Oslo Bioinformatics Workshop Week 2022

Statistical principles in machine learning for small biomedical data

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Some of the figures in this presentation are taken from "Elements of Statistical Learning" (Springer, 2009) and "An Introduction to Statistical Learning, with applications in R" (Springer, 2013) with permission from the authors.

Outline for Part 2

Measuring prediction performance

Sample splitting

Resampling methods

Which model is best for prediction?

Example: Regularization/Variable selection by Lasso

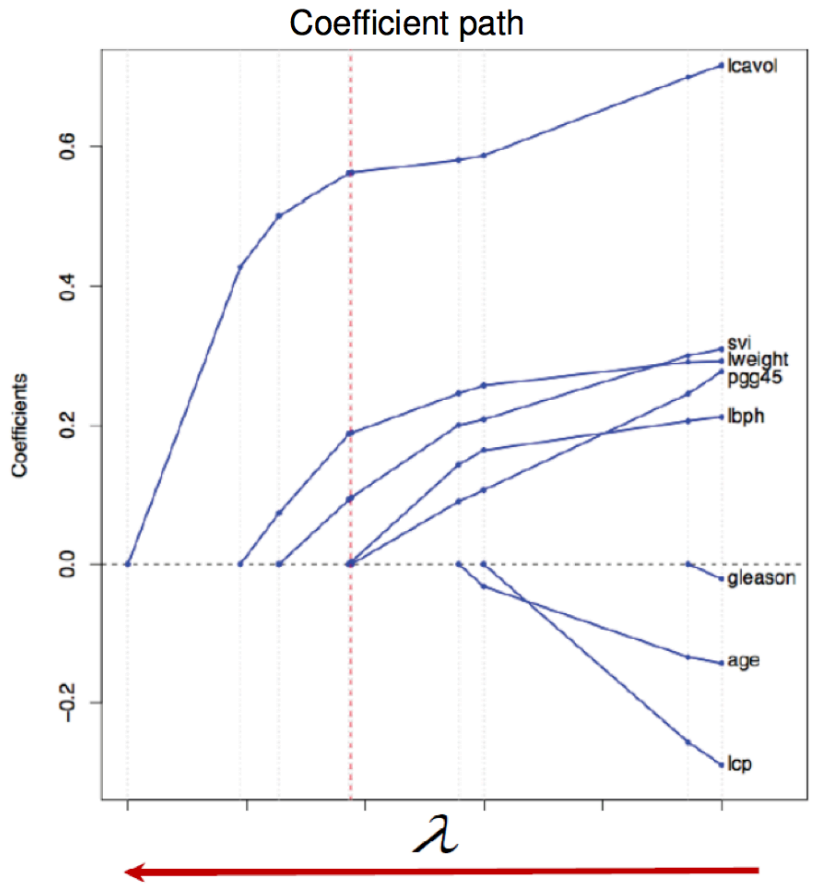
Idea:
Penalize (shrink towards zero) regression coefficients by adding penalty term to LS criterion.

Thereby, "non-relevant" coefficients are estimated as exactly 0 and can be excluded.

$$\hat{\beta}^{\text{lasso}} = \underset{\beta}{\operatorname{argmin}} \left\{ \sum_{i=1}^{N} \left(y_i - \beta_0 - \sum_{j=1}^{p} x_{ij}\beta_j\right)^2 + \lambda \sum_{j=1}^{p} |\beta_j| \right\}$$

Penalty controlled by regularization parameter λ:

- small $\lambda \Rightarrow$ many variables in model
- large $\lambda \Rightarrow$ few variables in model



$\Rightarrow$ How to select λ to minimize prediction error?

Measuring prediction performance

To evaluate model performance on a given data set, measure how well its predictions actually match the observed data.

How close is the predicted value to the true value for that observation?

- **Linear Regression:** Mean squared error:

$$\text{MSE} = \frac{1}{n}\sum_{i=1}^{n}(y_i - \hat{y}_i)^2$$

- **2-class Classification:** Brier score:

$$BS = \frac{1}{n}\sum_{i=1}^{n}(y_i - \hat{p}(y_i = 1|x_i))^2$$

Performance measures

Some models are used only for parameter estimation and testing

But:

- If used for prediction/classification, need to consider accuracy of predictions
- Two major aspects of prediction accuracy that need to be assessed:

  (1) Reliability or calibration of a model:
  - ability of the model to make unbiased estimates of the outcome
  - observed responses agree with predicted responses

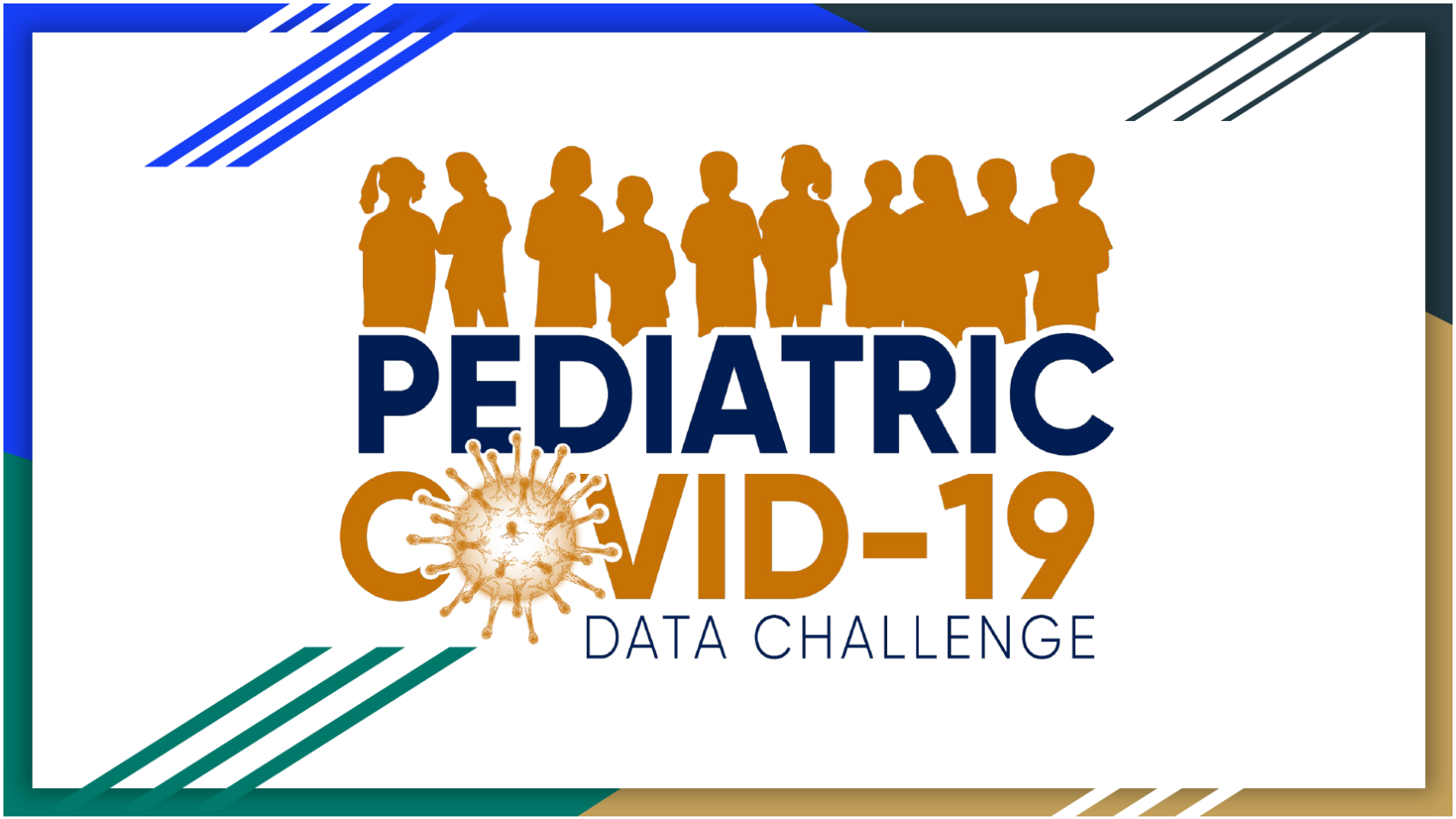
  (2) Discrimination ability:
  - the model is able, through the use of predicted responses, to separate subjects

Performance measures for classification tasks

Steyerberg et al, 2010 (Table 1)

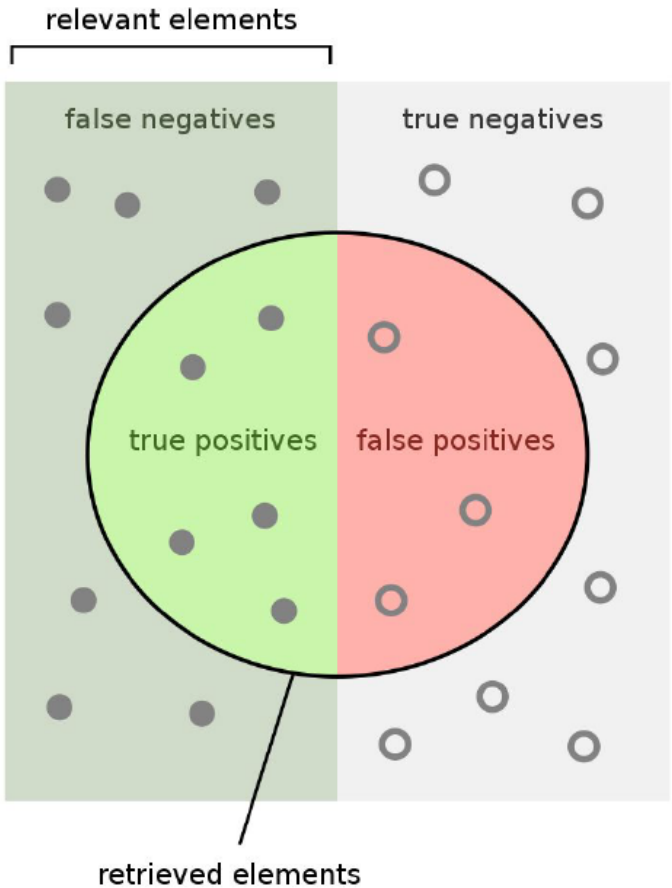
Aspect	Measure	Visualization	Characteristics
Overall performance	R^2 Brier → Brier score	Validation graph	Better with lower distance between Y and $\hat{Y}$. Captures calibration and discrimination aspects.
Discrimination	C statistic → AUC	ROC curve	Rank order statistic; Interpretation for a pair of patients with and without the outcome
	Discrimination slope	Box plot	Difference in mean of predictions between outcomes; Easy visualization
Calibration	Calibration-in-the-large	Calibration or validation graph	Compare mean(y) versus mean($\hat{y}$); essential aspect for external validation
	Calibration slope		Regression slope of linear predictor; essential aspect for internal and external validation related to 'shrinkage' of regression coefficients
	Hosmer-Lemeshow test		Compares observed to predicted by decile of predicted probability

Example: Data challenge model performance evaluation



https://drive.hhs.gov/pediatric_challenge.html

Example: Data challenge model performance evaluation



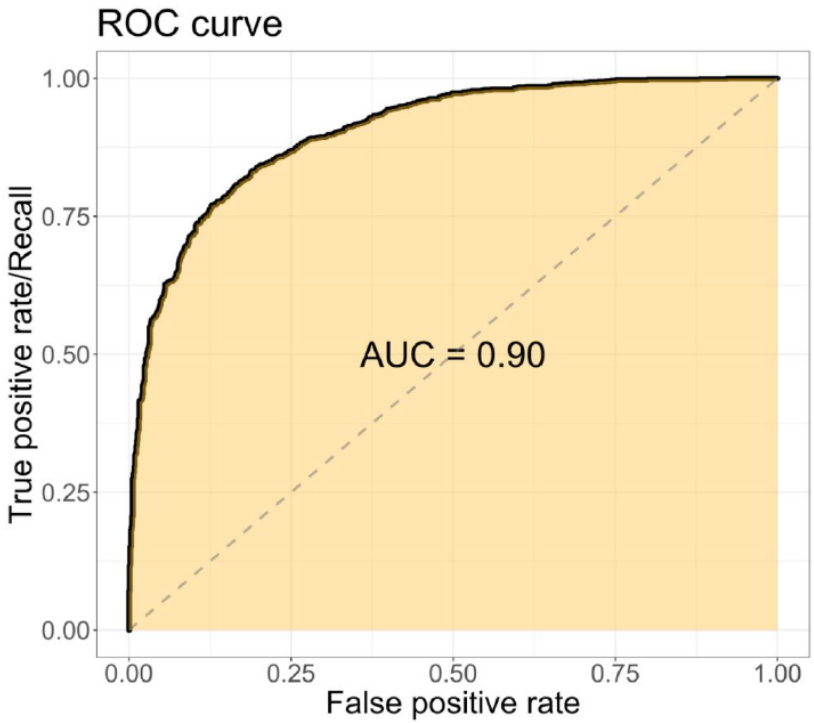
How many retrieved items are relevant?

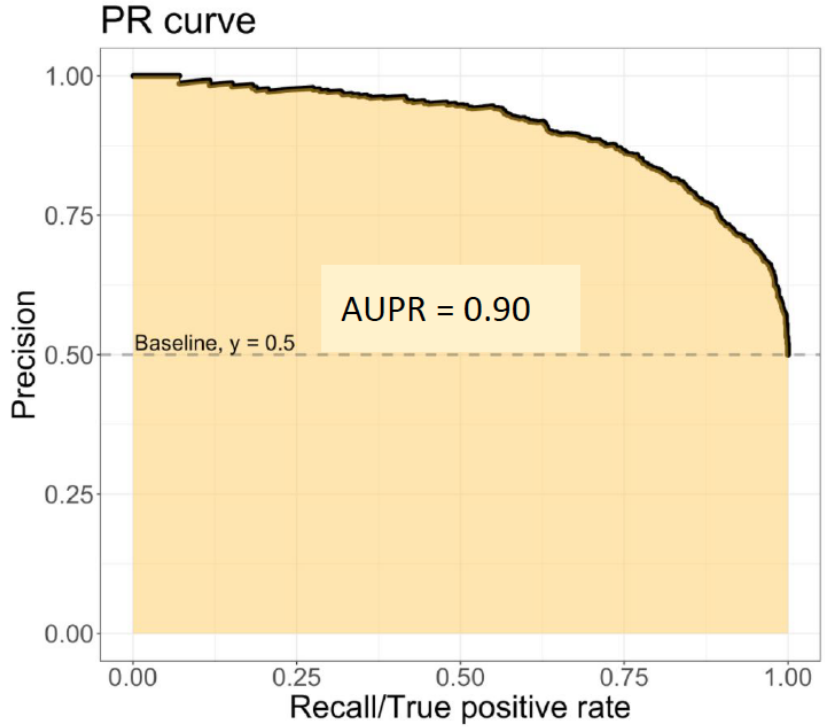
$$\text{Precision} = \frac{\text{true positives}}{\text{retrieved elements}}$$

How many relevant items are retrieved?

$$\text{Recall} = \frac{\text{true positives}}{\text{relevant elements}}$$

Example: Data challenge model performance evaluation





$$F_\beta = (1 + \beta^2) \cdot \frac{\text{precision} \cdot \text{recall}}{(\beta^2 \cdot \text{precision}) + \text{recall}}$$

Example: Data challenge model performance evaluation

Quantitative score (85 %):

$$\frac{1}{3}\left(\left(\max_{\text{threshold } t} F_2(t)\right)^2 + \text{AUPR}^2 + \left(\text{Mean}(\text{AUROC}) - \text{Var}(\text{AUROC})\right)^2\right)$$

Qualitative score (15 %):

- Timeliness
- Interpretability
- Context Utility
- Technical Reproducibility
- Prediction Reproducibility

How to estimate the performance measure

in an unbiased manner?

How to estimate performance in an unbiased manner?

Need: Model assessment/validation to ascertain whether predicted values from the model are likely to accurately predict responses on future subjects or subjects not used to develop the model

Two modes of validation

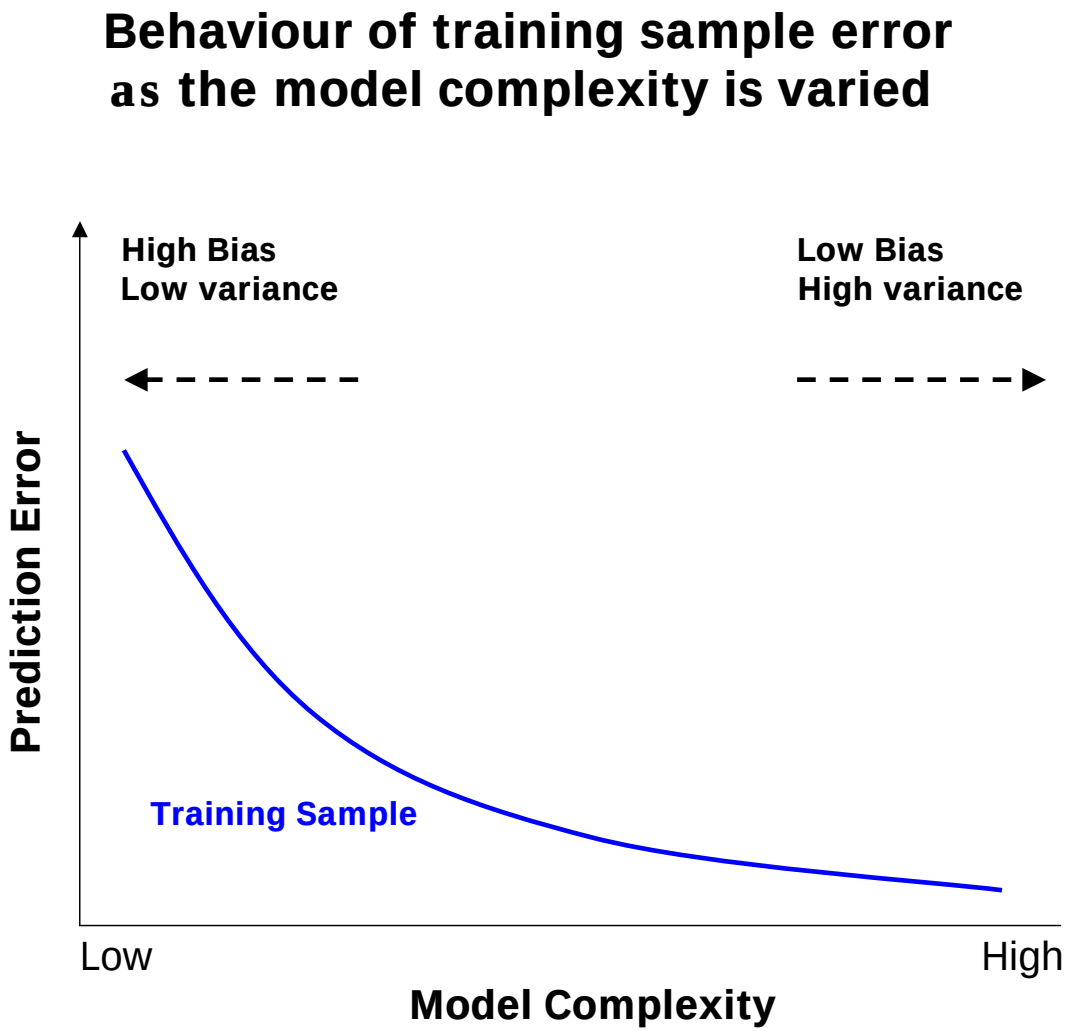
- External:
  Use different sets of subjects for building the model (including tuning) and testing
- Internal:
  (i) Apparent (or training) error: evaluate fit on same data used to create fit
  (ii) Data splitting and its extensions
  (iii) Resampling methods

- **Two fundamental problems with estimation on the training data:**
  - The final model will over-fit the training data. Problem is more pronounced with models with a large number of variables.
  - The error estimate will be overly optimistic (too low).
- A much better idea is to **split the data** into disjoint subsets or use **resampling methods**

- **Training error**: Classification error in the training data set
- **Generalisation error**: Expected error for the classification of new samples $\rightarrow$ This is what we want to estimate!

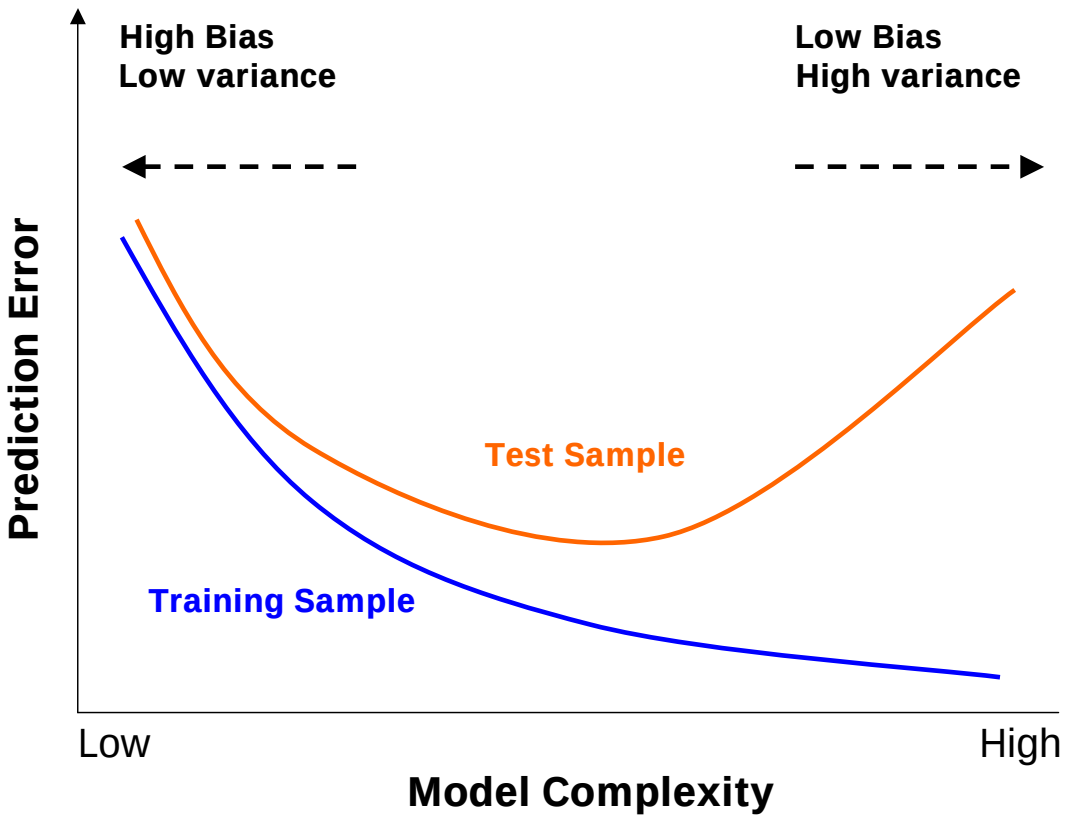
The training error is a bad estimator for the generalisation error!

Over-fitting is a major problem



Over-fitting is a major problem

Behaviour of test and training sample error as the model complexity is varied



The Bias-Variance Trade-Off

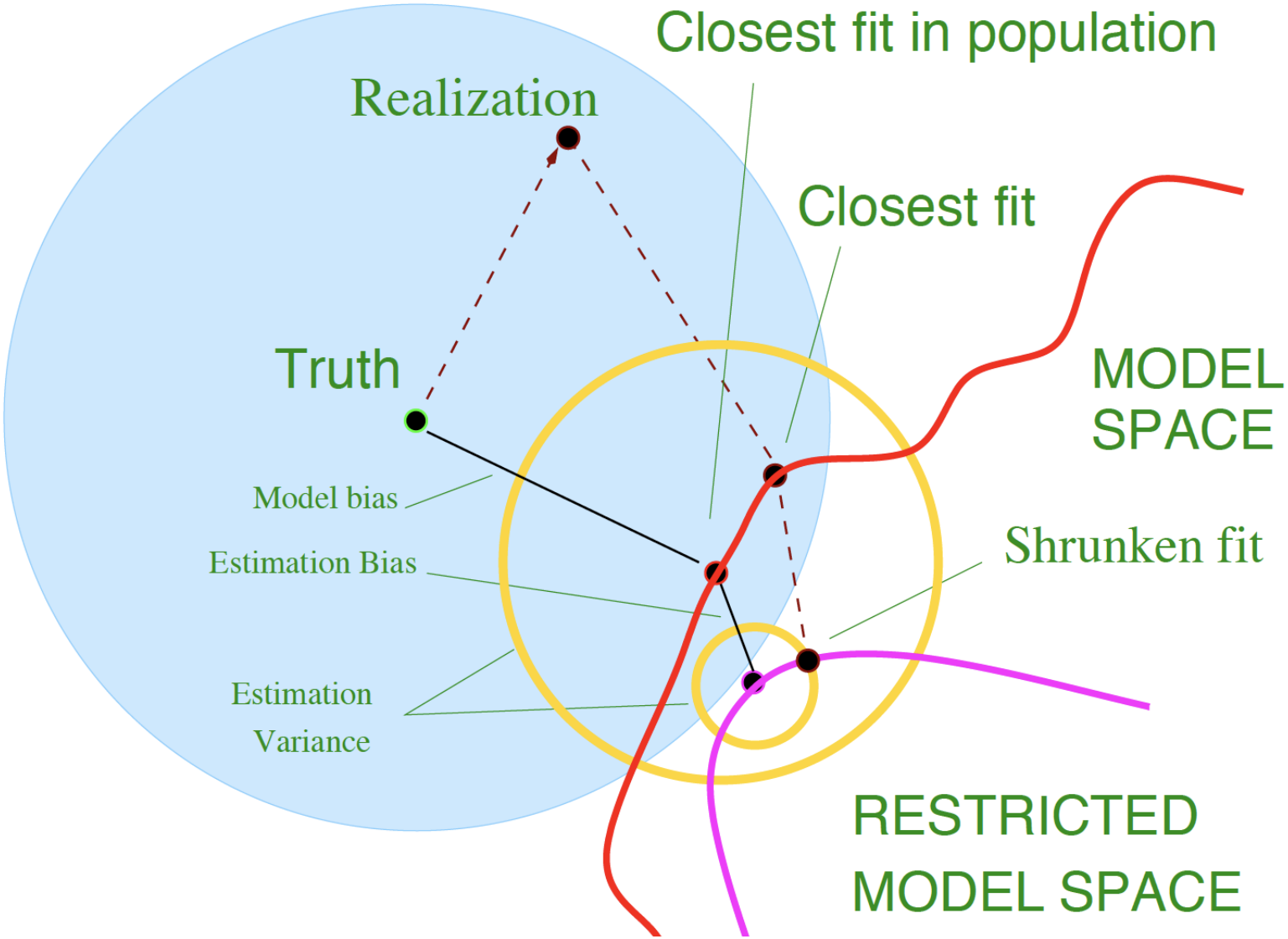
- A simple model might have more model bias, but
- A complex model has more model variance.

For $Y = f(X) + \epsilon$ with $E(\epsilon) = 0$ and $Var(\epsilon) = \sigma_\epsilon^2$, the expected prediction error of $\hat{f}(X)$ at point x_0 with squared error loss is:

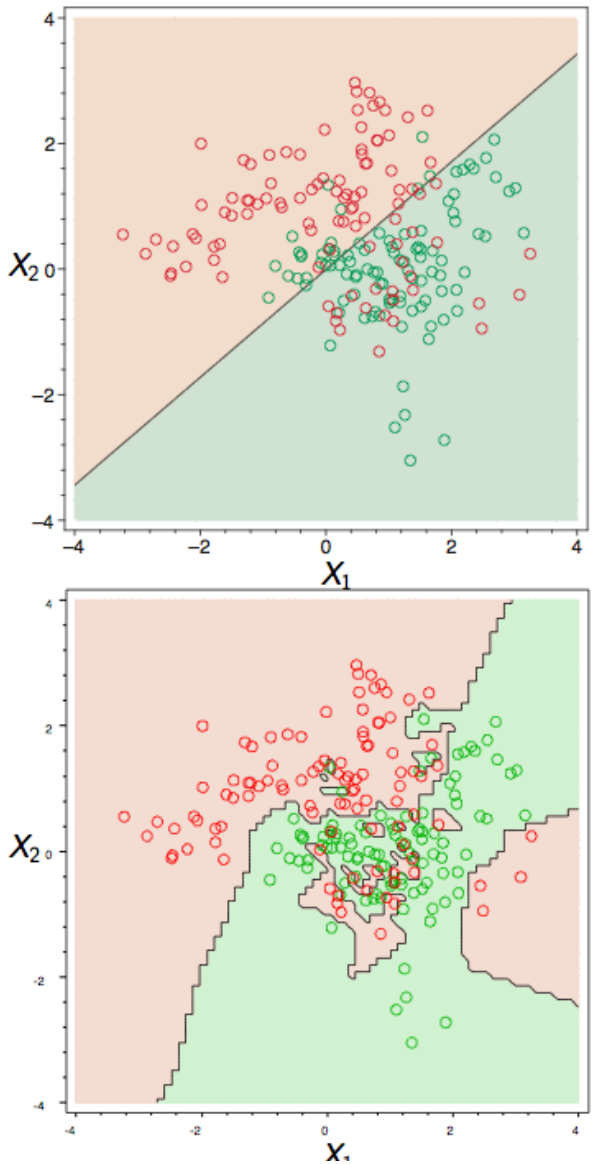
$$\begin{aligned}
\mathrm{Err}(x_0) &= E[(Y - \hat{f}(x_0))^2 | X = x_0] \\
&= \sigma_\varepsilon^2 + [\mathrm{E}\hat{f}(x_0) - f(x_0)]^2 + E[\hat{f}(x_0) - \mathrm{E}\hat{f}(x_0)]^2 \\
&= \sigma_\varepsilon^2 + \mathrm{Bias}^2(\hat{f}(x_0)) + \mathrm{Var}(\hat{f}(x_0)) \\
&= \text{Irreducible Error} + \mathrm{Bias}^2 + \text{Variance}. \qquad (7.9)
\end{aligned}$$

from Hastie et al. (2009), chapter 7.3

The Bias-Variance Trade-Off



The danger for over-fitting is higher with complex models



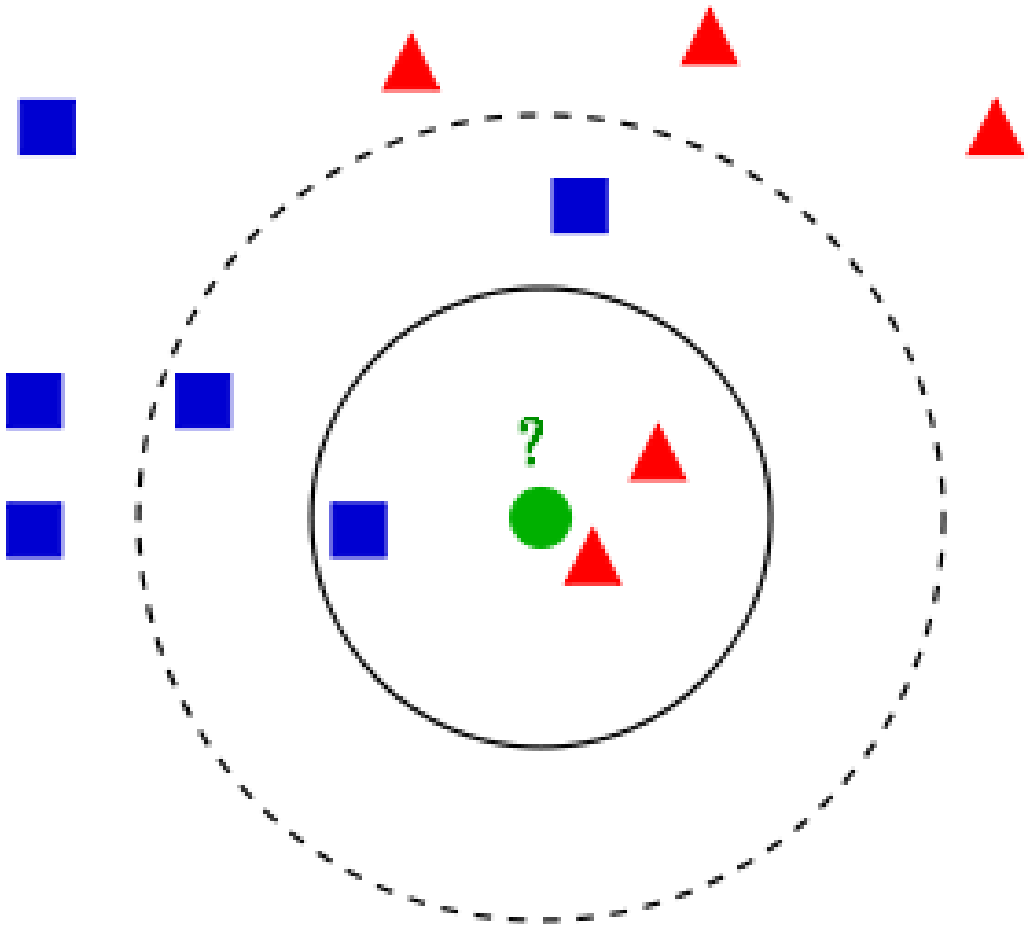
Linear model

- Low complexity
- Stable (linear) decision boundary
- Generalisation error might be hardly larger than the training error

1-Nearest-neighbour method

- High complexity
- Unstable (highly non-linear) decision boundary
- Large over-fitting likely: Generalisation error probably much larger than training error

k-Nearest-neighbour method



Wikipedia.org

- k=3: Classify the test sample as a red triangle.
- k=5: Classify the test sample as a blue square.

Model building, selection and assessment

1. How to decide which method is the "best", i.e. has the smallest generalisation error, in a specific situation?
2. And how large is that smallest generalisation error anyway?

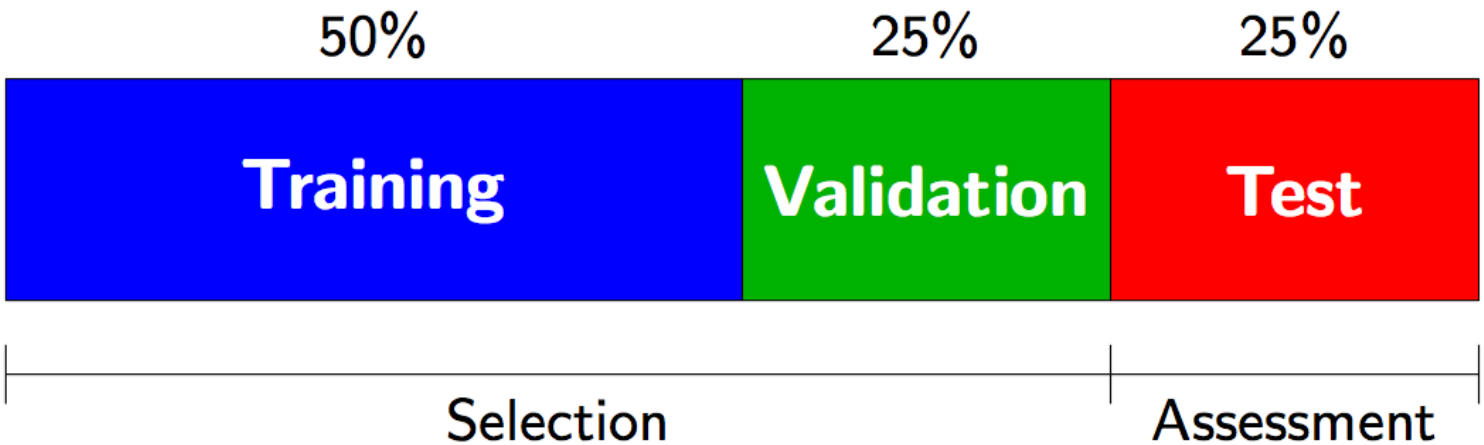
- **Model building and selection**: For a variety of different methods
  1. Fit ("train") the models,
     i.e. perform parameter tuning/ variable selection
  2. Estimate the prediction errors.
  3. Choose the "best" method for a specific situation.
- **Model assessment**
  - For the final selected model estimate the generalisation error on *new data*.

Sample splitting

→ Split data in several independent subsets before model building.

Sample splitting

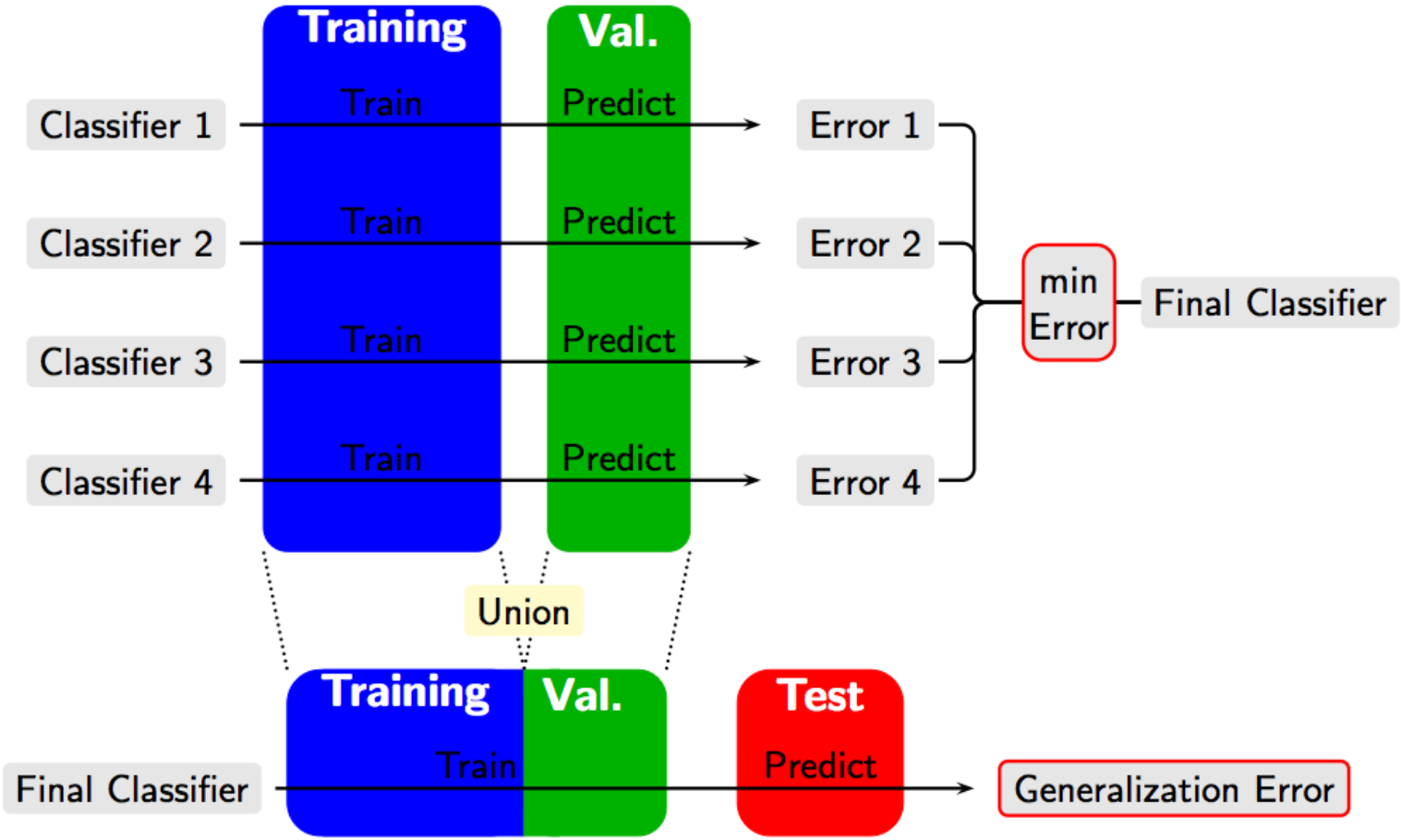
In a data-rich situation, we can split the available data.



- **Training set**: Fit ("train") the various prediction models
- **Validation set**:
  - Estimate the prediction errors of the models
  - Final model: Choose model with smallest prediction error
- **Test set**: Estimate the generalisation error by applying the final model to a new test data set

Sample splitting

Model building and selection →



→ Model assessment

Drawbacks of sample splitting

One-time sample splitting has two **basic drawbacks**:

- We may not be able to afford the "luxury" of setting aside a portion of the data set for testing, as it might result in a large loss of power.

- The assessment can vary greatly when taking different splits:

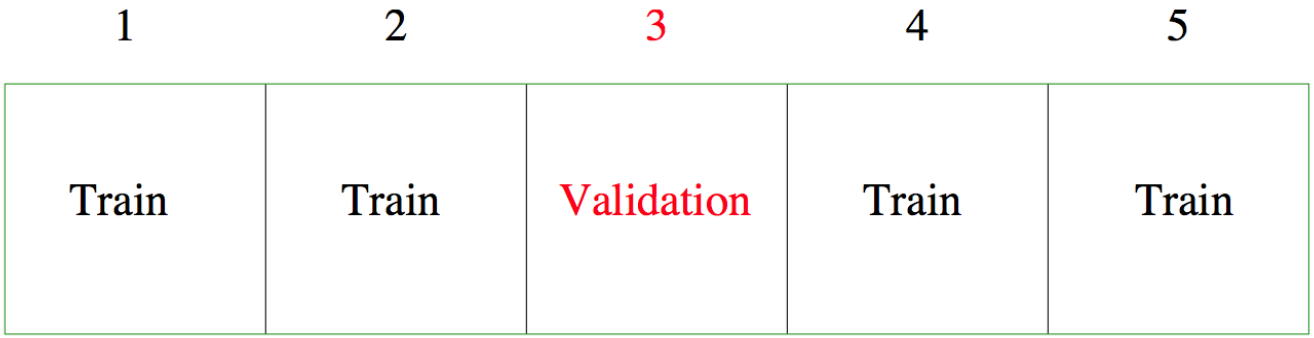
  Since it is a single train-and-test experiment, the estimate of the error rate will be misleading if we happen to get an "unfortunate" split.

Resampling methods

- → Cross-validation
- → Bootstrapping

Cross-validation

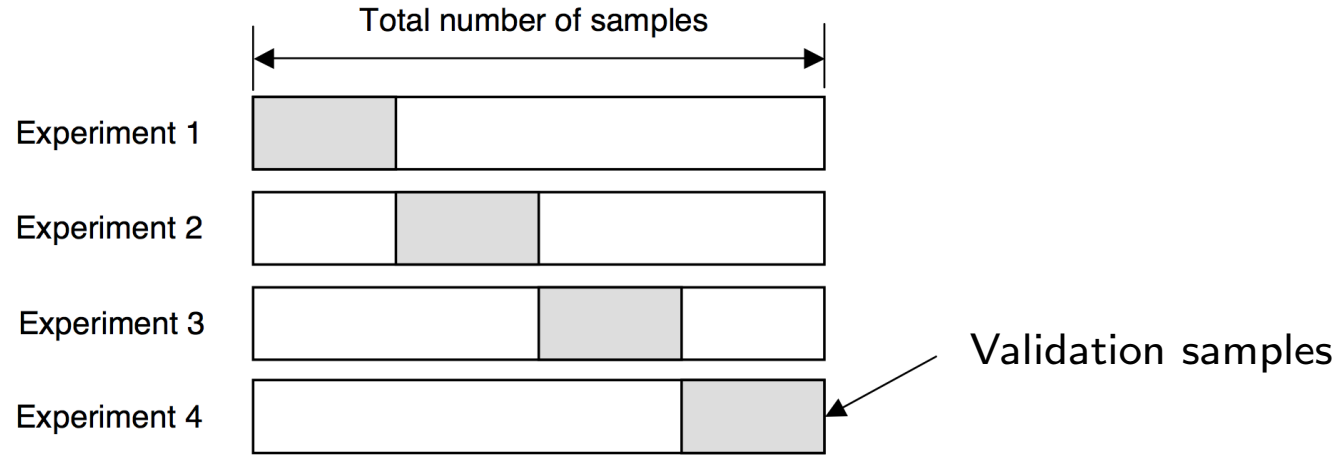
- Alternative to data splitting in not so data-rich situations (i.e. most of the time...)
- Partition the data set into K roughly equal-sized subsets
- Each subset will be the test data set once, with the remaining samples making up the training data



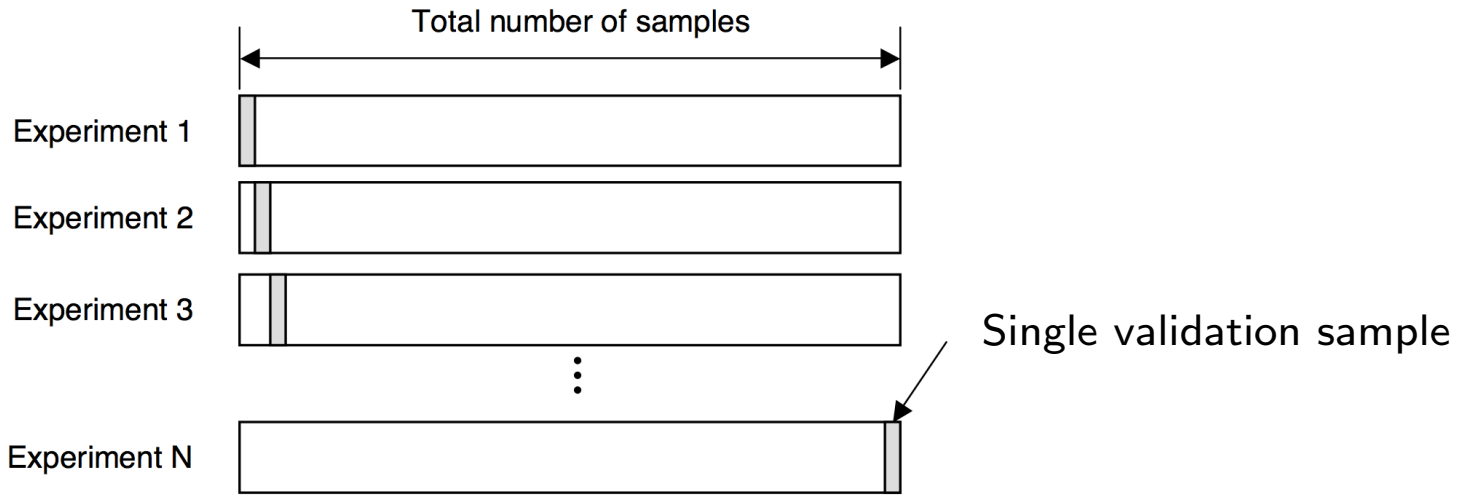
- Cross-validation error: The results are pooled from all test sets to estimate the performance of the model (each case is used exactly once).

Cross-validation

- *K*-fold cross-validation

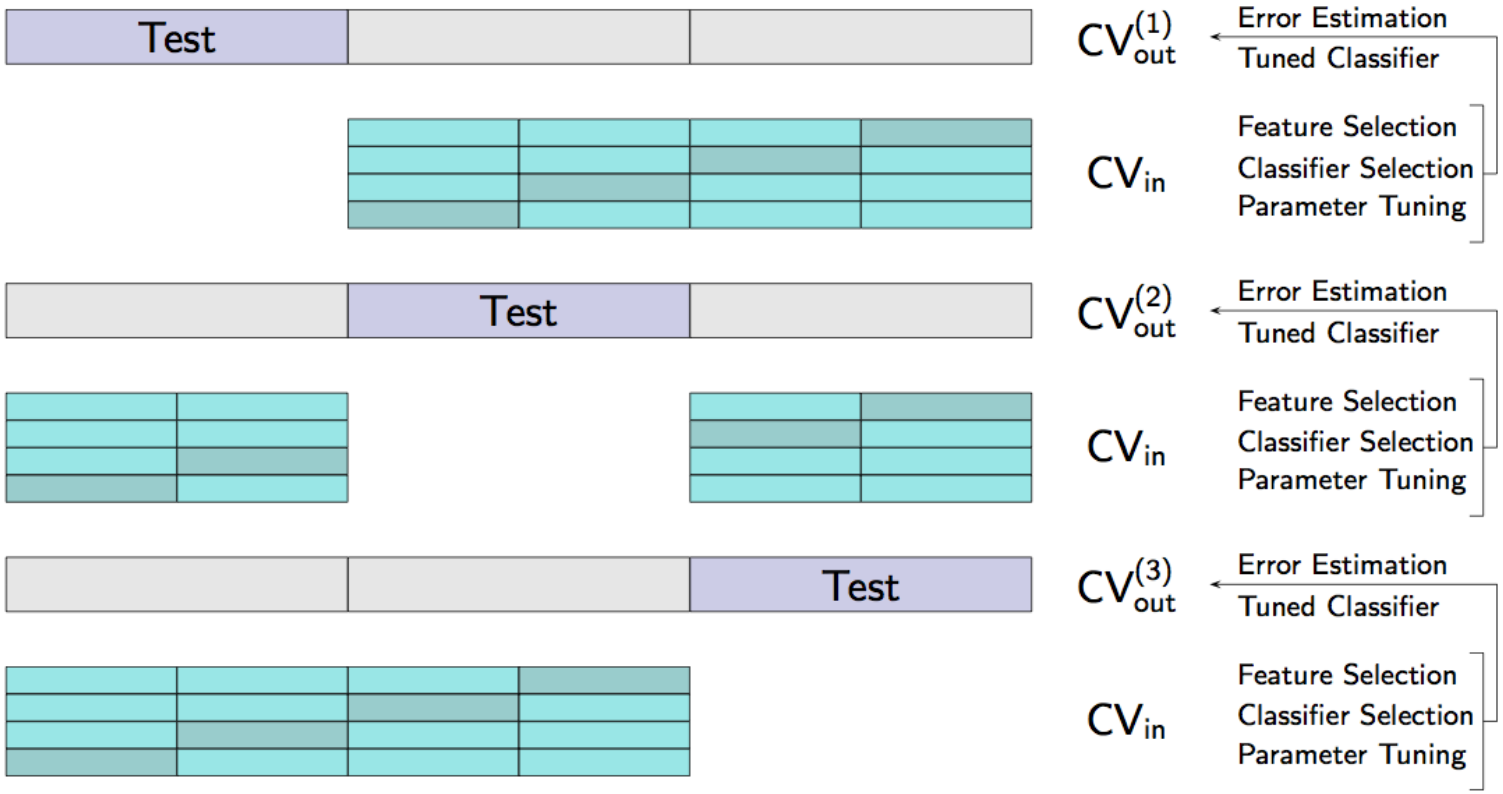


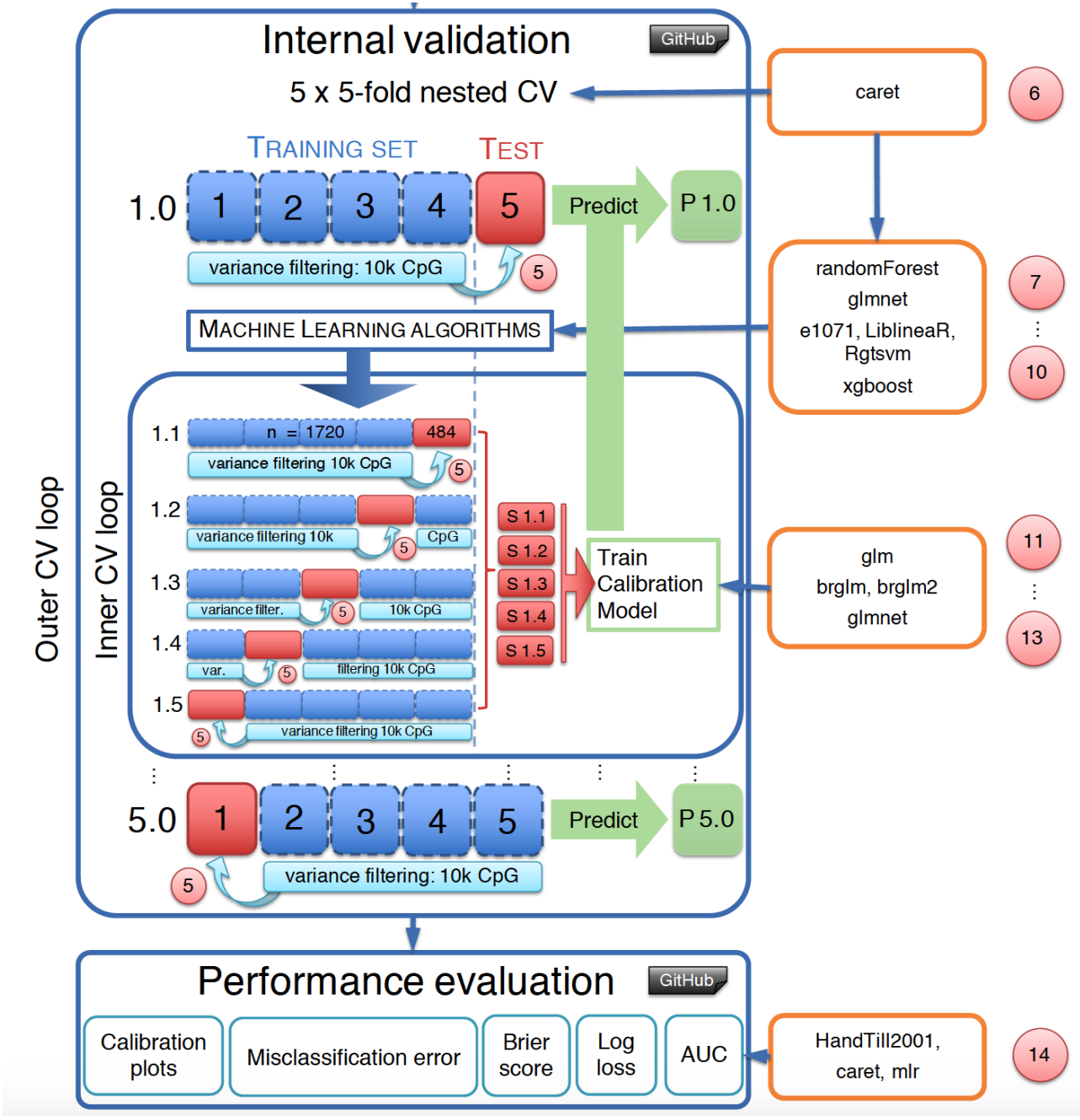
- Leave-one-out cross-validation



Nested cross-validation

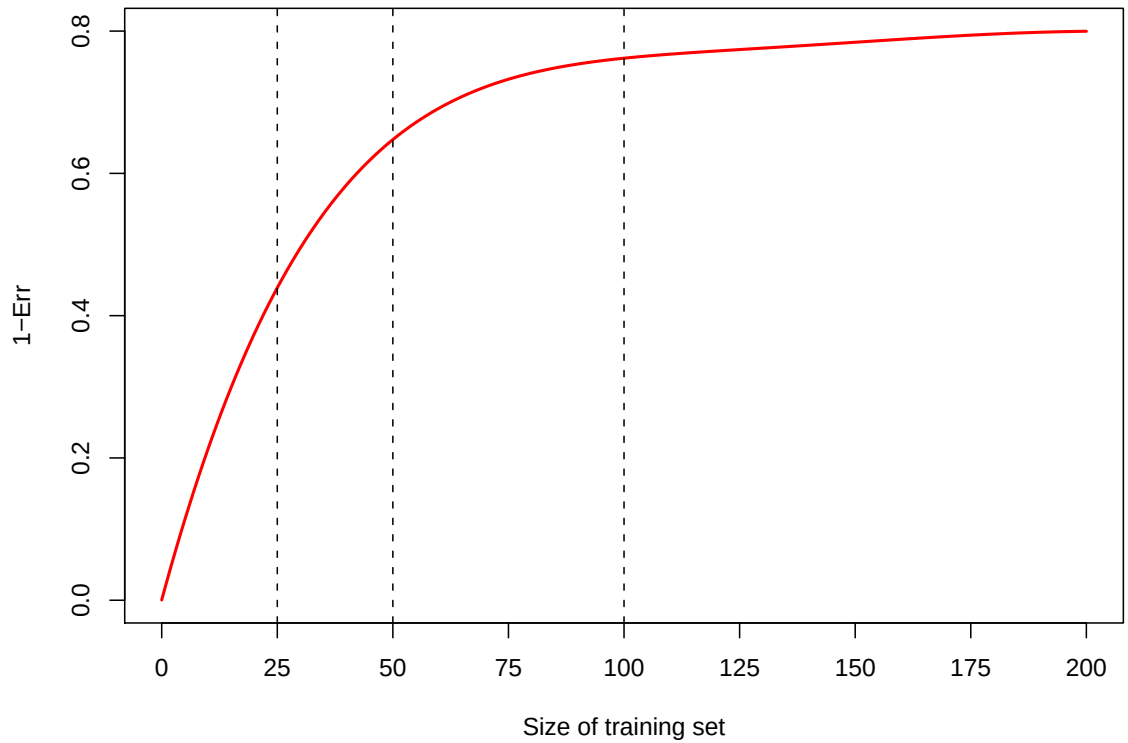
- Inner CV loop: Model building and selection
  - Feature selection, model selection, parameter tuning
  - Choose the model with the smallest CV error within inner loop
- Outer CV loop: Model assessment
  - Estimate the generalisation error for the final model





from: Maros et al. (2020)

K-fold cross-validation: Training set size bias



Hypothetical learning curve:
The performance of the predictor improves as the training set size increases to about 100 observations.

Increasing this number further brings only a small benefit.

Drawbacks of cross-validation

- **Leave-one-out CV:** may have large variance
- **K-fold CV:** may have large bias, depending on the choice of the number of observations to be held out from each fit. The bias is possibly severe for training set sizes < 50, say. If the learning curve has a considerable slope at the given training set size, 5 or 10-fold CV will strongly overestimate the true prediction error.

- Possible solution: estimate prediction error by **bootstrapping**