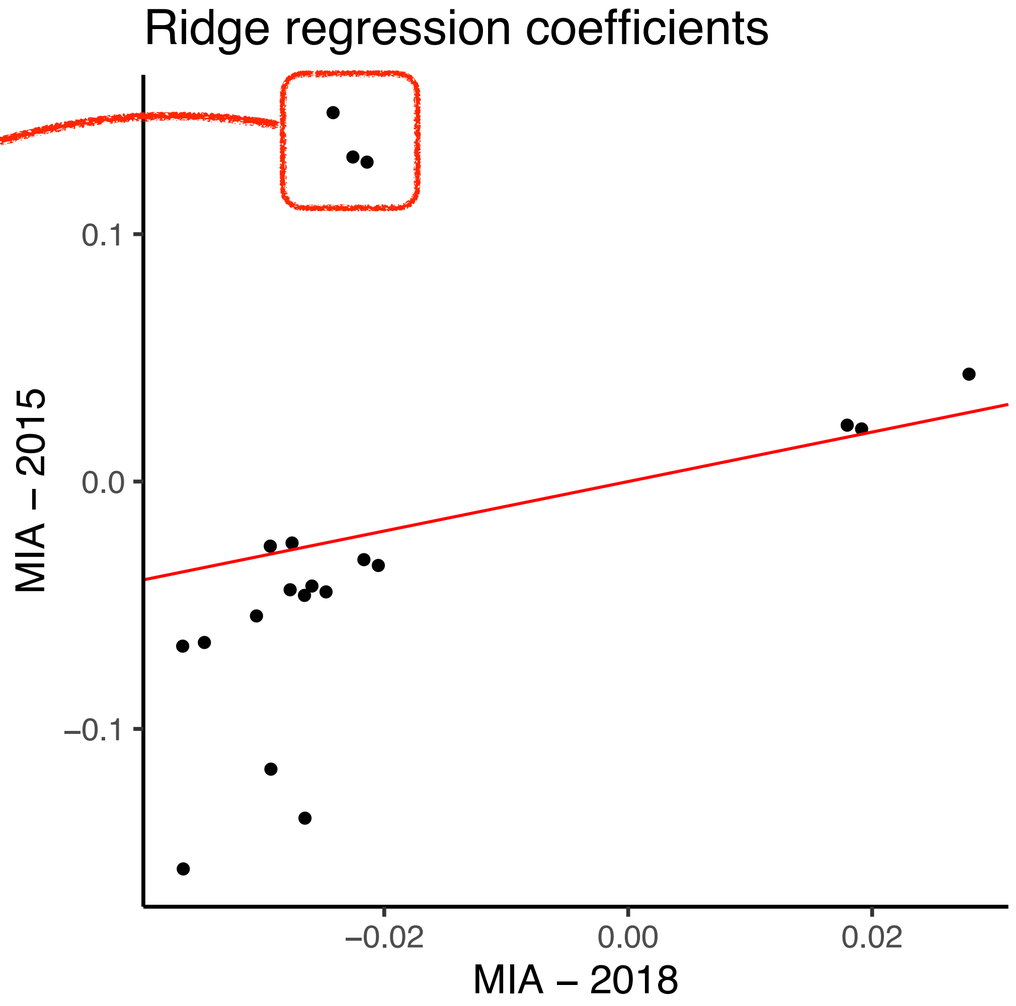
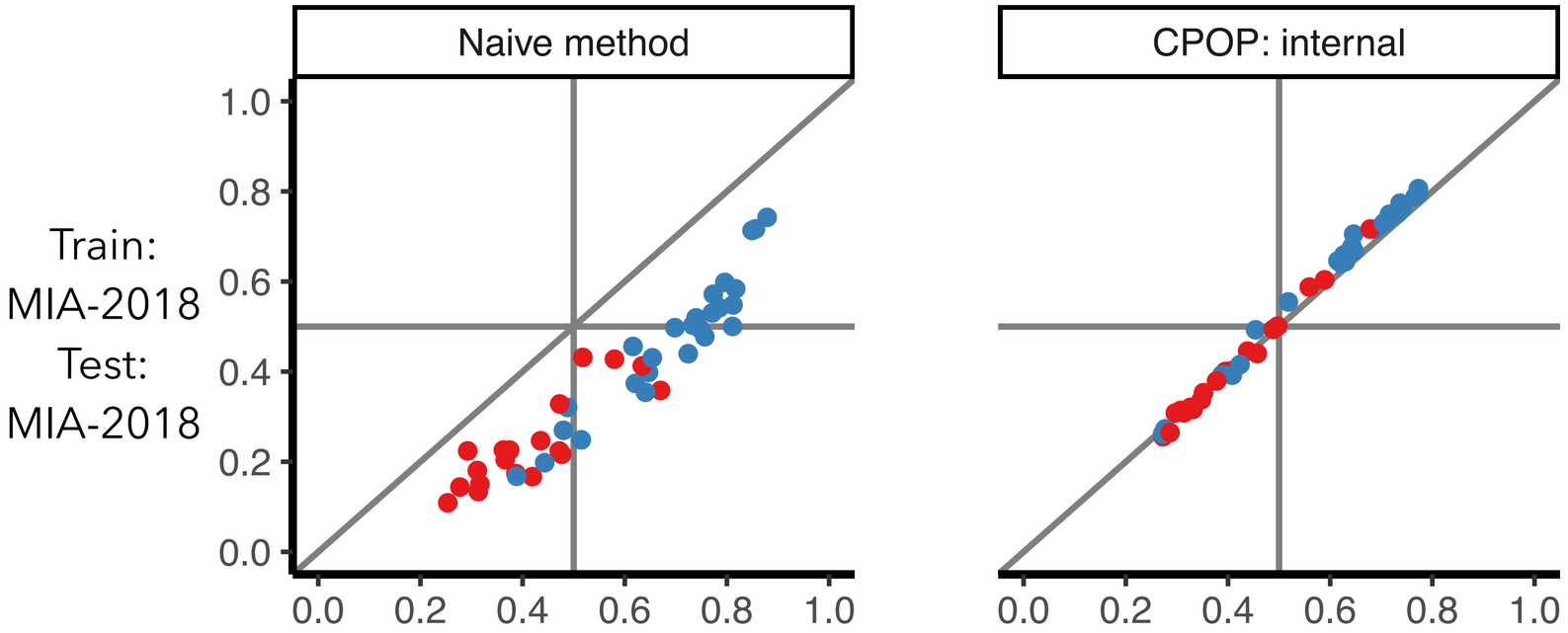
features with unstable estimates across data



Results

CPOP results 1: MIA 2015 vs 2018 data

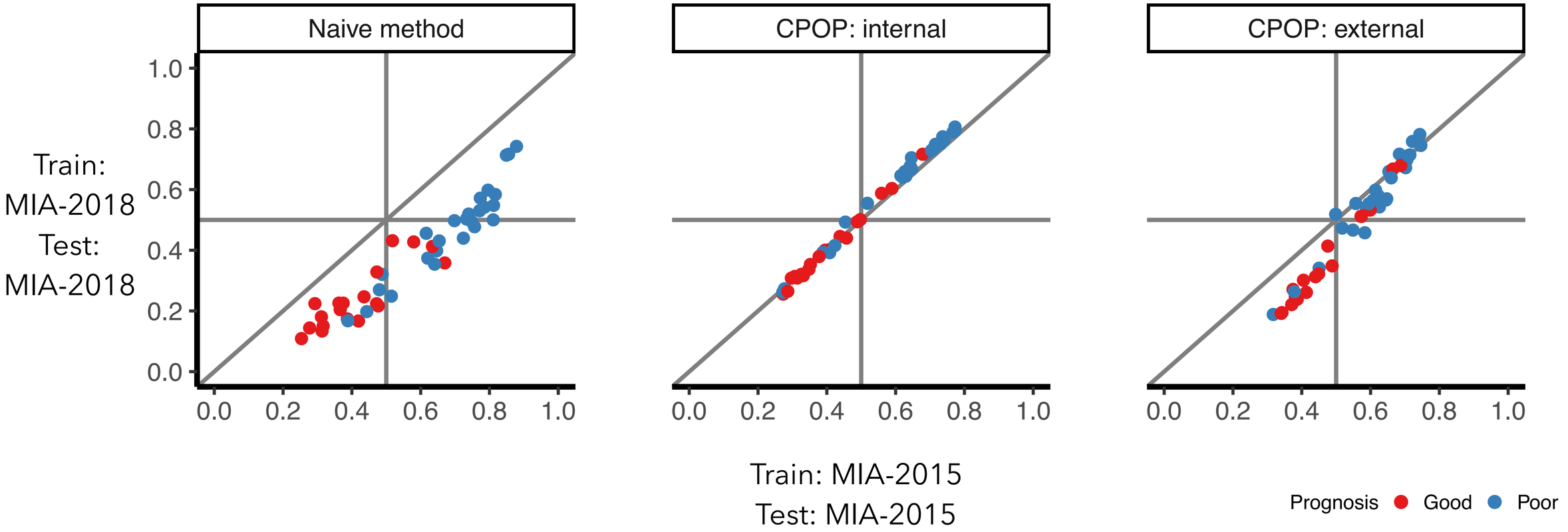


Train: MIA-2015
Test: MIA-2015

Prognosis Good Poor

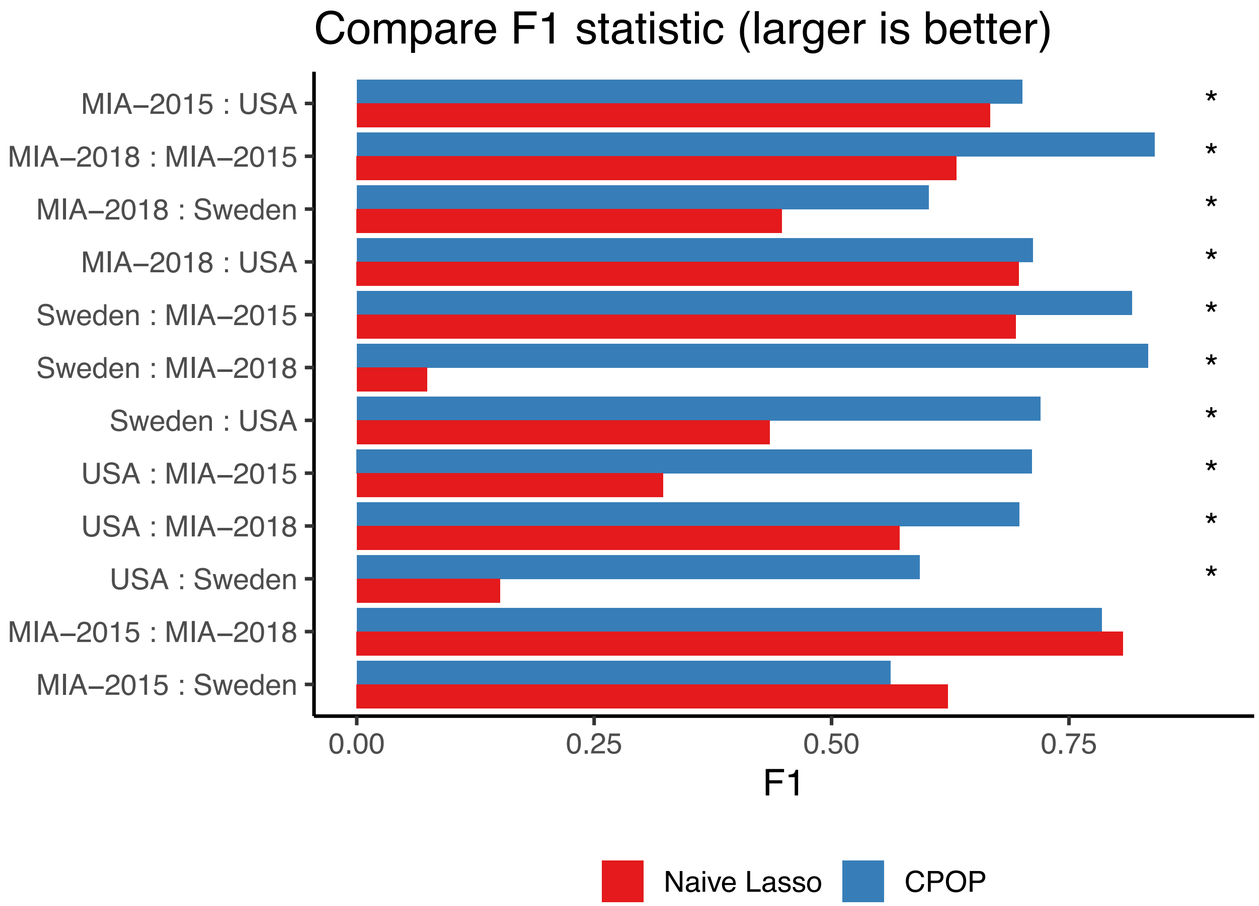
Small deviation in predicted values across datasets

CPOP results 1: MIA 2015 vs 2018 data



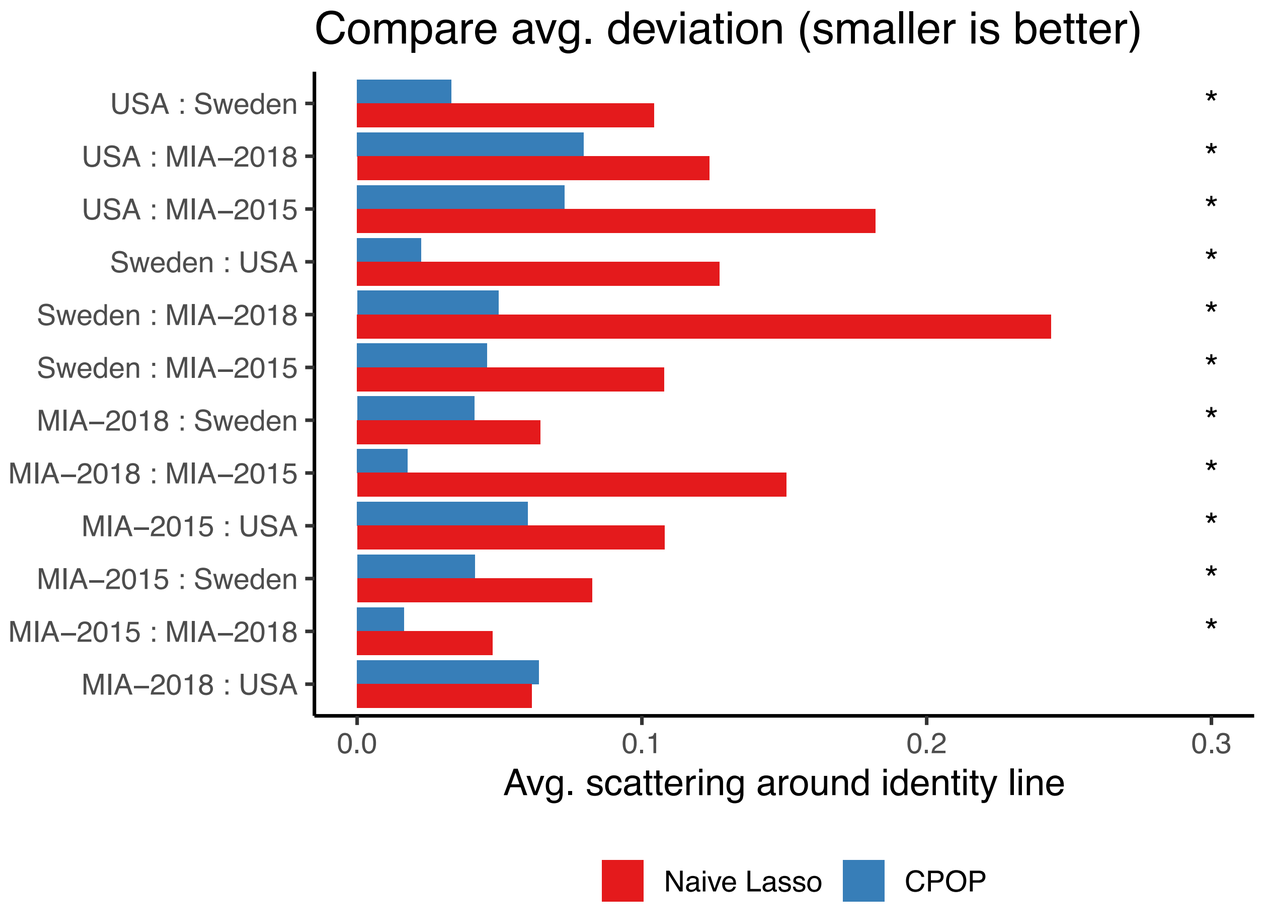
Small deviation in predicted values across datasets

CPOP results 2: four melanoma data



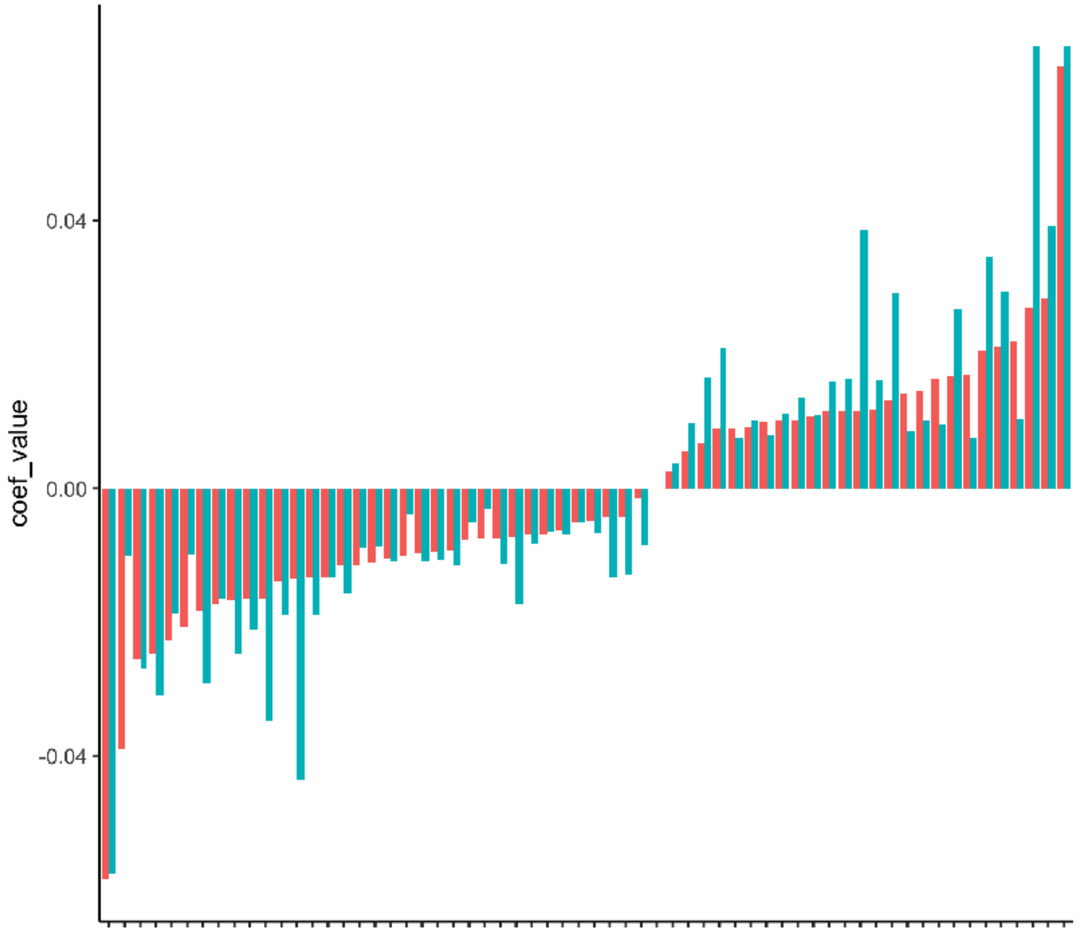
CPOP is highly predictive

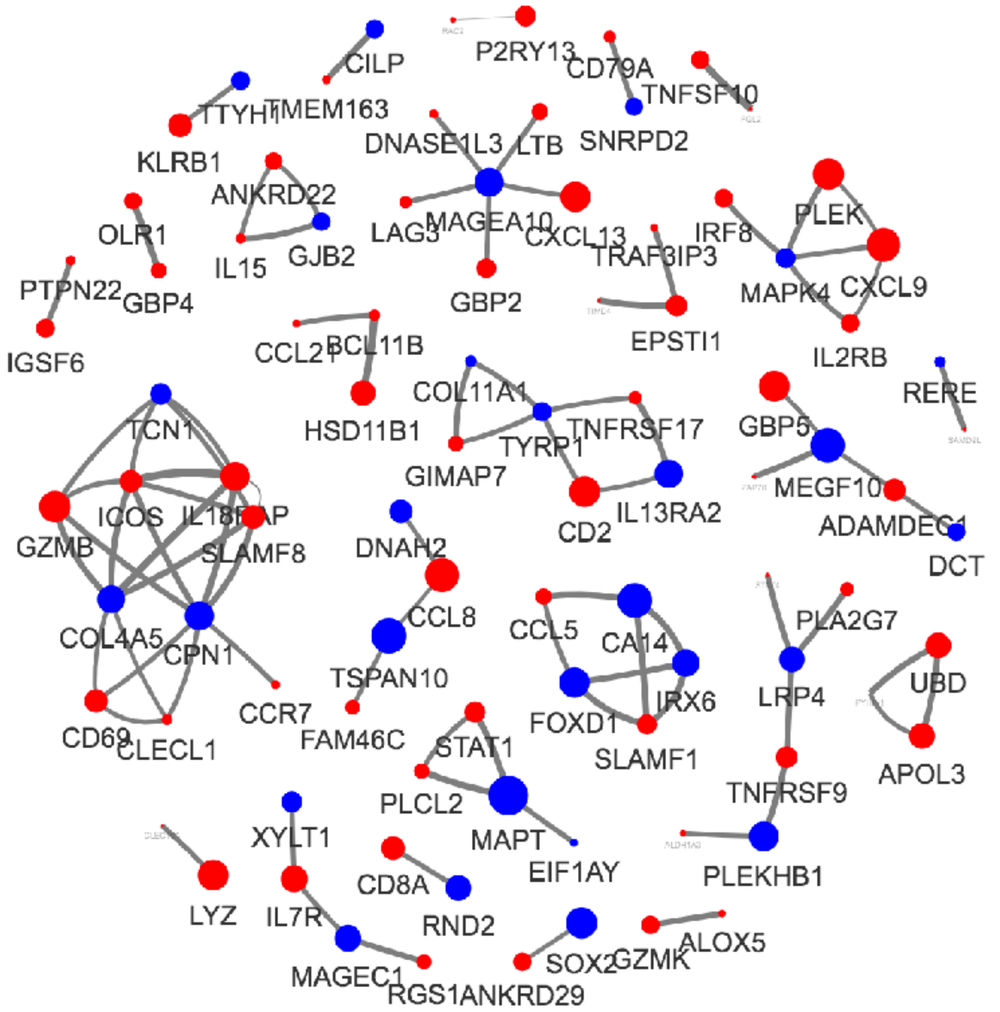
CPOP results 2: four melanoma data



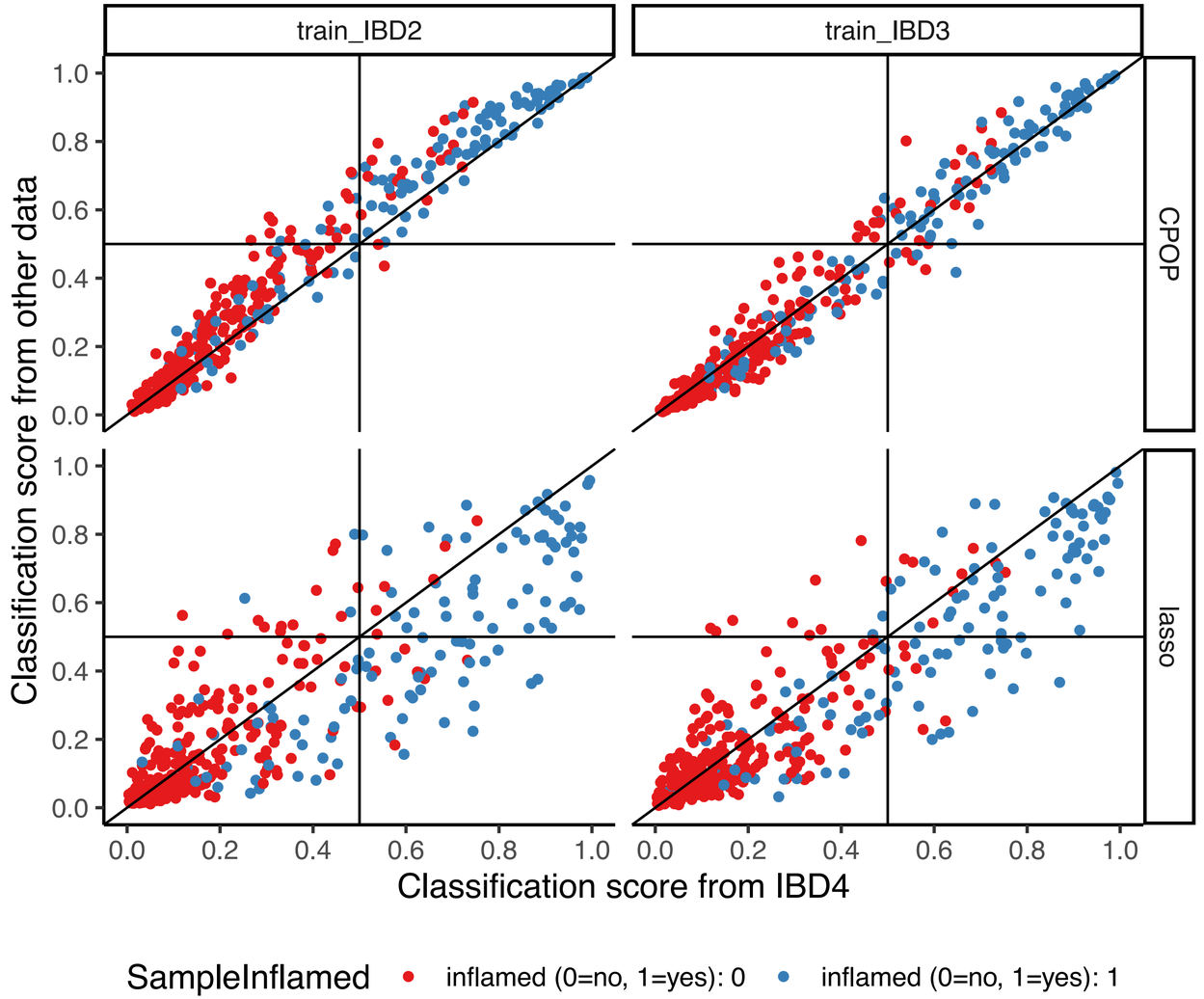
CPOP is highly stable

CPOP features





CPOP results 3: prospective prediction on inflammatory bowel disease



Concluding remarks

- Integrates clinical implementation constraints into the model

    1. Log-ratios enable prospective and multi-centres prediction

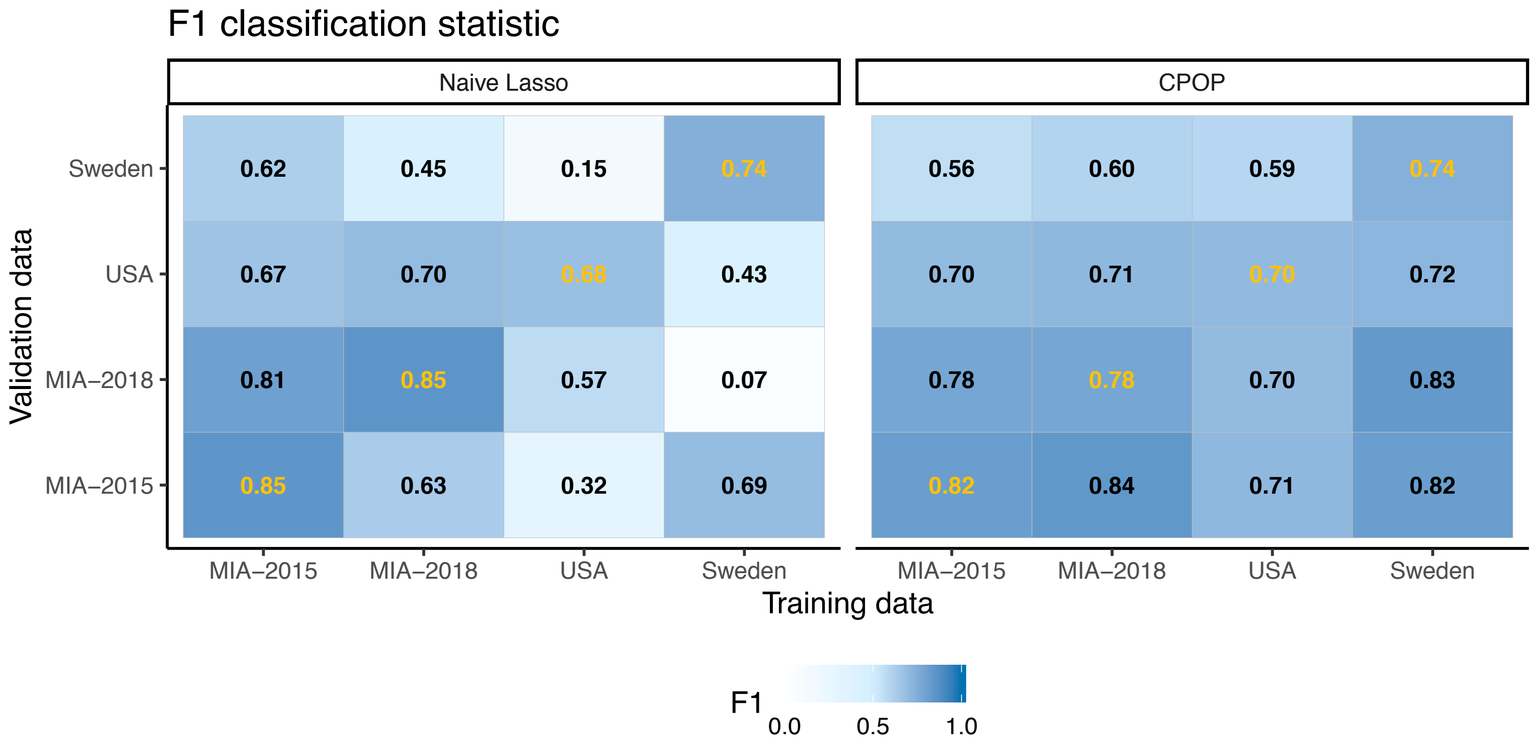
    2. Stable variable selection and estimation components

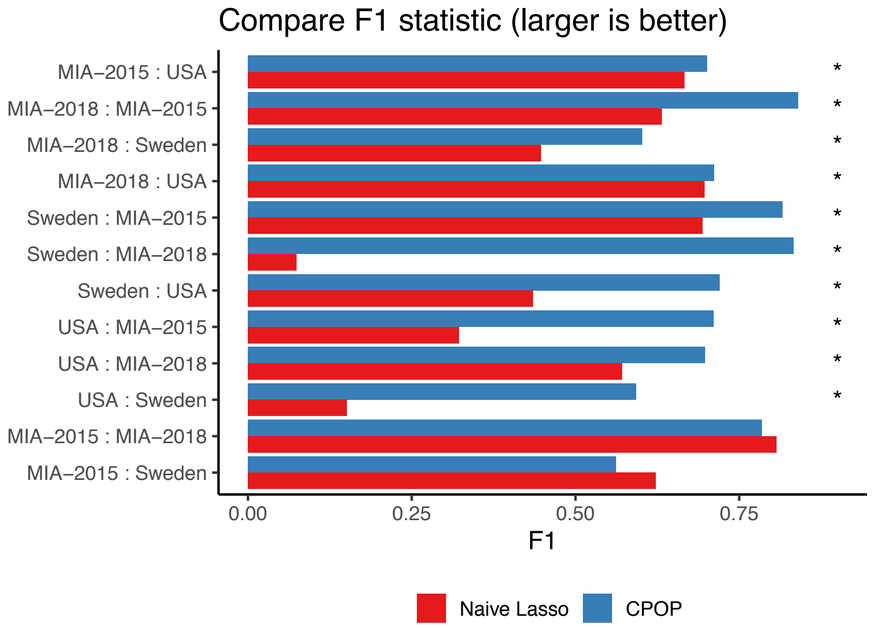
- A flexible framework with many adaptable components

- Potentials to handle data with higher relevance to precision medicine (e.g. drug sensitivity)

I think that is all.

CPOP results 2: four melanoma data





CPOP is highly predictive

Motivation for CPOP: one patient cohort, two gene expression data

$$X_1\hat{\beta}_1 \approx X_2\hat{\beta}_2$$

loosely translate to

$$X_1 \approx X_2$$

column-wise

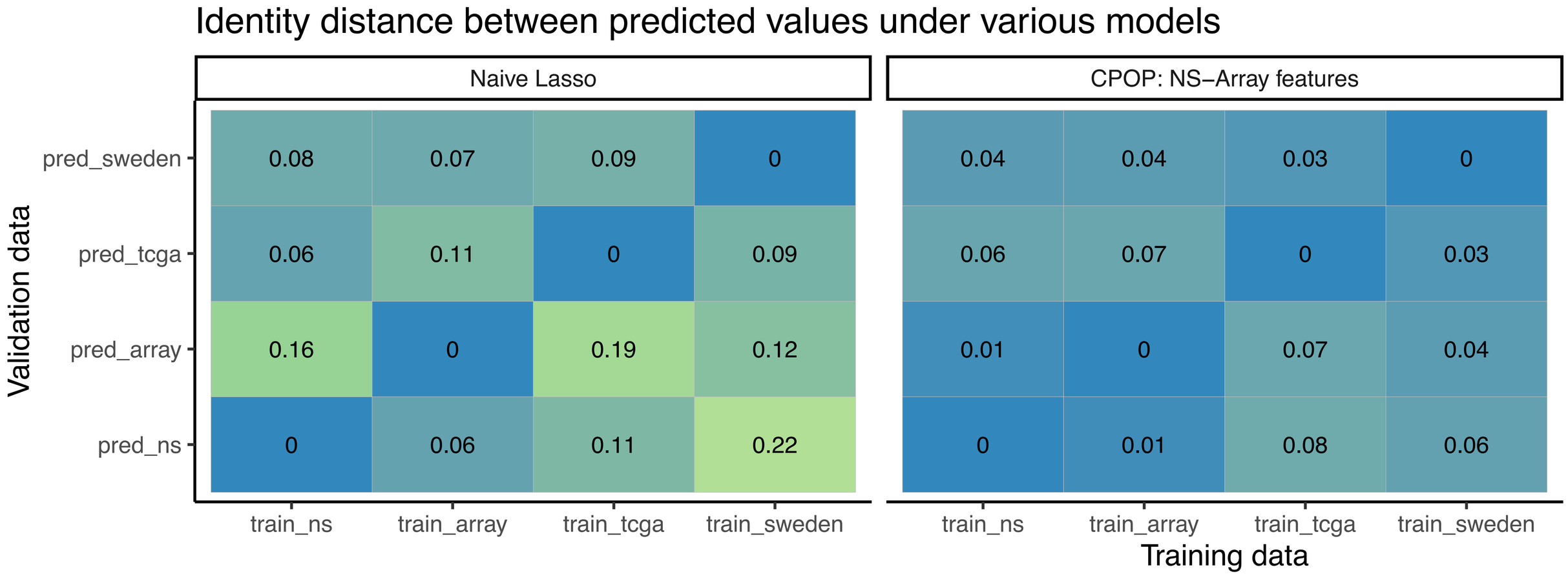
(feature distribution stability)

$$\hat{\beta}_1 \approx \hat{\beta}_2$$

element-wise

(mode estimation stability)

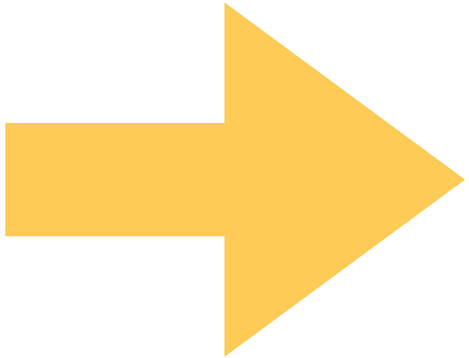
CPOP results 1: four melanoma data



Small deviation in predicted values across datasets

Framingham heart disease risk score:

- Age (Years)
- Cholesterol (mg/dL)
- If smoker (Yes/No)
- HDL cholesterol (mg/dL)
- Systolic blood pressure (mm Hg)



$$\hat{y} = X\hat{\beta}$$

20 points model

Concluding remarks

- CPOP is a flexible procedure that allows for:
  - cross-platform omics prediction
  - stable single-patient prediction
- Not everyone can smooth-sailing through the PhD process, find your own way to deal with it (e.g. insert random pictures into your slides)

But what about breast cancer?

- Alvarado et. al. (2015) reported poor concordance in the prediction scores
- Hyeon et. al. (2017) considered NanoString as a viable alternative to RT-PCR

Name	Predictors	Targets	Prediction	Technology	Legit?
Oncotype DX	21 genes	ER +	Score	qRT-PCR	ASCO, NCCN
Prosigna	50 genes	Hormone receptor +	Score	NanoString	FDA 510k
MammaPrint	70 genes	Any ER status	Binary	DNA microarray	FDA

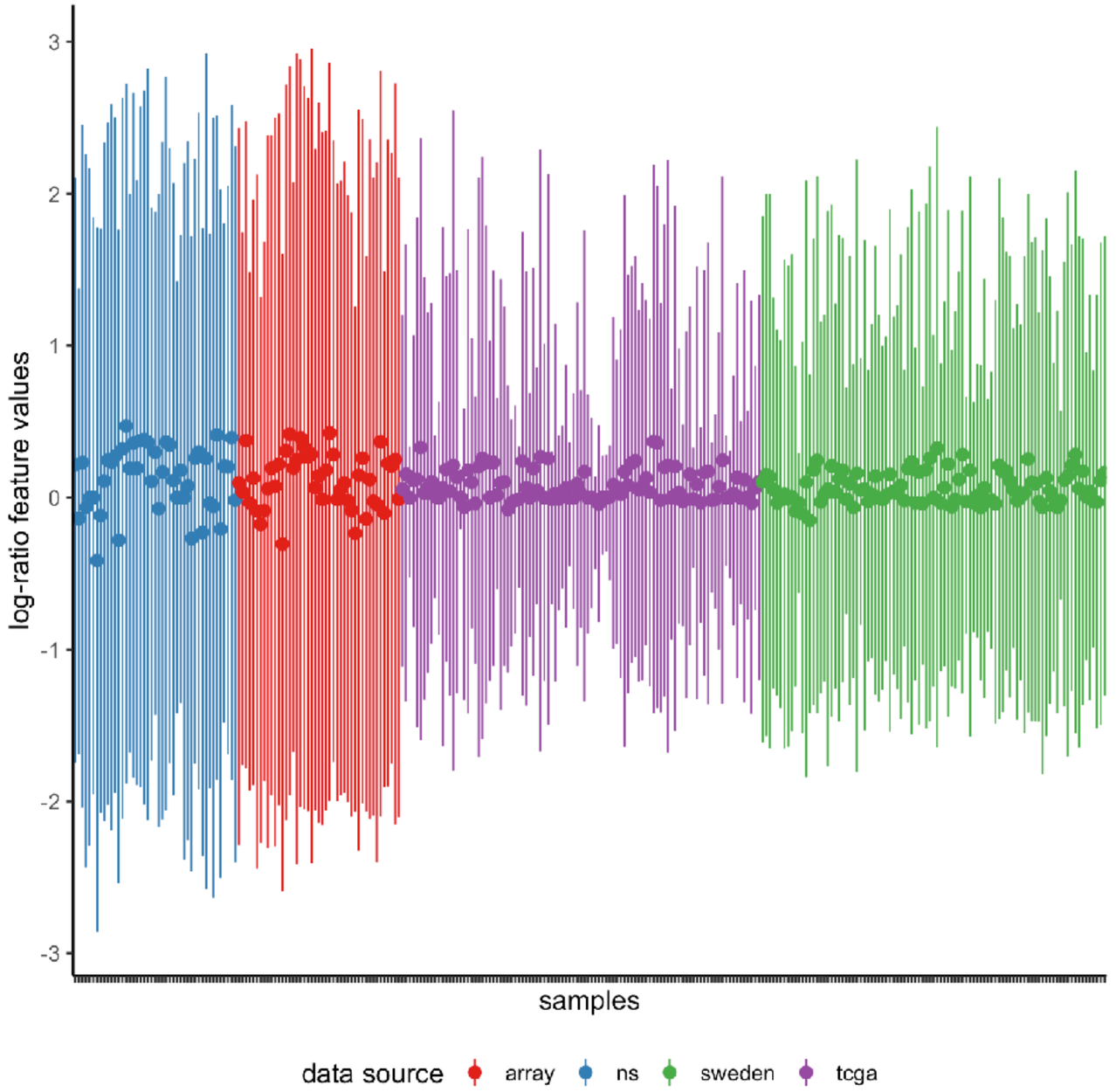
Is log-ratio really a new innovation?

Here is a list of papers that uses genes as predictors

Here is a list of papers that uses a single ratio for prediction

Our contribution is the advocation using a whole collection of ratios for prediction

This has extra implications in terms of the statistics, but we are happy to tackle these.



Within-sample feature standardisation