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Offen im Denken

SFB 876 Providing Information by Resource-Constrained Data Analysis

Project C1

Feature selection in high dimensional data for risk prognosis in oncology

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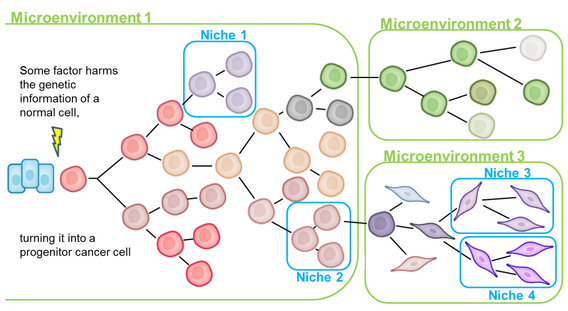
Problem

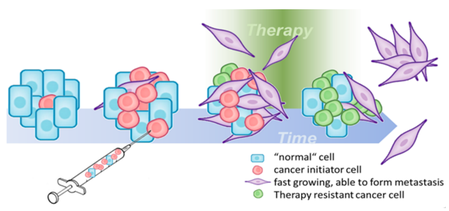
Cancer is an Evolutionary Process

Progression of cancer is driven by both natural selection and therapy, which requires adaptation to different niches and microenvironments.



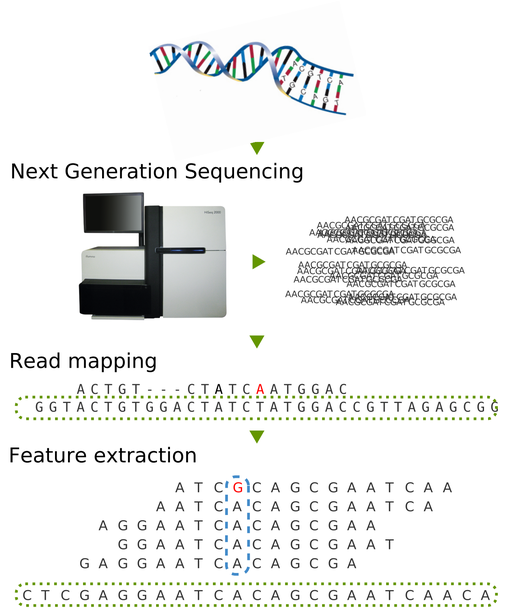
Tumours are Moving Targets

- Understanding inter- and intra-tumour heterogeneity
- Identifying genomic biomarkers for risk prognosis



[Schulte et al. 2018]

Feature Extraction and Selection from High-Throughput Sequence Data



Extremely high feature dimension vs. small number of samples:

- Up to millions of genetic variants
- How to find interpretable tumour-specific variants?

Analysis of Multiple Data Types C4

- Next-generation sequencing, microarrays, arrayCGH
- Gene expression, methylation, copy number variations

Computational Efficiency

- Resource-efficient read mapping and alignment (using GPUs) [Köster and Rahmann 2014]
- Resource-efficient variant filtering

Methodology

Resource-Efficient Feature Generation from DNA

Detailed Analysis of Variant-Tolerant Read Mapping by Min-Hashing

- Min-hashing to estimate the Jaccard similarity

$$J(K_Q, K_R) := |K_Q \cap K_R| / |K_Q \cup K_R|$$

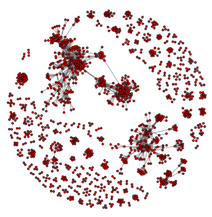
between k-mer sets K_Q, K_R

- Known variants yield additional k-mers which may be added to the reference K_R.
- We showed: beneficial only for variants with high population frequency. [Quedenfeld and Rahmann 2017]

Correspondence between specific SNVs and Methylation Level Changes

- Inter-individual methylation changes may often be traced to a single causative SNV.
- State (unmethylated, semi-methylated, fully methylated) requires discretisation of methylation level in $[0, 1]$.
- Achieved with beta mixture models; computed with a novel EM-type algorithm using moment estimators in the M step. [Schröder and Rahmann 2017]

Identification of Sparse Feature Graphs



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- Preliminary: Model similarity between protein complexes
- Focus: Dependencies between expression levels of genes
- Estimation of inverse covariance matrix $\Theta = \Sigma^{-1}$ with partial correlations

Penalized likelihood approach, assuming multivariate normal distribution:

$$\min_{\Theta \in \mathbb{R}^{p \times p}} \; -\log\det\Theta + \mathrm{tr}(S\Theta) + R(\Theta)$$

LASSO:

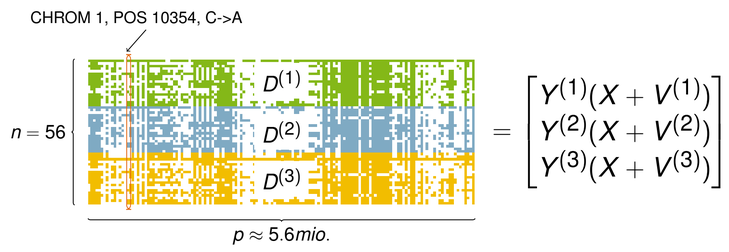
- $R(\Theta) = \lambda \|\Theta\|_1$
- Determine λ by controlling the family-wise error rate (restrictive) or by cross-validation (sample dependent)

SLOPE:

- $R(\Theta) = \sum_{i=1}^{p^2} \lambda_i |\Theta|_{(i)}$
- Determine λ_i by False Discovery Rate (FDR) control
- Efficient saddle point optimisation for the Dantzig selector formalisation

[Lee, Brzyski, and Bogdan 2016]

Tumour Subtype Identification



- Biclustering of patients and variants by a modified Boolean matrix factorization (BMF)

$$\min_{X,V,Y} \sum_{a=1}^{c} \|D^{(a)} - Y^{(a)} \cdot (X + V^{(a)})^T\|^2 + S(X, Y)$$

V indicates tissue-specific variants for each cluster, $S(X, Y)$ regulates specificity of V [Hess and Morik 2017]

- Solve NP-hard BMF by proximal alternating minimization of relaxed objective
- Determine the rank by FDR control

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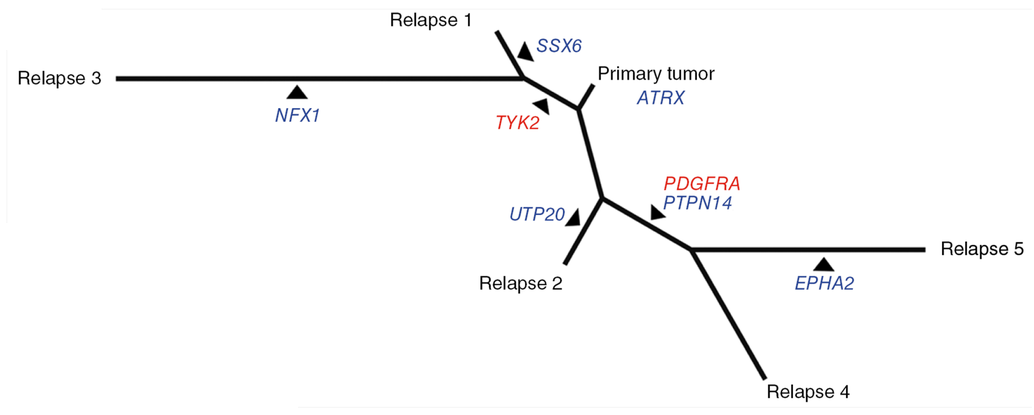
[Hess, Morik, and Piatkowski 2017; Hess, Piatkowski, and Morik 2018]

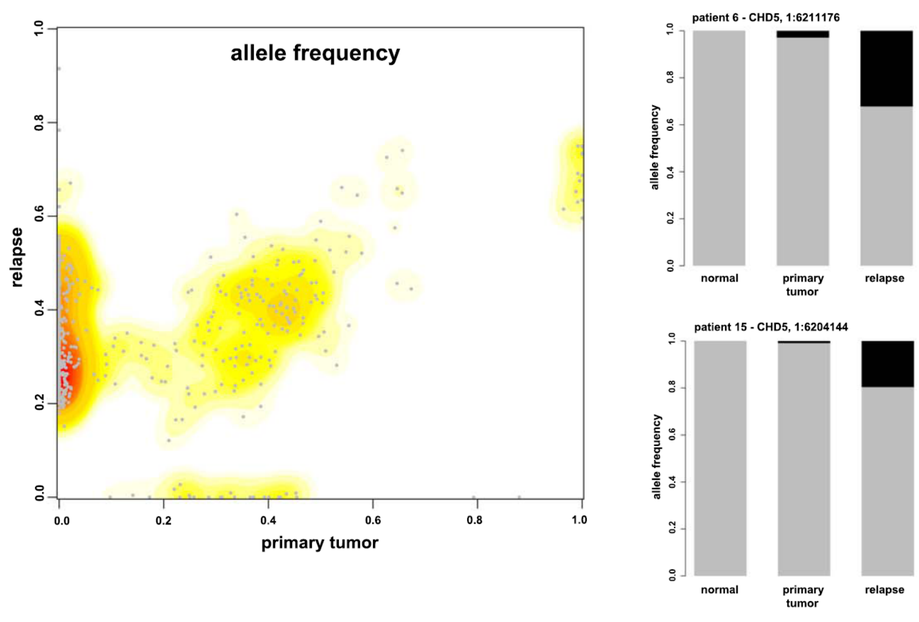
Results

Tumour Evolution

- Mutational dynamics were analyzed in one primary tumour and multiple relapse samples from a single neuroblastoma patient.
- A phylogenetic tree was built according to Hamming distances between the primary tumour and the relapse samples (Neighbor Joining).
- A stable pattern of bifurcation emerged, suggesting that at least two different subclones developed independently from the primary tumour.
- Every branch has 100% bootstrap support and is robust against various perturbations of the input data. [Schramm et al. 2015]



Intratumoural Heterogeneity



- Allele frequency shifts between matched pretreatment primary and relapse neuroblastomas.
- Most SNVs detected in relapse tumours are below the whole-exome sequencing detection limit in the primary tumour. [Schramm et al. 2015]

Artificial Intelligence Group

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