

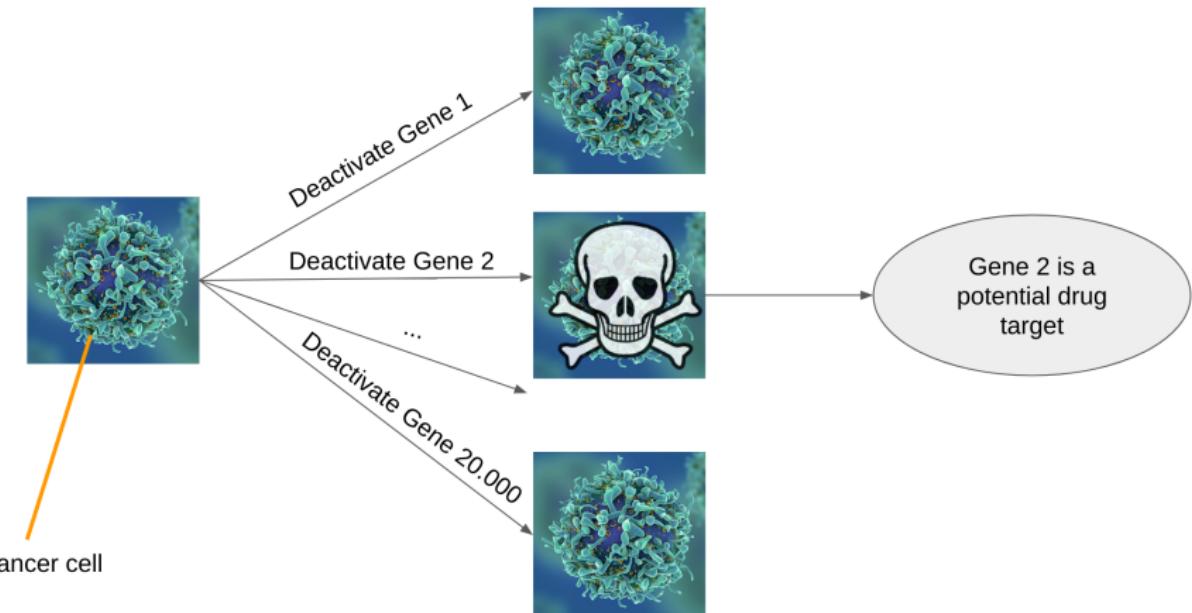
PAVOOC - An AI integrated web-app for CRISPR target recommendation

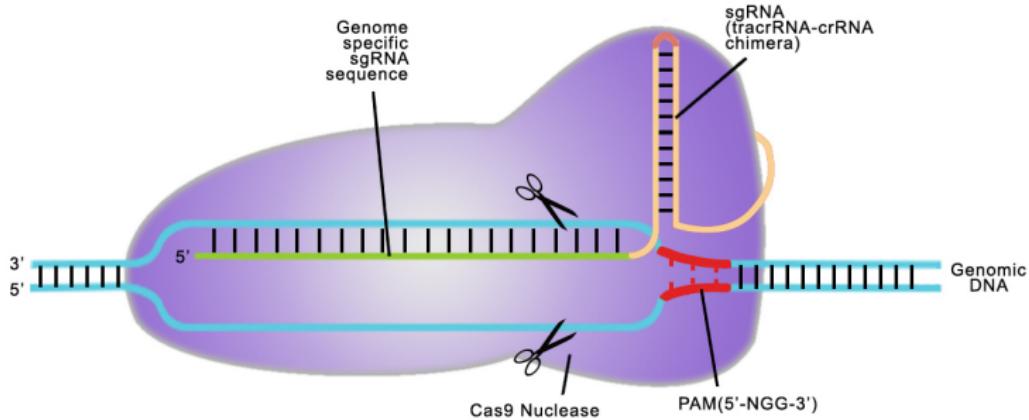
Moritz Schäfer | Technische Universität Berlin & Bayer Pharma | Prediction and visualization of on- and off-targets for CRISPR

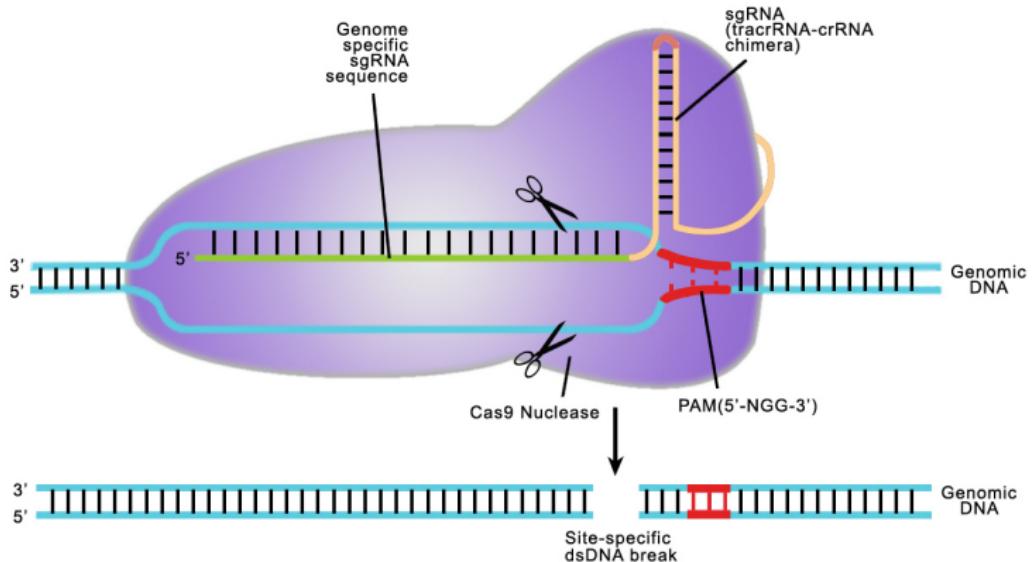


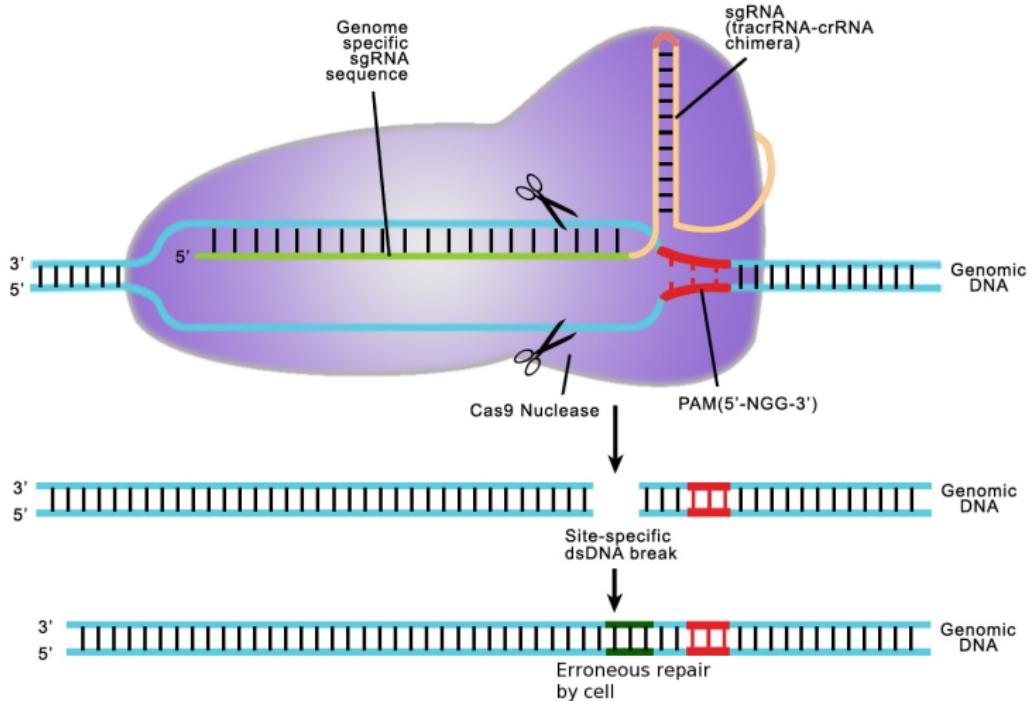


Target discovery



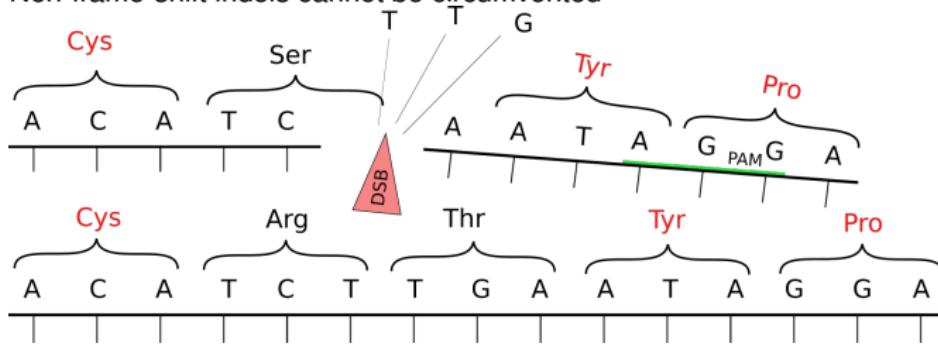






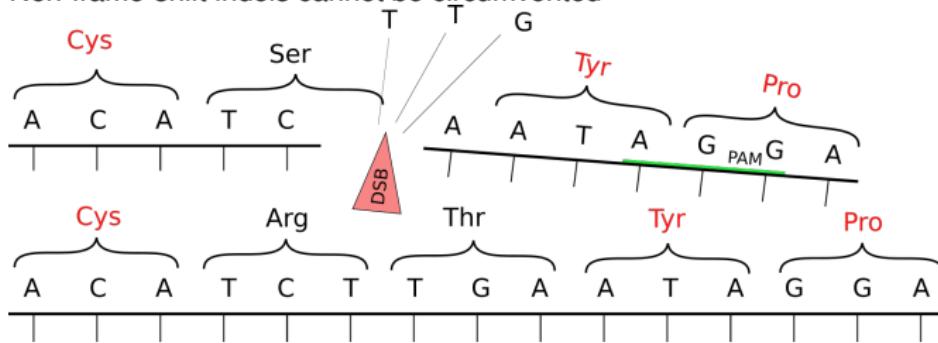
Problems

- Non-frame-shift-indels cannot be circumvented



Problems

- Non-frame-shift-indels cannot be circumvented



- Guide performance varies significantly



Solution

- Cutting-edge guide efficacy scoring



Solution

- Cutting-edge guide efficacy scoring
- Web based guide design tool



Live Demo

<http://pavooc.me>

Guide efficacy prediction – Dataset

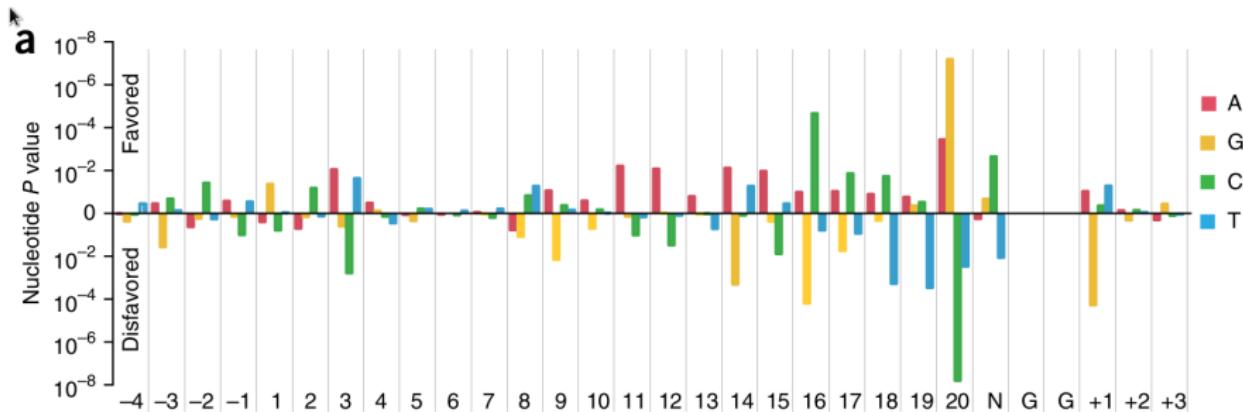
Guide	Measured efficacy
GTTAGGGGTCCGTACTCAGCAAGG	0.86
ACACTGCCGAGCGATGAGGATGG	0.42
AAGGTGAAGGAGGATGCGGCGGG	0.53
GAAAAGATAAGGTCACTGACCCGG	0.12
GCAAGTCACTGAGTGCAGAACGG	0.73
GCATTGGTAAGCGCACAGGAAGG	0.70
AAGACTGGCGCATGGTCCACTGG	0.57
...	...

- 1,837 data rows from 2014
- 3,473 data rows from 2016
- Efficacy relates to cell proliferation after CRISPR application

"Optimized sgRNA design to maximize activity and minimize off-target effects of CRISPR-Cas9", 2016, John G. Doench et al.



Guide efficacy prediction – 2014



"Rational design of highly active sgRNAs for CRISPR-Cas9–mediated gene inactivation", 2014, John G. Doench et al.



Guide efficacy prediction – 2016 (Azimuth)

Pairwise nucleotide features



Guide efficacy prediction – 2016 (Azimuth)

Pairwise nucleotide features

ACTATCTATCGTACGA**TT**GA



Guide efficacy prediction – 2016 (Azimuth)

Pairwise nucleotide features

ACTATCTATCGTACGA**TT**GA

ACTATCTATCGTACGAC**AAG**

"Optimized sgRNA design to maximize activity and minimize off-target effects of CRISPR-Cas9", 2016, John G. Doench et al.



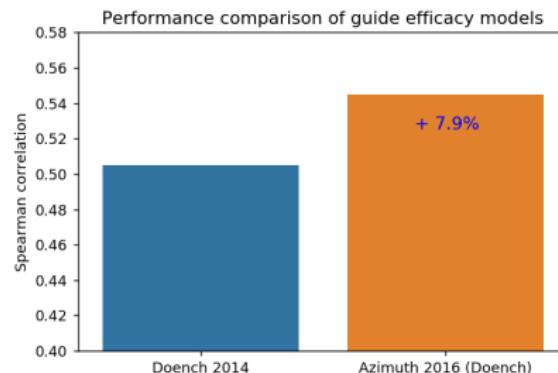
Guide efficacy prediction – 2016 (Azimuth)

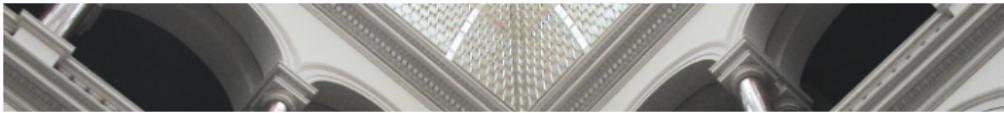
Pairwise nucleotide features

ACTATCTATCGTACGA**TT**GA

ACTATCTATCGTACGAC**AAG**

"Optimized sgRNA design to maximize activity and minimize off-target effects of CRISPR-Cas9", 2016, John G. Doench et al.

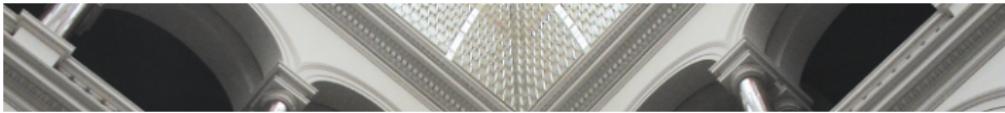




Convolutional neural networks

Well performing guides:

GTAGGGGTCCGTACTCAGCA
CAGGGTCCGTACTCAGAGGA
CTAGCGTAGAGCGCACTGCA
ACTGAGCTAGCGTAGAAGCA
TGAGCTAGCGTAGAGCACCA
ACTGAGCTAGCGTAGTAGCT
AGCGTAGAGCGCGCTGCC
GAGCGCACTGAGCTAGAGAA
ATAGAGCGCCTGAGCTCGCA
CGTAGAGCGCACTGAGAGCT



Convolutional neural networks

Well performing guides:

AGCA

AGGA

TGCA

AGCA

ACCA

AGCT

CGCC

AGAA

CGCA

AGCT



Convolutional neural networks

Well performing guides:

AGCA

AGGA

TGCA

AGCA

ACCA

AGCT

CGCC

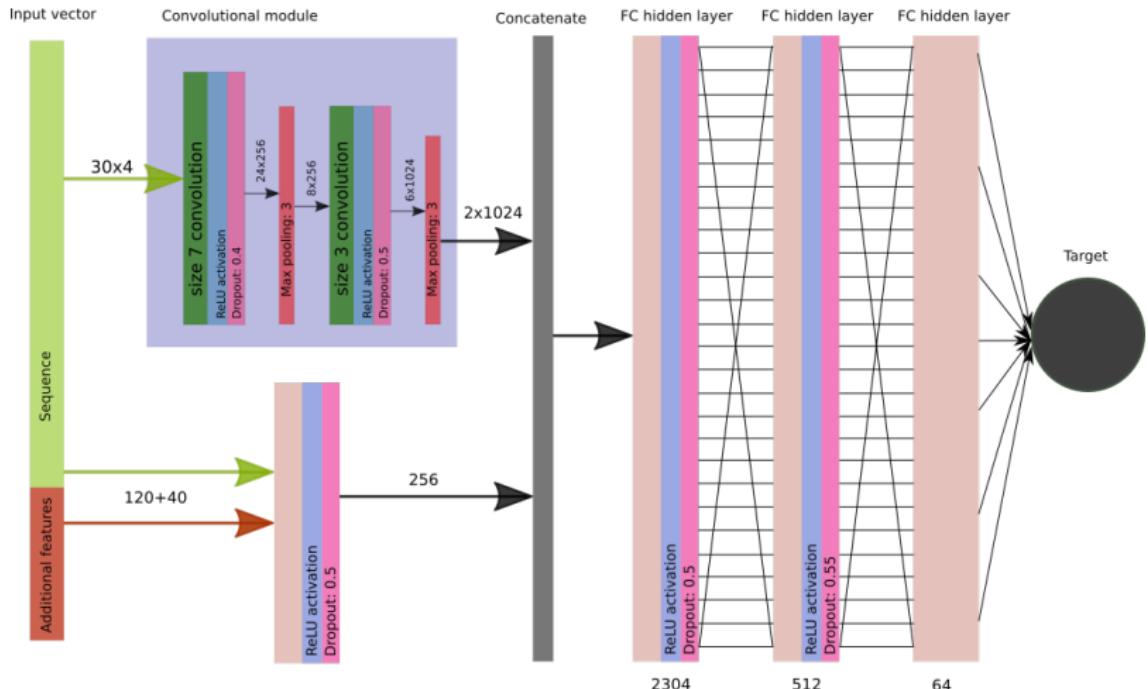
AGAA

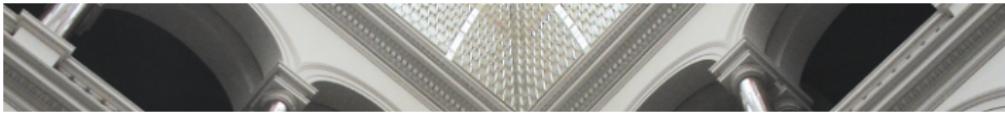
CGCA

AGCT

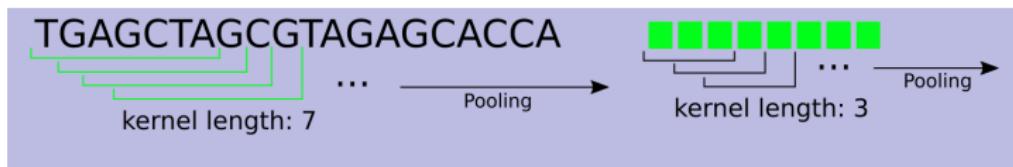
Learned filter: [A G C A]

Model architecture

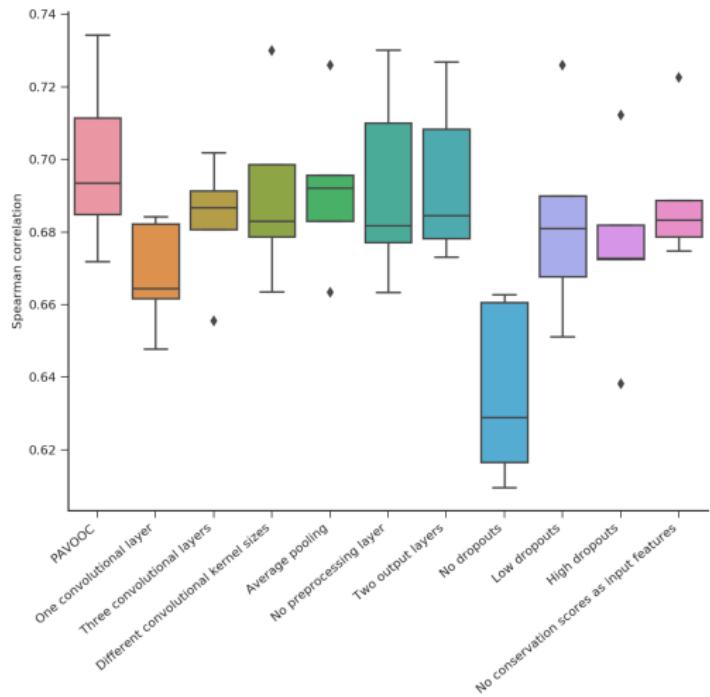




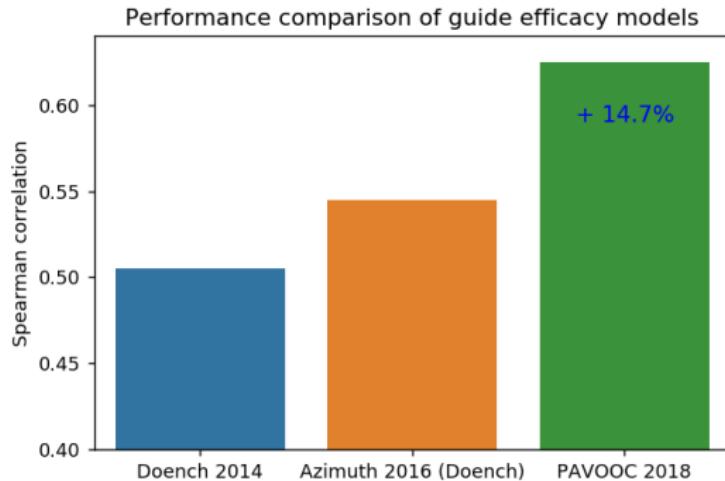
Model architecture – Convolution module



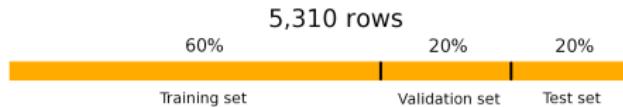
Model optimization



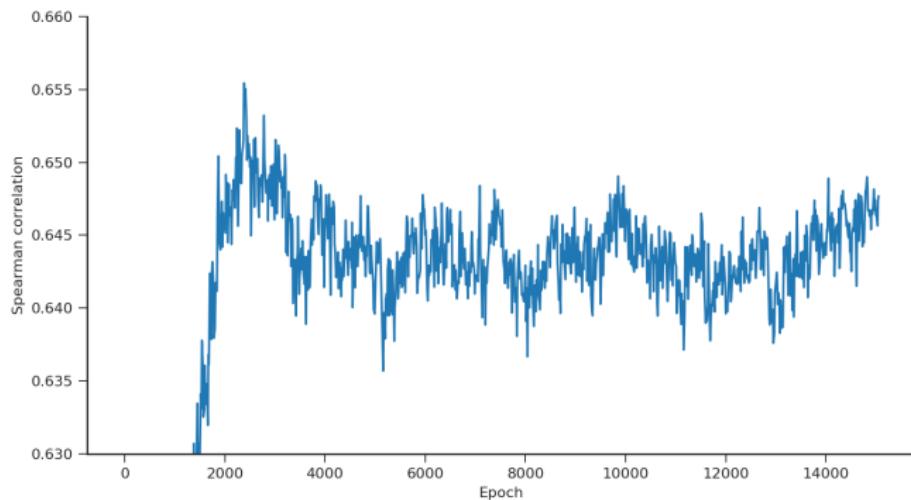
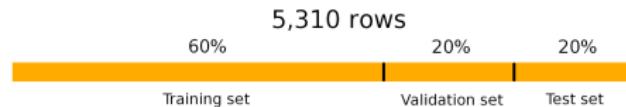
Model architecture



Performance evaluation



Performance evaluation





Conclusion and Takeaways

- Cas9 efficacy depends on complex biological coherences
- DL improves guide efficacy prediction
- DL feasible with ~5,000 rows



Future Work & Discussion

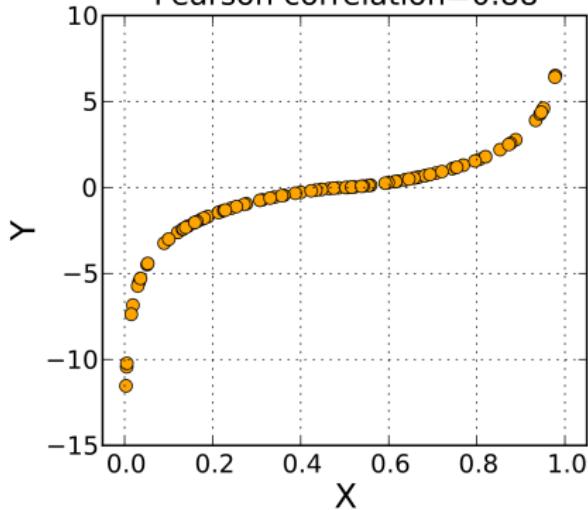
- Additional input features (chromatin accessibility)
- Evaluate model on different datasets
- Support additional species



End

Spearman correlation

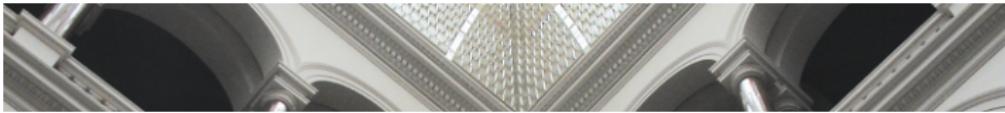
Spearman correlation=1
Pearson correlation=0.88





Spearman correlation

- Test set labels: [0.2, 0.3, 0.5, 0.9]
- Test set predictions: [0.4, 0.6, 0.7, 0.8]
- Spearman correlation: 1.0



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Advantages:

- Ranking mimicks the task of guide selection

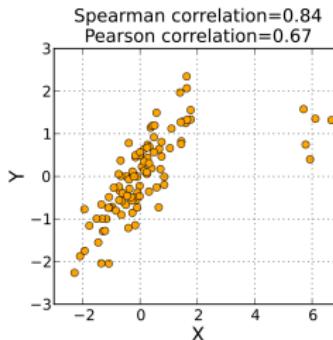


Spearman correlation

- Test set labels: [0.2, 0.3, 0.5, 0.9]
- Test set predictions: [0.4, 0.6, 0.7, 0.8]
- Spearman correlation: 1.0

Advantages:

- Ranking mimicks the task of guide selection
- Robust against outliers





Acknowledgements

- Prof. Manfred Opper (supervisor at TU Berlin)
- Dr. Andreas Steffen (supervisor at Bayer)
- Dr. Djork-Arne Clevert (machine learning scientist at Bayer)
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- Bayer Pharma AG