Deep learning-based feature importance ranking for DNA methylation data in breast cancer risk stratification

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Background

DNA methylation

- Epigenetic mechanism at CpG sites
- Alterations are known to be correlated with cancer

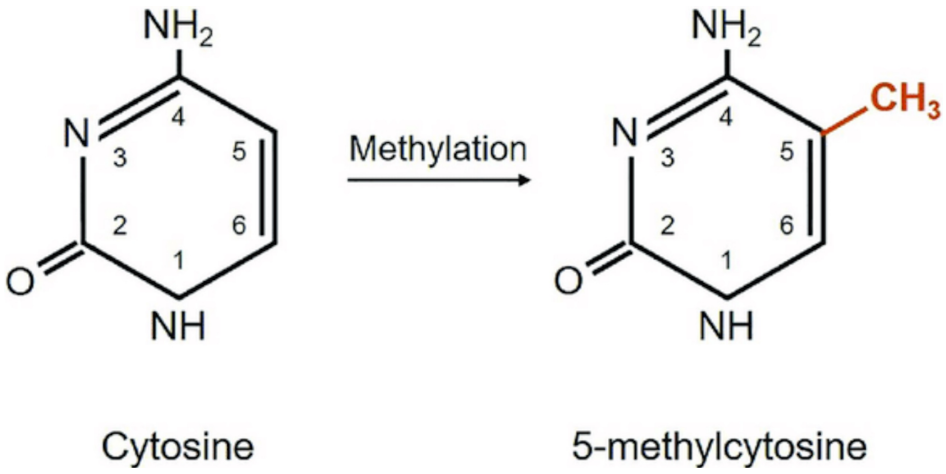

Fig. 1: DNA methylation mechanism

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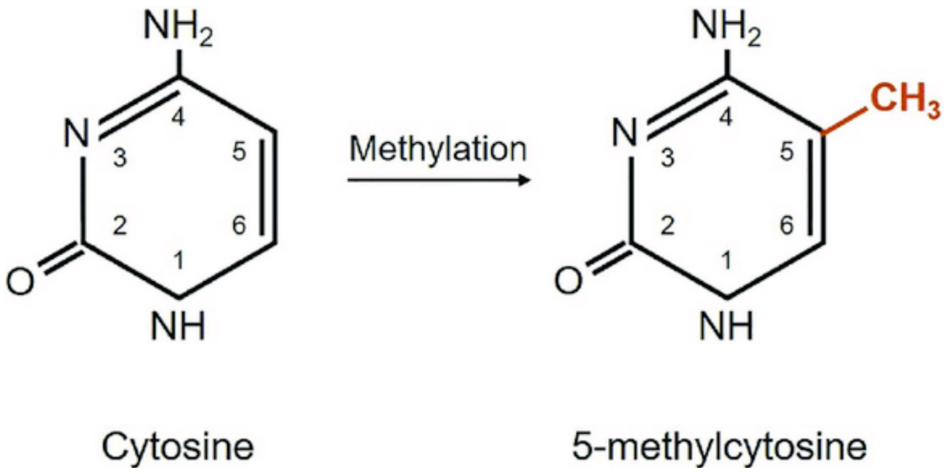

Fig. 1: DNA methylation mechanism

Breast cancer

- Most common cancer worldwide
- Early diagnosis often leads to better prognosis

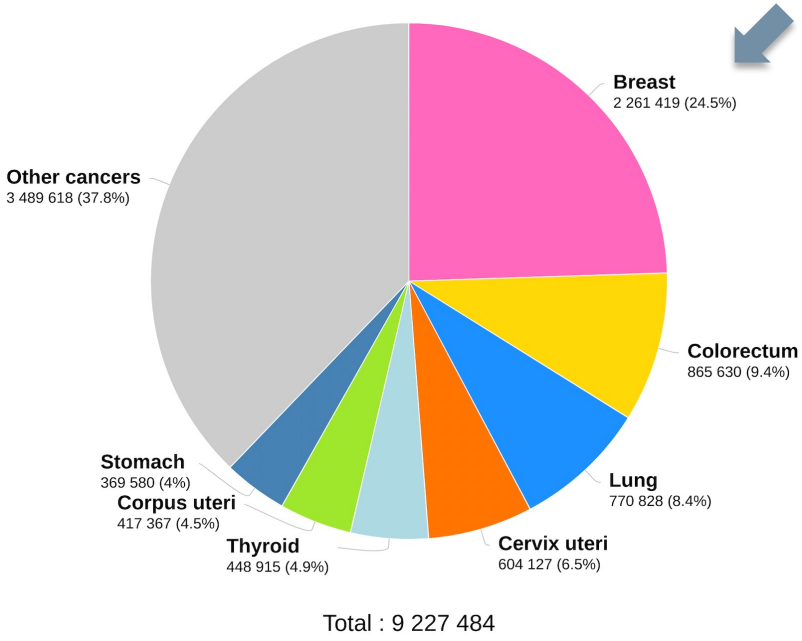

Fig. 2: Number of cancer cases among females in 2020

Objective

Goal

Discovery of the most important methylation features for detecting breast cancer risk several years before the diagnosis

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Production of a feature importance ranking of methylation features according to their relevance in a model predicting breast cancer risk

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Survival model

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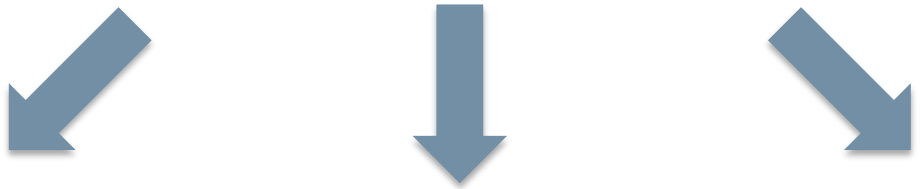

Individual regions | Survival model | Cases-controls use

Challenges

High dimensionality

Challenges

High dimensionality

Non-linear interactions

Challenges

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Interpretability

Challenges

High dimensionality

Non-linear interactions

Methodology based on a dimensionality reduction technique, followed by a regularized deep survival pre-trained model, and then an adequate feature importance algorithm

Interpretability

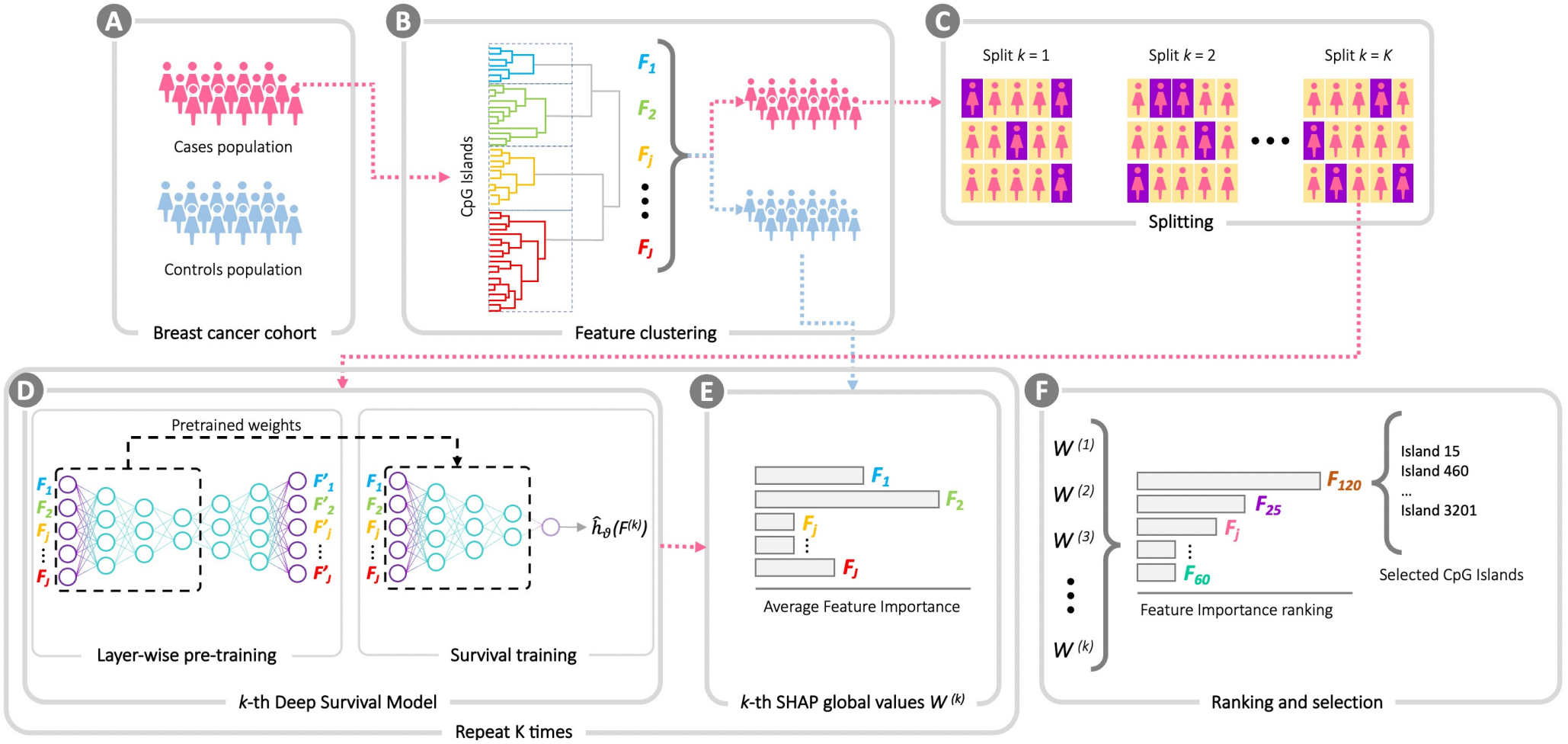
EPIC dataset (Riboli et al., 2002)

- Prospective case study with methylation data from blood samples
- Both cancer cases and matched controls
- Subjects characterized by time to diagnosis, cohort and beta values
- Group CpG sites in CpG islands

Patient	Time to disease	Study	cg03725447	cg25215298	cg03256938	cg18297246
200109360008_R01C01	6.986995	Breast	0.192584	0.277721	0.881829	0.449754
7766130100_R06C01	NaN	Breast	0.084782	0.343562	0.848235	0.481278
6042316165_R01C01	8.966461	Colon	0.216812	0.320498	0.898258	0.450233
7668610146_R06C01	NaN	Colon	0.178374	0.311865	0.900772	0.412366
3999875083_R05C02	16.169747	Lung	0.180652	0.324830	0.866643	0.533926
3999875048_R03C02	NaN	Lung	0.210455	0.318499	0.864264	0.415800

Fig. 3: Example of observations in the EPIC dataset

Methodology pipeline



Feature clustering

Biological information is shared among the CpG islands

Feature clustering used to reduce dimensionality

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Feature clustering used to reduce dimensionality

- It works as hierarchical clustering but grouping features instead of samples
- Using the Euclidean distance and the Ward linkage

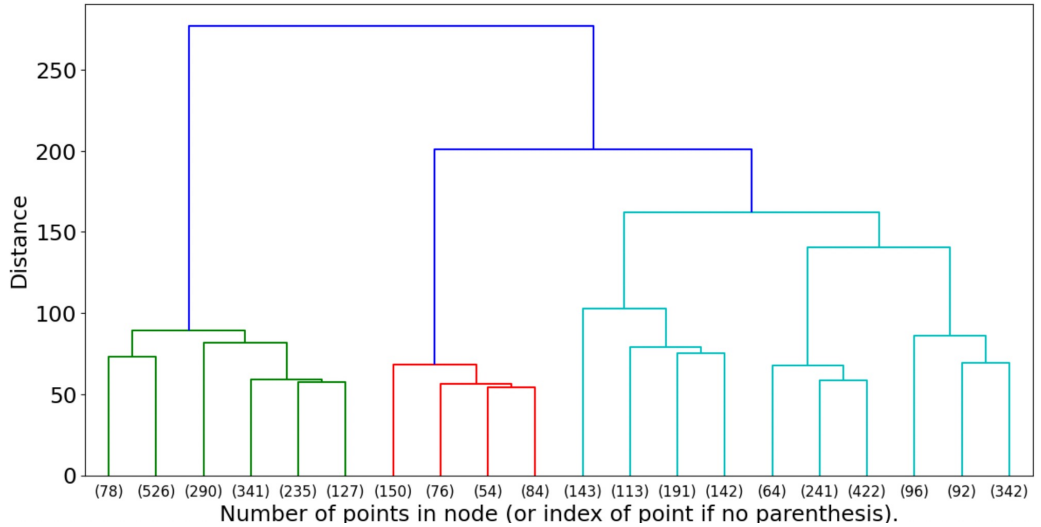

Fig. 4: Feature clustering dendrogram

Deep survival modelling

Survival training

Inspired by DeepSurv (Katzman et al., 2018)

$$\mathcal{L}(\theta) = -\frac{1}{N_{E=1}} \sum_{i:E_i=1} (\hat{h}_\theta(\mathbf{X}_i) - \log(\sum_{j \in \mathcal{R}(T_i)} e^{\hat{h}_\theta(\mathbf{X}_j)})) + \lambda \|\theta\|_2^2$$

Models interactions

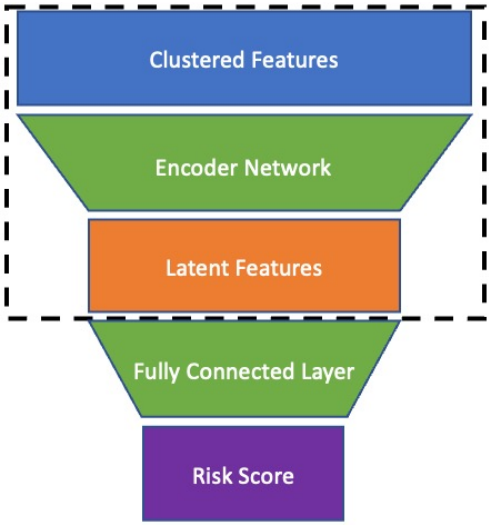

Fig. 6: Deep survival model

Deep survival modelling

Autoencoder pre-training

Layer-wise procedure

$$\mathcal{L}(\mathbf{x}, \mathbf{x}') = \frac{\sum_{i=1}^{n} |x_i - x_i'|}{n}$$

Regularization and generalization

Survival training

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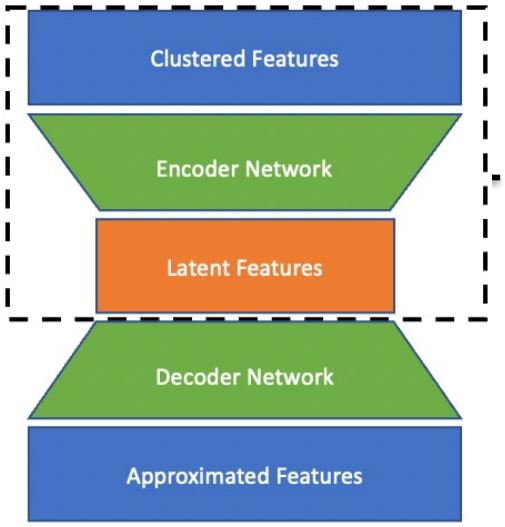

Fig. 5: Autoencoder model

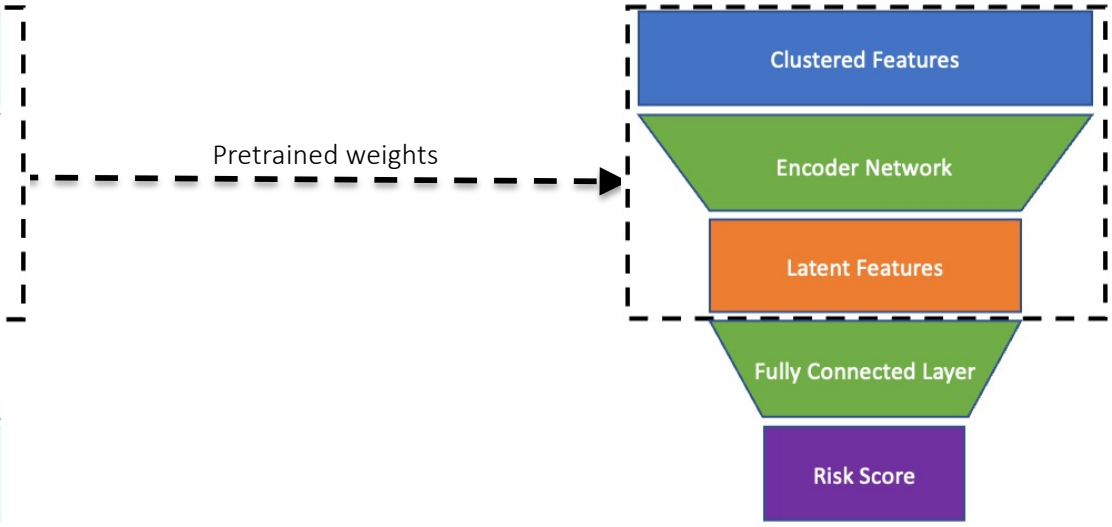

Fig. 6: Deep survival model

Feature importance ranking

Kernel SHAP (Lundberg et al., 2017)

$$\phi_j = \sum_{S \subseteq \{x_1,\dots,x_p\} \setminus \{x_j\}} \frac{|S|!(p-|S|-1)!}{p!} (v_{\mathbf{x}}(S \cup \{x_j\}) - v_{\mathbf{x}}(S))$$

- Deals with interacting features
- Uses a reference dataset

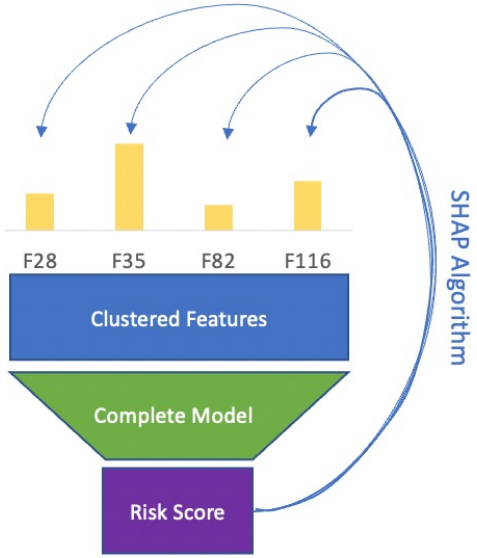

Fig. 7: SHAP values computation

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Fig. 7: SHAP values computation

Averaging, ordering and selection

- Exploit an ensemble approach
- Sort features according to their importance
- Select the first features in the ranking

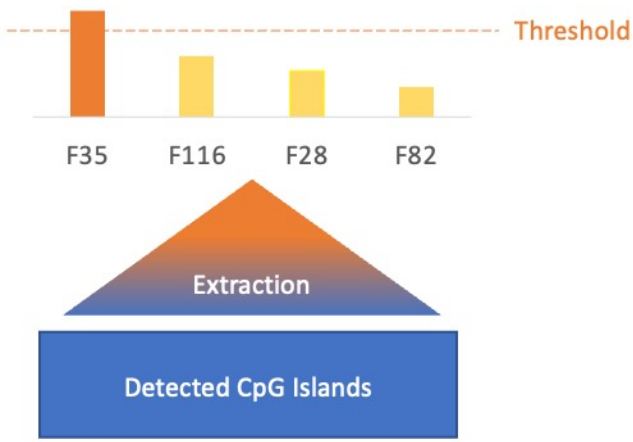
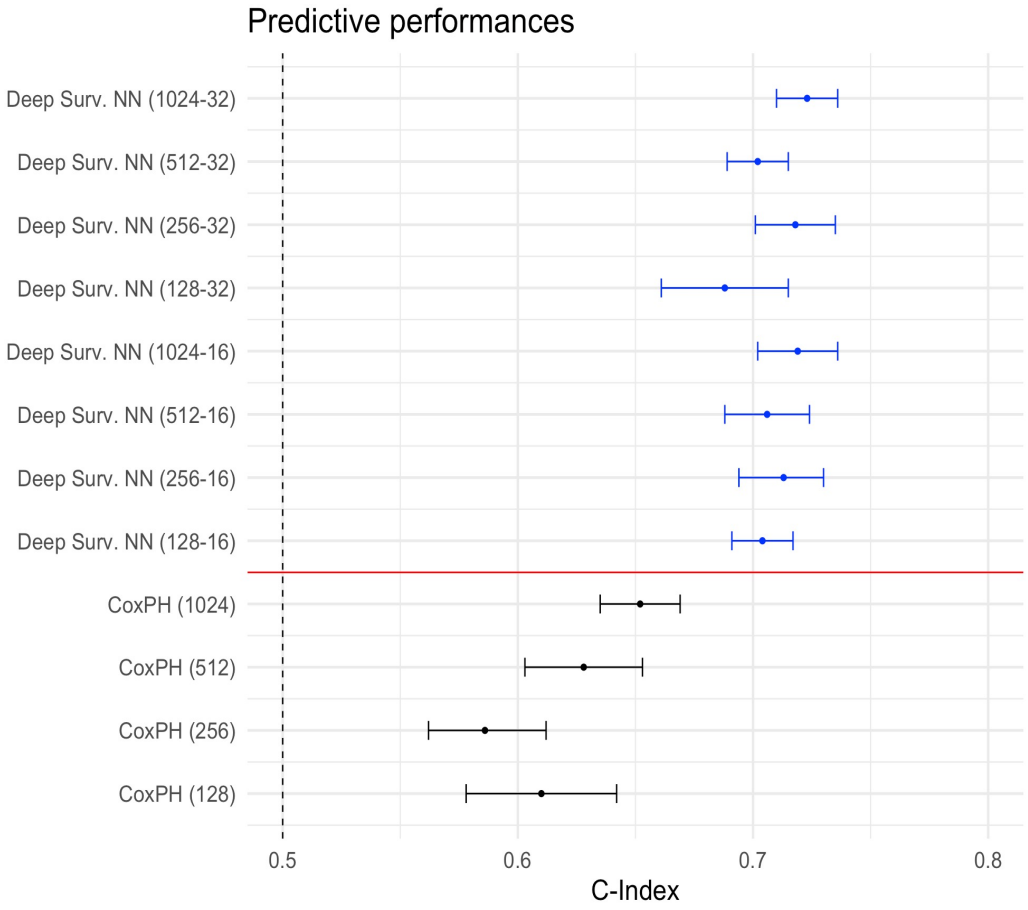
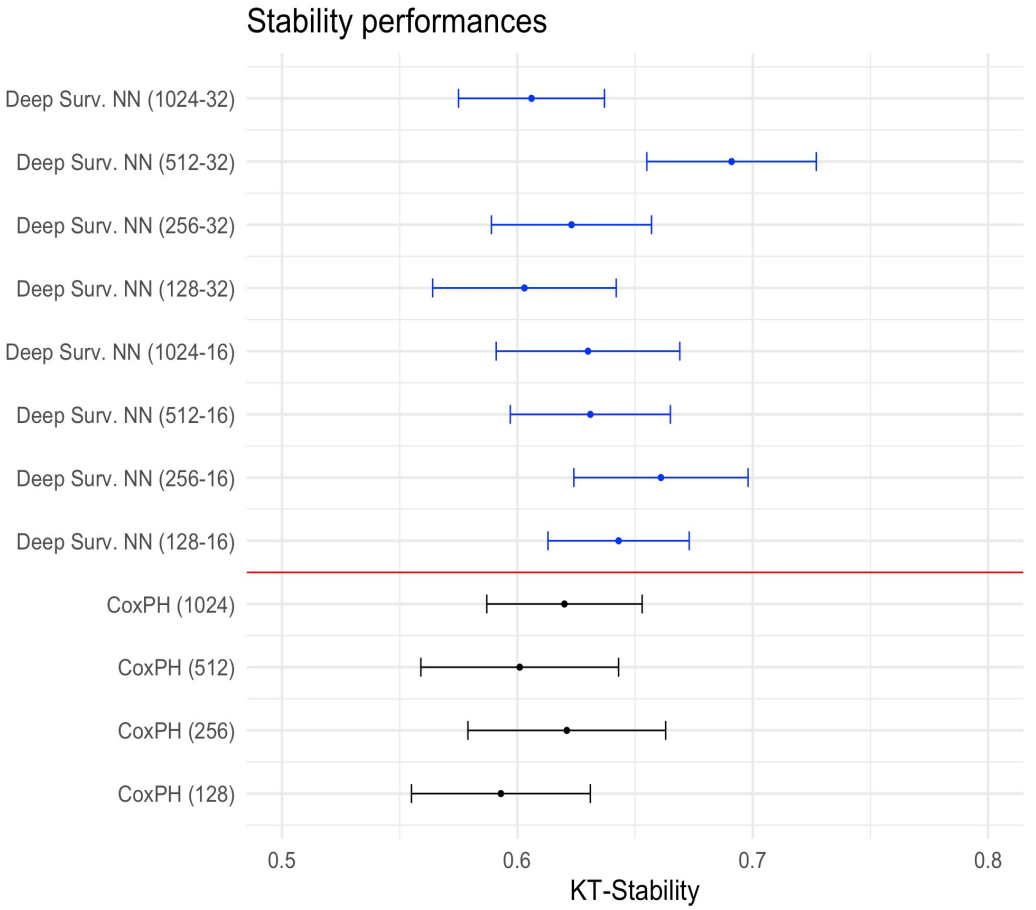


Fig. 8: Selection of the most important CpG islands

Performances of the methods





Ranking and selection

- Feature 120, composed of 20 CpG islands, selected as ranked first

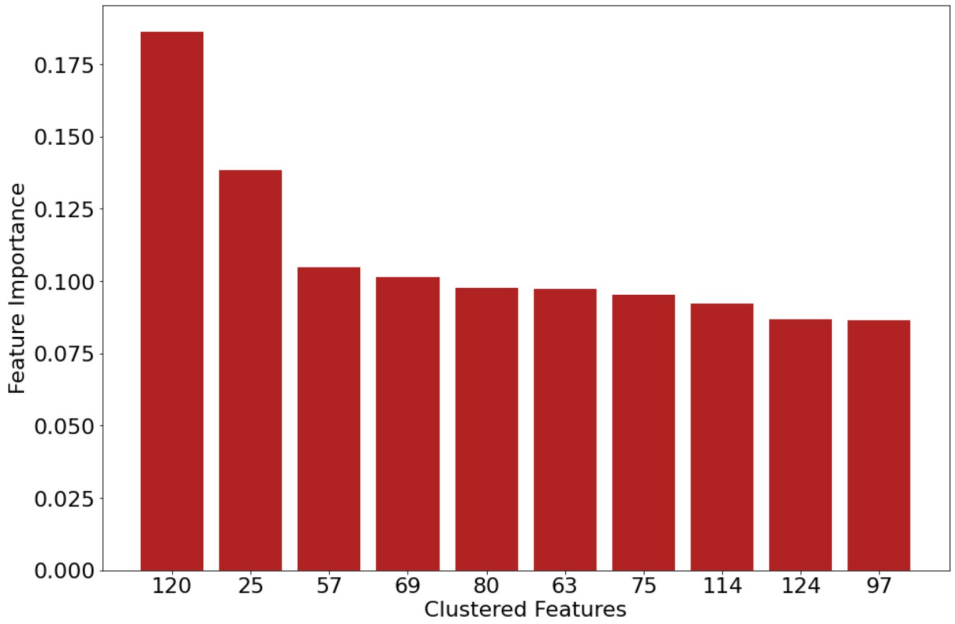
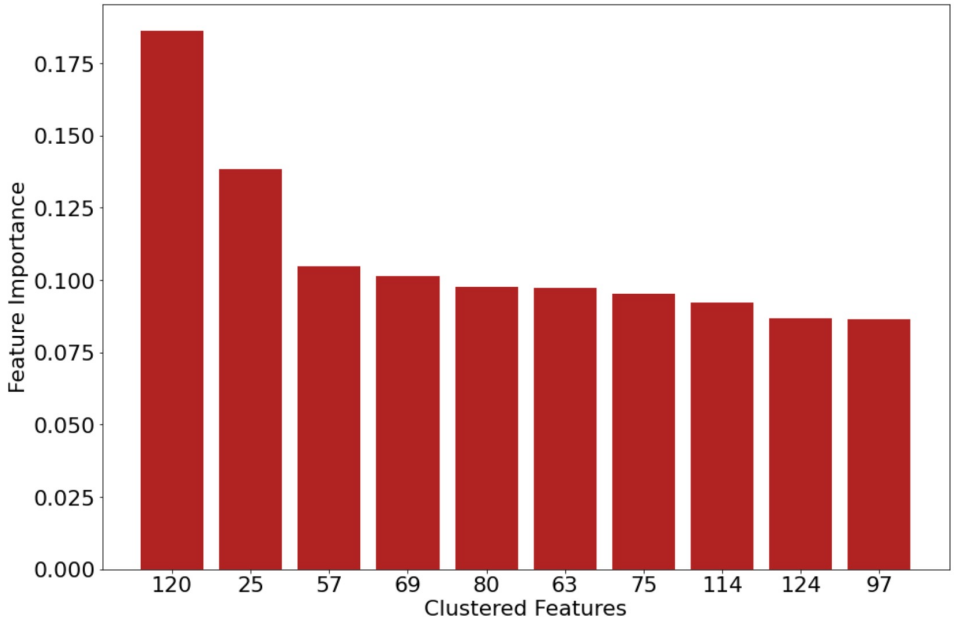


Fig. 9: Importance of the first 10 ranked features

Ranking and selection

- Feature 120, composed of 20 CpG islands, selected as ranked first
- Clear decreasing trend of methylation with respect to the time to diagnosis



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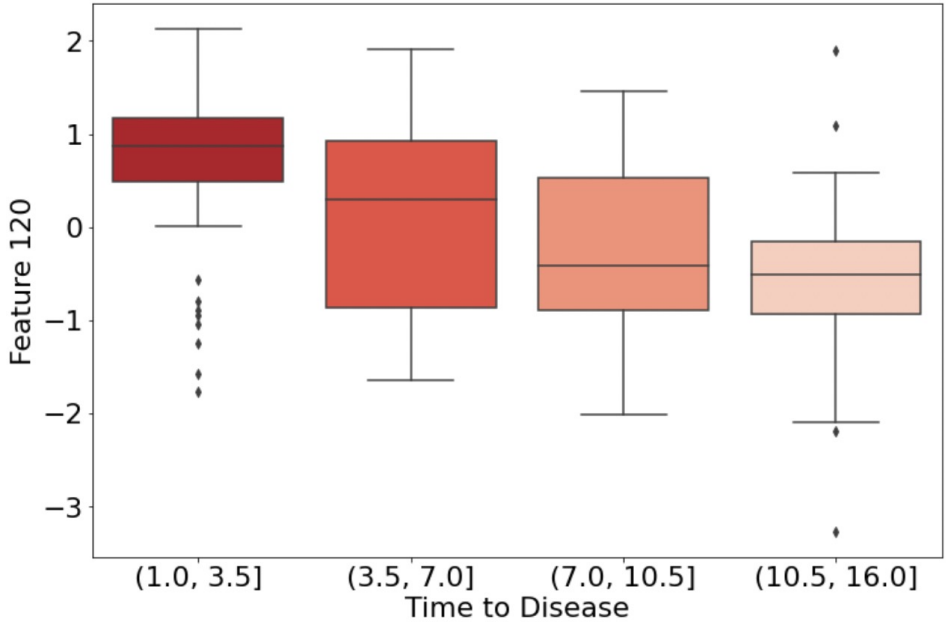

Fig. 10: Boxplot of Feature 120 divided by time categories

Post-hoc analysis

- Significant difference in the survival profiles of low and high methylated subjects
- High methylation is a risk factor

CpG island	Log-rank p-value	Hazard ratio [95% interval]
1:90945518-90945656	3.88e-08	2.03 [1.57, 2.63]
1:158090642-158091676	1.26e-03	1.51 [1.17, 1.94]
2:100086548-100088317	3.36e-04	1.58 [1.23, 2.03]
4:149584089-149584799	3.18e-07	1.93 [1.49, 2.49]
6:1570179-1570756	5.62e-07	1.89 [1.47, 2.43]
6:43530362-43531683	1.16e-05	1.75 [1.36, 2.25]
6:166137998-166138866	3.77e-03	1.45 [1.12, 1.86]
8:21701267-21701566	1.85e-08	2.05 [1.59, 2.65]
8:145119282-145120028	5.20e-06	1.82 [1.40, 2.36]
9:34618796-34619343	2.30e-12	2.49 [1.92, 3.24]
10:102493904-102494072	3.66e-03	1.45 [1.13, 1.87]
10:119294070-119294143	3.04e-04	1.58 [1.23, 2.04]
14:87862626-87863008	7.93e-05	1.65 [1.28, 2.12]
16:85096322-85097146	2.39e-07	1.96 [1.51, 2.53]
18:75811758-75814395	2.23e-08	2.04 [1.58, 2.63]
19:1704275-1706659	2.51e-11	2.35 [1.82, 3.05]
19:13070446-13070515	1.78e-02	1.36 [1.05, 1.75]
20:21438169-21438255	4.91e-07	1.90 [1.47, 2.44]
20:21449303-21449404	1.04e-02	1.39 [1.08, 1.78]
22:37180713-37182260	3.10e-09	2.17 [1.67, 2.82]

Fig. 11: Comparison of subjects with different methylation levels

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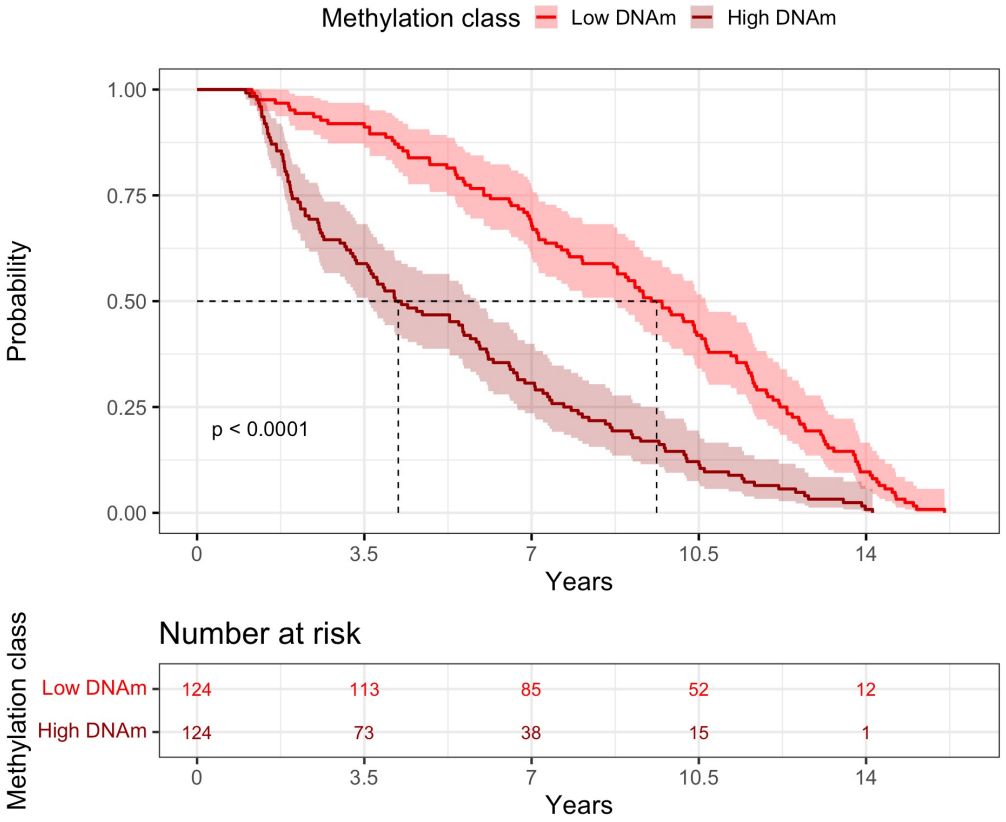

Fig. 12: Kaplan-Meier curves of island 9:34618796-34619343

Weighted Kolmogorov-Smirnoff test (Charmpi et al., 2015)

Obtains meaningful biological results and validates the methodology

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All 8 pathways are correlated with cancer, 5 specifically with breast cancer

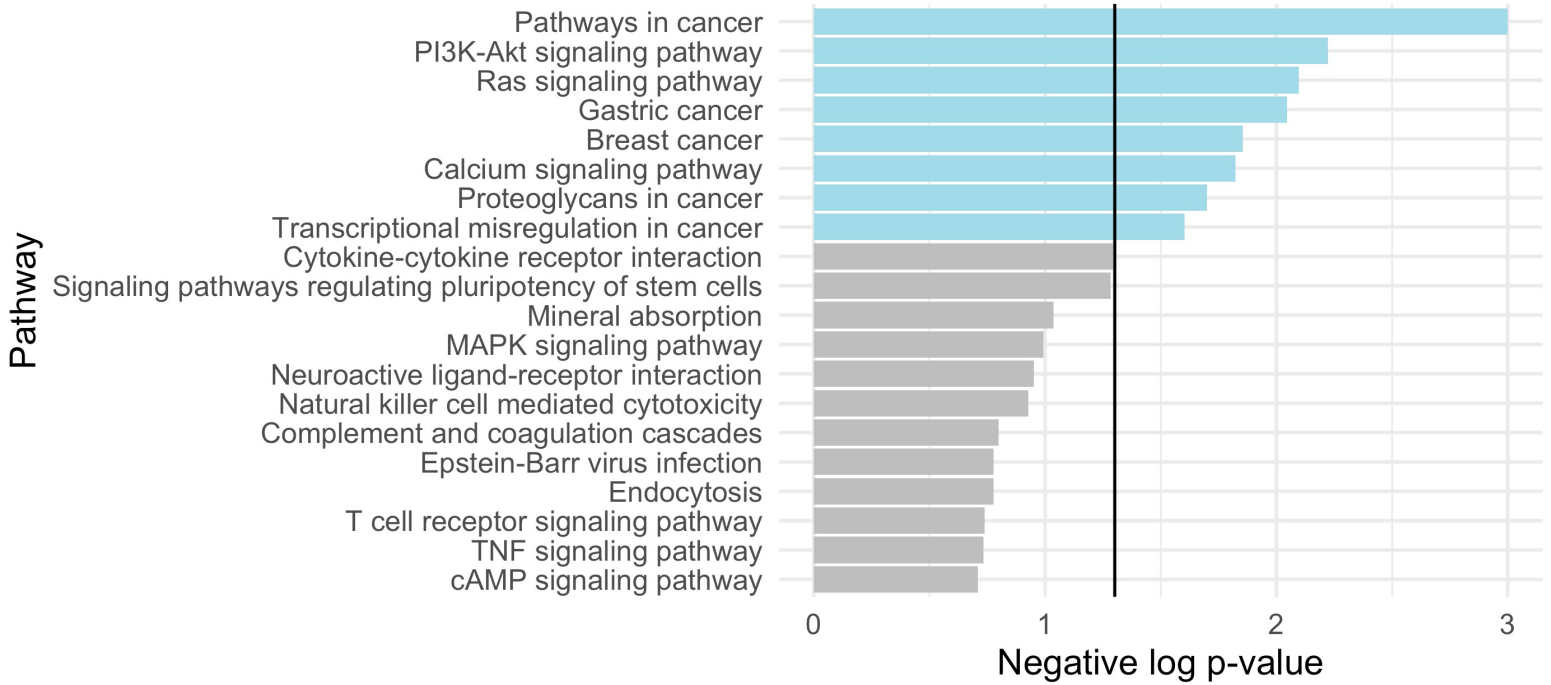

Fig. 13: Barplot of the significant pathways

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- Apply the Deep SHAP algorithm

Bibliography

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