technische universität
dortmund

SFB 876 Providing
Information by Resource-
Constrained Data Analysis

Universitätsklinikum Essen

UNIVERSITÄT DUISBURG ESSEN
Offen im Denken

Project C1

Feature selection in high dimensional data for risk prognosis in oncology

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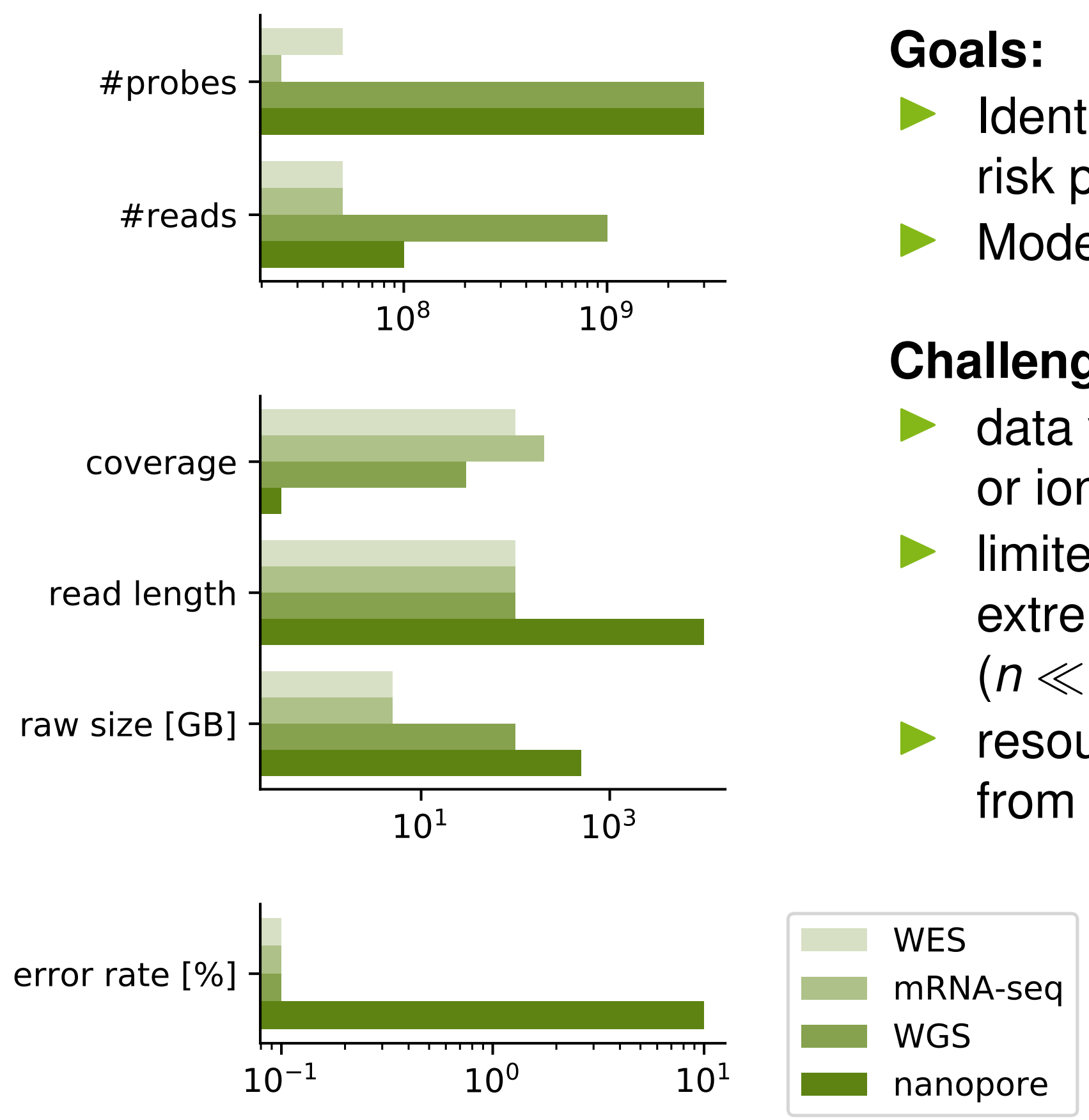
Problem

New Dimension of Data Volume: Whole genome & nanopore sequencing

Features are derived from molecular probes or sequences (reads).



Goals:

- Identifying molecular biomarkers for risk prognosis
- Modeling prediction functions

C4

Challenges:

- data volume (100s of GBs sequence or ion current data)
- limited number n of samples vs. an extremely high number p of features ($n \ll p$ problem)
- resource-efficient feature generation from raw data

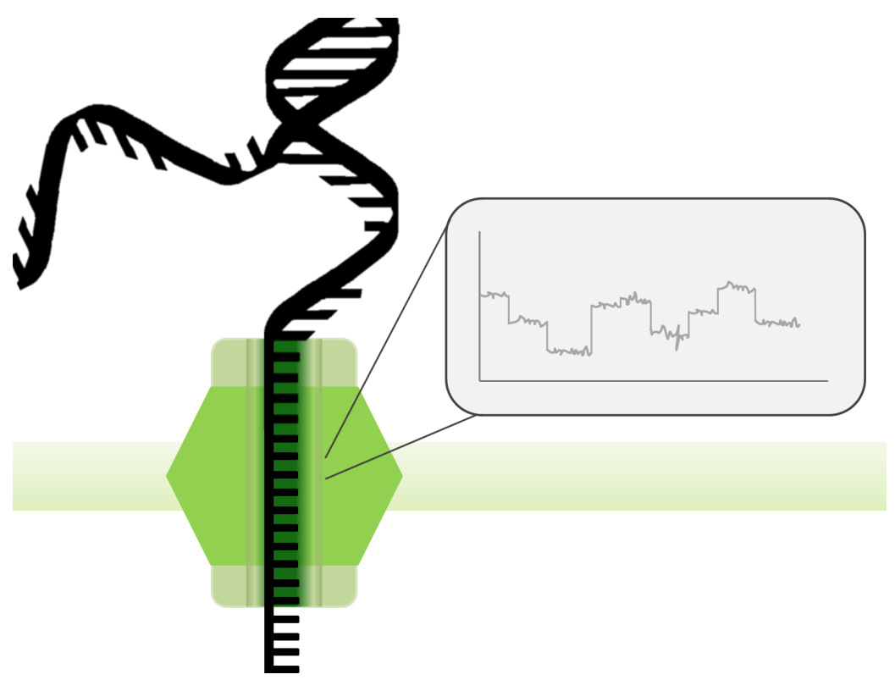
New Sequencing Technology: MinION nanopore

- Small portable device (size of a USB stick)
- Analysis on a laptop
- Large lab infrastructure no longer necessary
- Democratisation of access to sequencing
- One flow cell can generate 10–20 Gb of DNA sequence data.
- Ultra-long reads are possible (>100 Kbp)
- Disadvantage: high error rates (10–15 %)

Source: http://www.bio-itworld.com/uploadedImages/Bio-IT_World/Top_Headlines/2014/12-Dec/MinION%20close%20up.jpg

Goals:

- Real-time algorithms that convert the changes in ion currents at the nanopores immediately into the corresponding DNA sequence
- Prognostic biomarkers from liquid biopsies and nanopore sequencing
- Collaboration about detection and extraction of tumor vesicles



B2

Planned Research

Efficient Whole Genome Analysis with DNA k-mers

Use genomewide-unique k-mers ($k \in \{21, 23, 25, \dots\}$) for

- single nucleotide variant (SNV) discovery
- copy number variants (CNVs)
- structural variants (translocations, fusions)
- methylation analysis from WGBS data
- gene expression analysis from RNA-seq

Feature generation from whole genomes on a standard laptop:

- Output only unique k-mers that deviate from expected count: new k-mers, lost k-mers, surprising copy number, …
- Project deviant k-mers to biological entities (regions, genes, transcripts, pathways)
- Detect enrichment of deviant k-mers and deviant biological entities in tumour samples

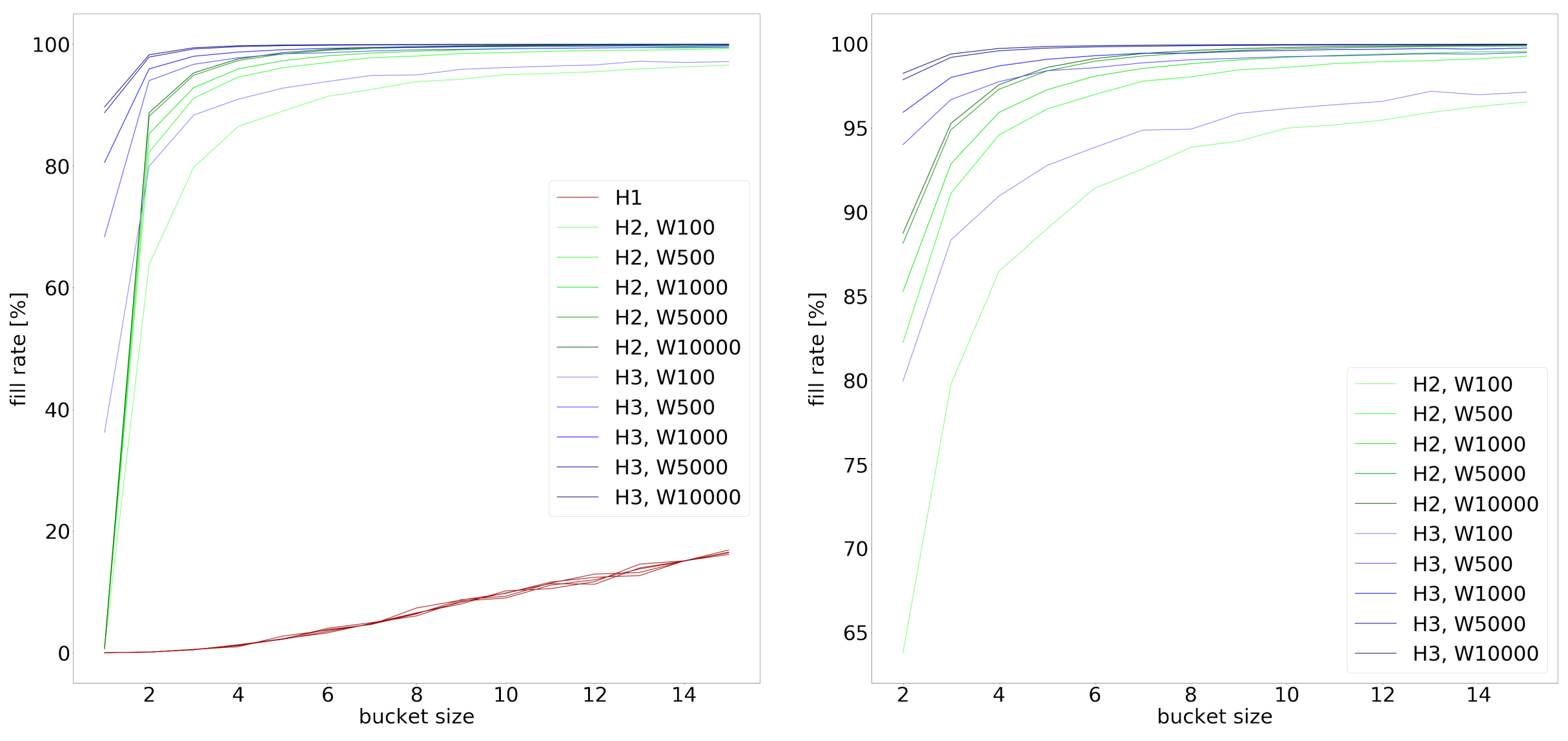
Feature reduction:

- Aggregation: Variant → Gene → Pathway
- Clustering of similar features with graph-based methods

A6

Key Data Structure: Efficient DNA k-mer Key-Value Store

Challenge: small hash table **and** fast look-ups
Speed bottleneck: cache misses during memory look-ups
New proposal: 3-way bucketed Cuckoo hashing with quotienting

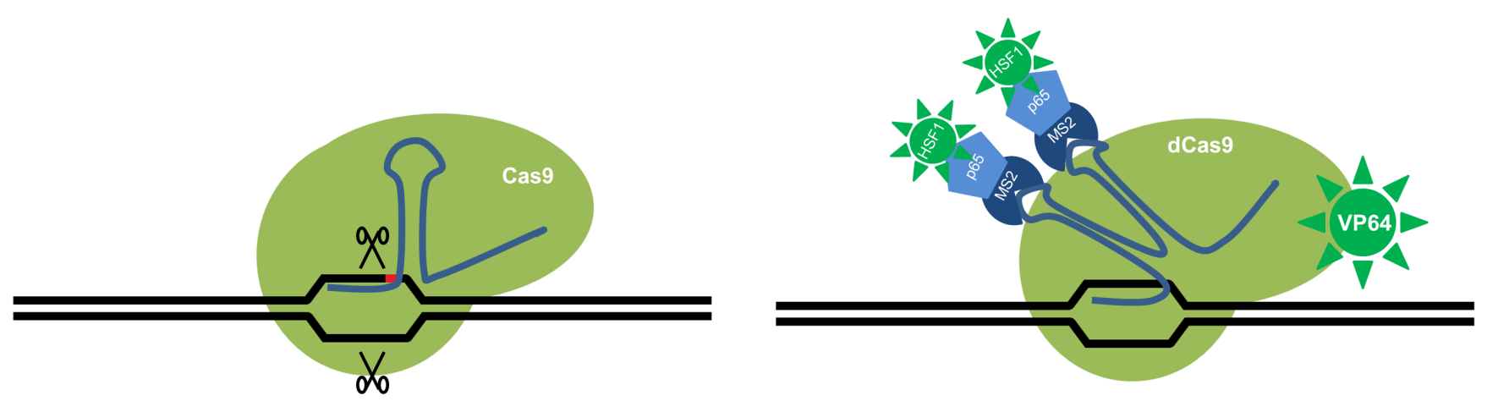


Maximal fill rates of hash table for different numbers of hash functions (H: 2 or 3), bucket sizes (x-axis, 1–15) and bounds on random walk length during insertion (W: 100, 500, 1 000, 5 000, 10 000).

Look-up needs H cache misses in the worst case.

Gene Knock Outs by CRISPR / Cas9 Genome Editing

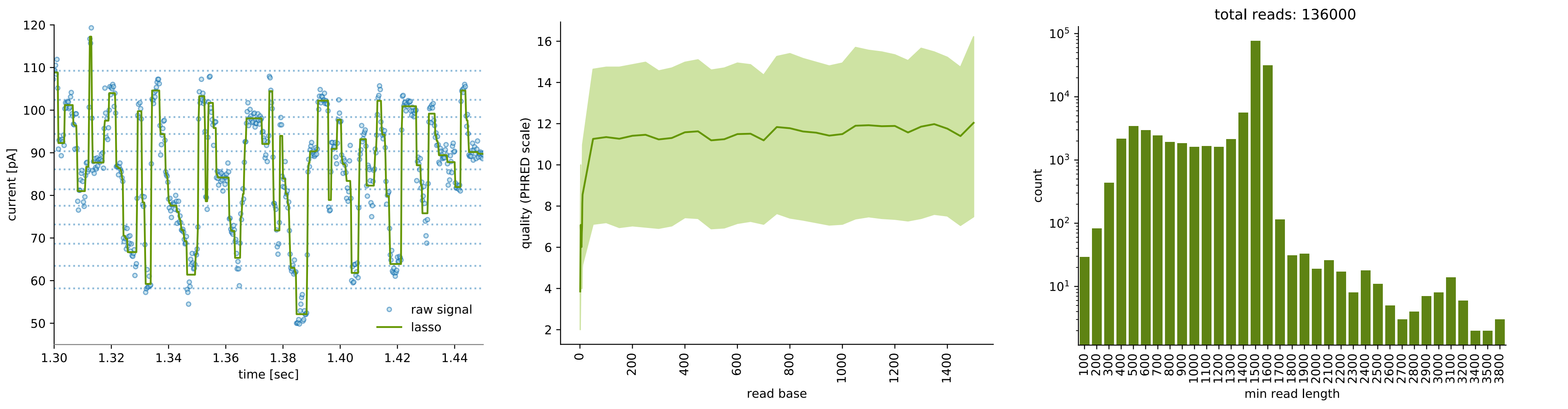
- Cultivation of human cancer cells *in vitro* (2D/3D)
- Transfection with Cas9 ribonucleoproteins or lentiviral transduction
- Double strand break generation by Cas9 to create a gene knock-out
- The inactive nuclease Cas9 complex with three activation domains activates transcription (CRISPR SAM).



- Fluorescence activated cell sorting (FACS)
- Quantitative Polymerase chain reaction (qPCR)
- MinION RNA sequencing

Analysis of Ion Current Data

Establishment of the technology and preliminary experiments on microbiomes:



Computational challenge: Lightweight conversion of ion current signal to DNA sequence

- Signal segmentation: Fused LASSO; given signal $y = (y_i)$,

$$\min \; f(x) := \sum_{i=1}^{n} (x_i - y_i)^2 + \lambda \cdot \sum_{i=1}^{n-1} |x_{i+1} - x_i|.$$

- Discretisation of signal levels; new efficient algorithms for discretised fused LASSO, where x_i must be from a finite known level set L.
- Learn mapping between k-mers of level set L to (modified) DNA sequence

Alternative approach:

- Work with k-mers of discretised signal space L directly (richer representation)
- Discover variants as for WGS analysis in L^k-space

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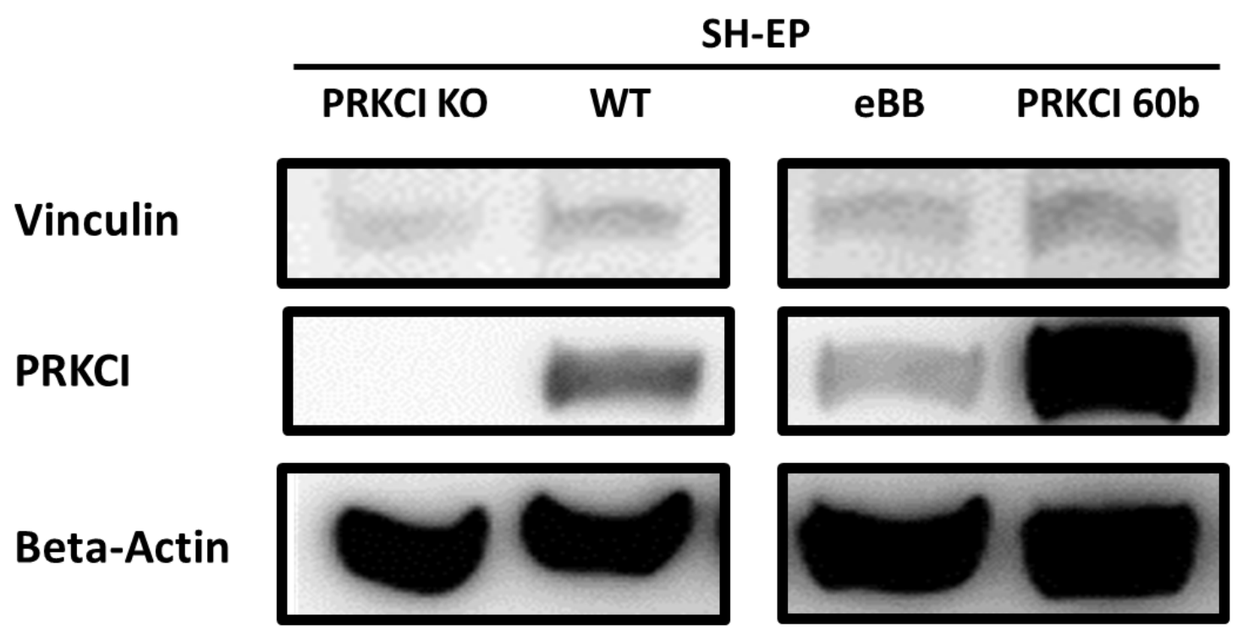
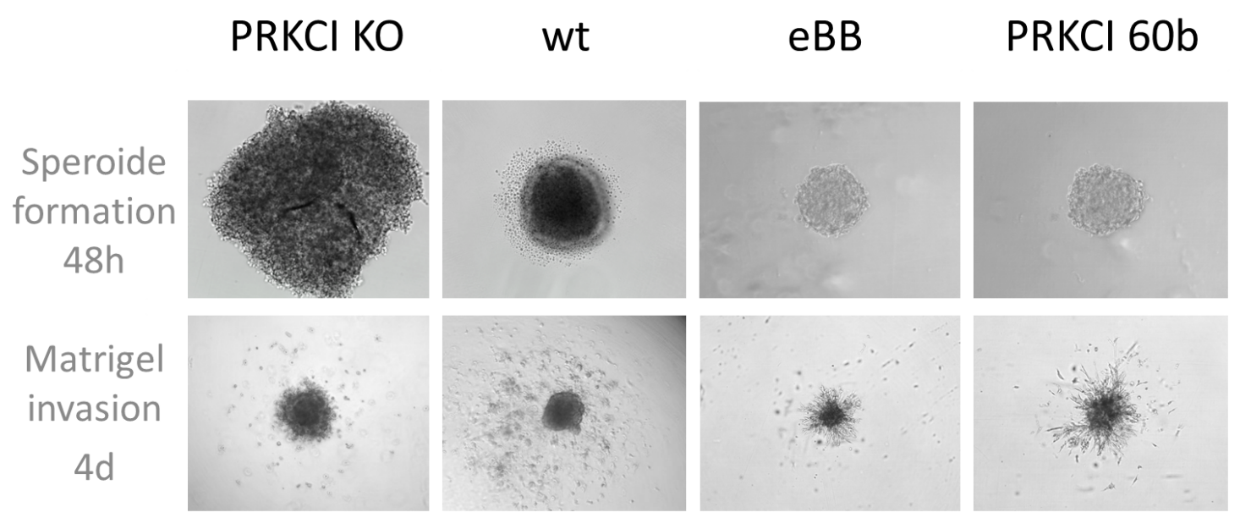
Biological Target Validation

- Validation of CRISPR / Cas9 based knock-out and overexpression by Western Blot analysis



- 3D culture reveals decreased spheroid formation ability and invasiveness upon PRKCI knock-out, while over-expression of PRKCI increases the invasiveness of SH-EP cells (neuroblastoma cell line).



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