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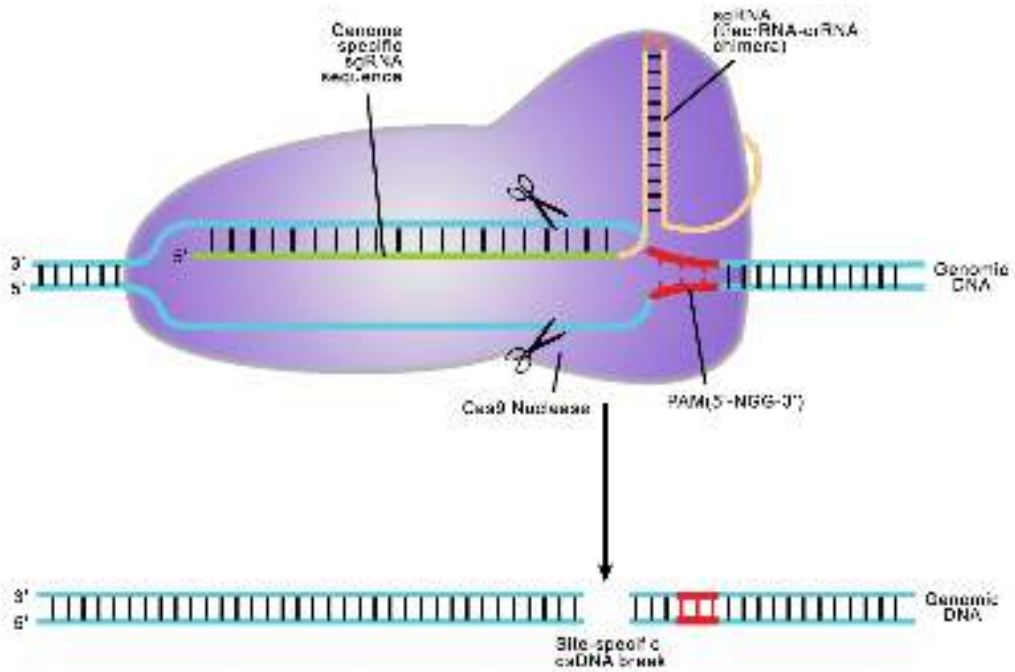
PAVOOC - Prediction and visualization of on- and off-targets for CRISPR

Moritz Schäfer | Technische Universität Berlin & Bayer Pharma | Master thesis

Background



- Knockout experiments used in drug target validation
- Sequence (partially) determines efficacy

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Problem

– Guide prediction scores still vary in performance

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- Guide prediction scores still vary in performance
- A lot of manual labor for guide selection

19	POLR2L	28,5	28	-3,00752118182
20	SPC24	29,5	42	-2,83403119872683
21	THAP1	31,5	27	-3,01155447143932
22	CDC123	32,5	44	-2,81699463079959
23	WDR74	37	68	2,58033320817648

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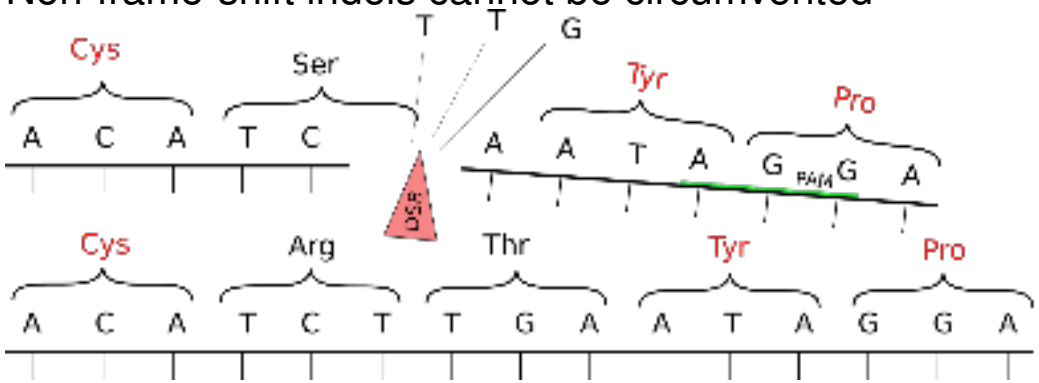
- Non-frame-shift indels cannot be circumvented



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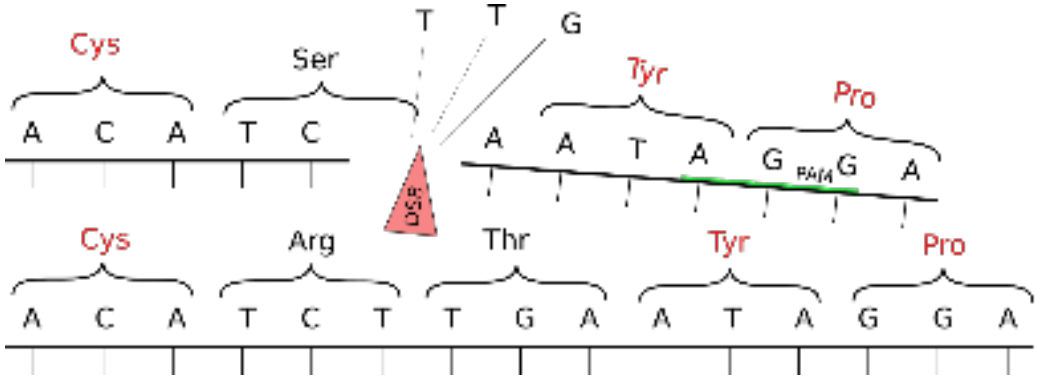
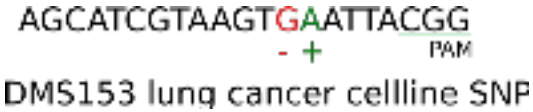


- Cancer cellline data affects certain guides



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Solution

- Cutting-edge guide efficacy scoring
- All-in-one guide design tool
- Web-based
- Functional domain-aware
- Incorporate cancer cellline data

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Guide efficacy prediction – Dataset

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

- 5310 data rows
- 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.

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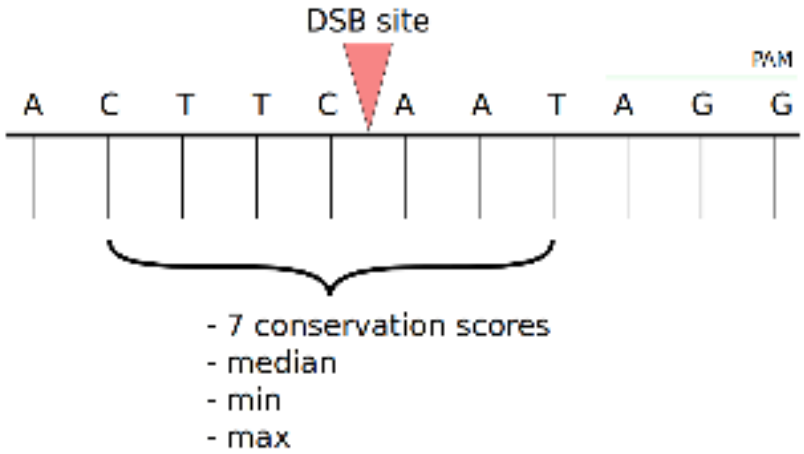
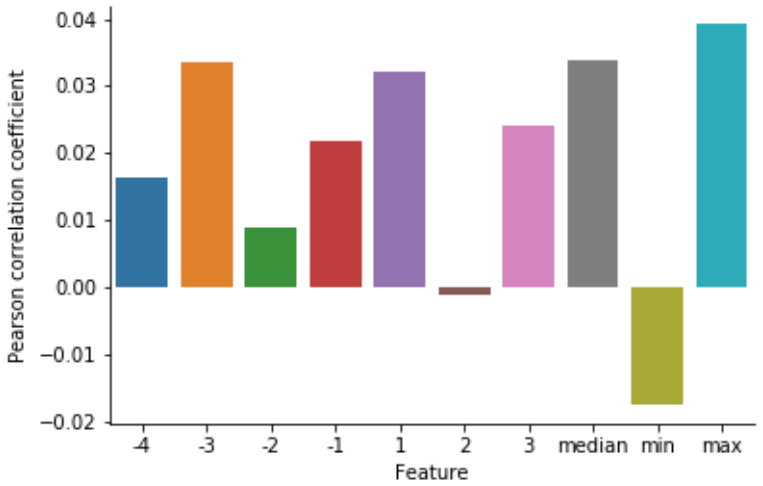
Conservation features

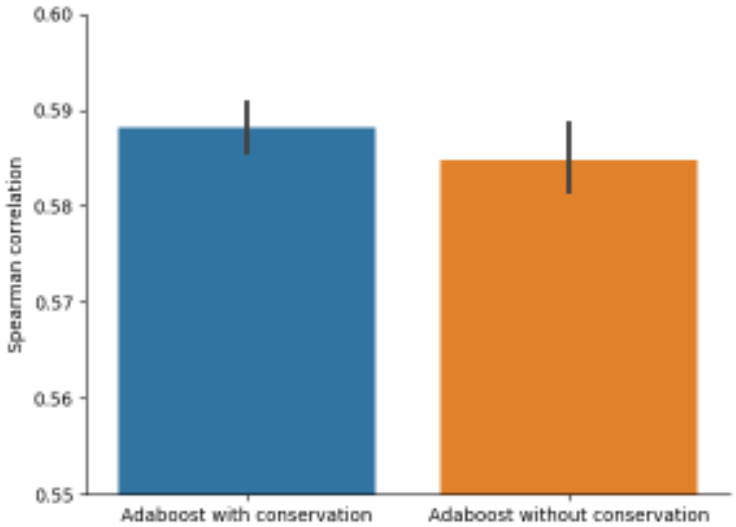


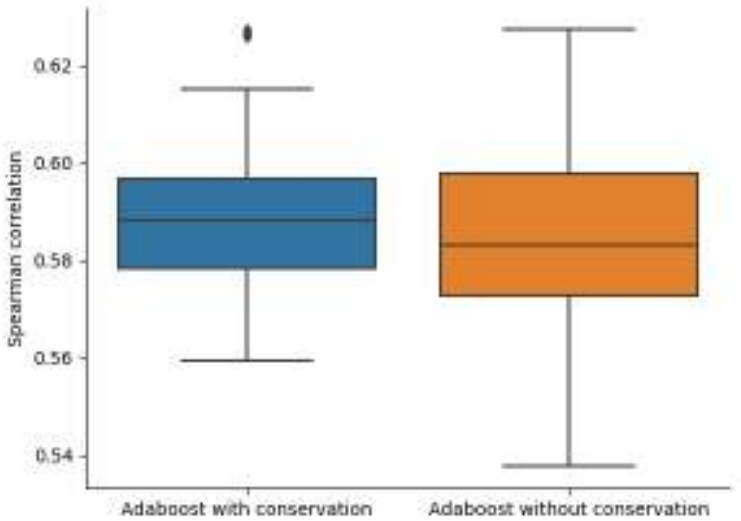


$p_{max} = 0.0043$

Conservation feature results

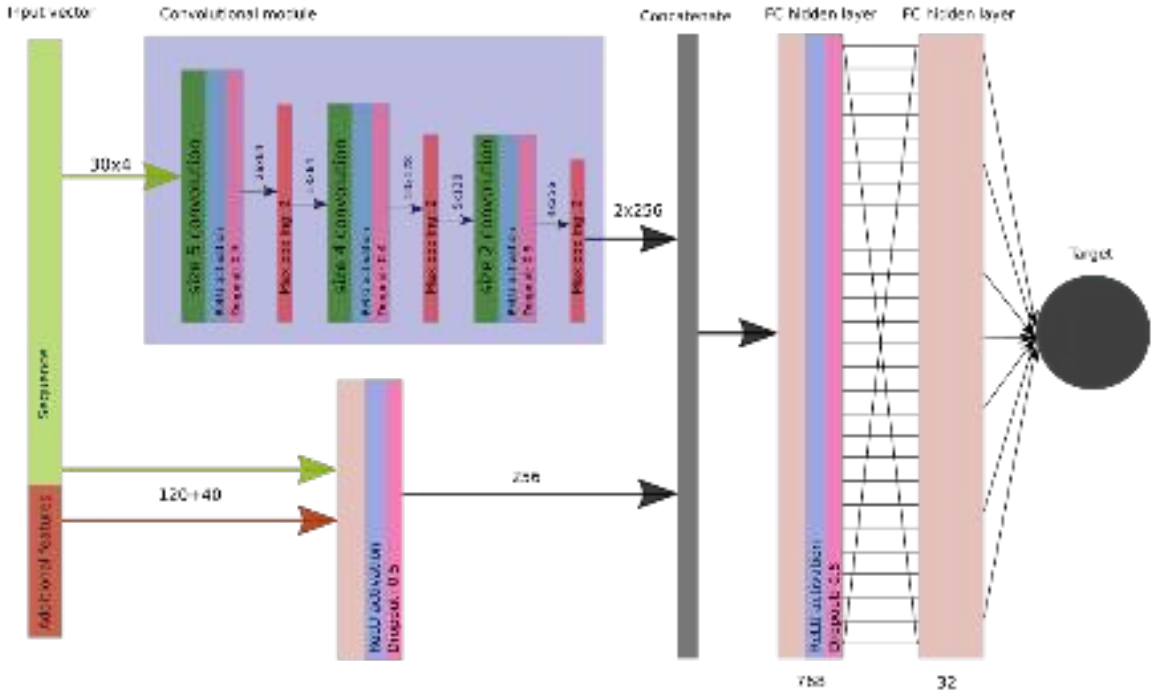
Comparison of 100 runs on adaboost





Deep Learning architecture

"Predicting the sequence specificities of DNA-and RNA-binding proteins by deep learning", 2015, B. Alipanahi et al.



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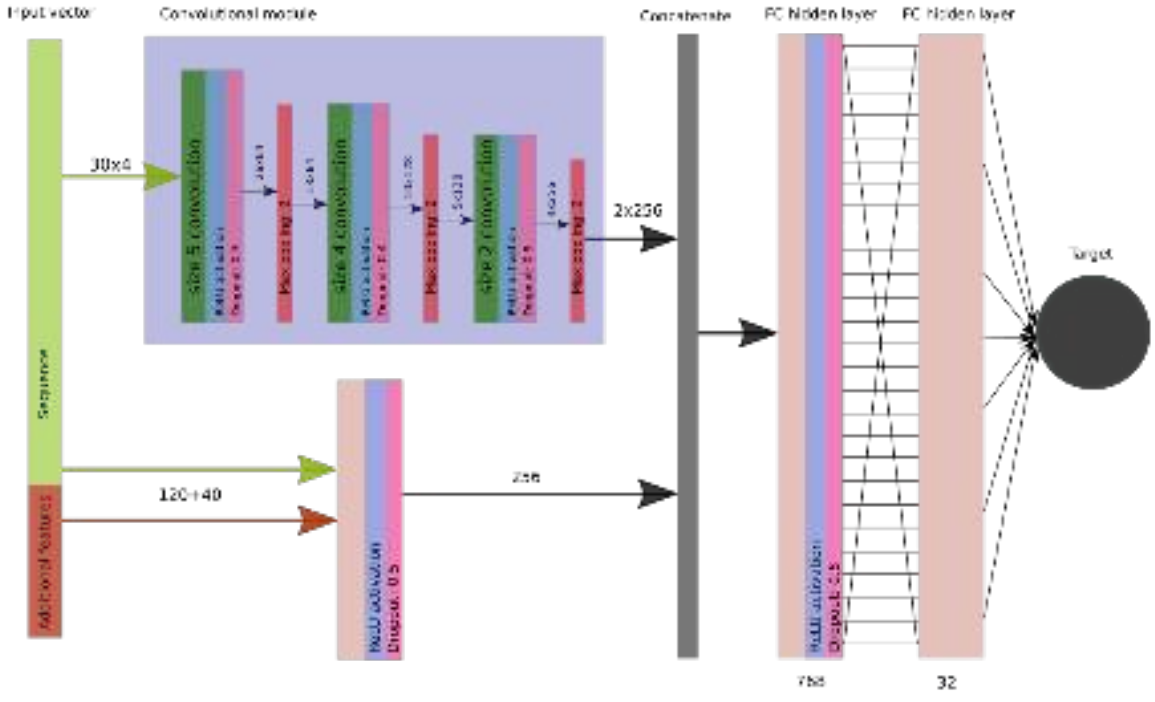

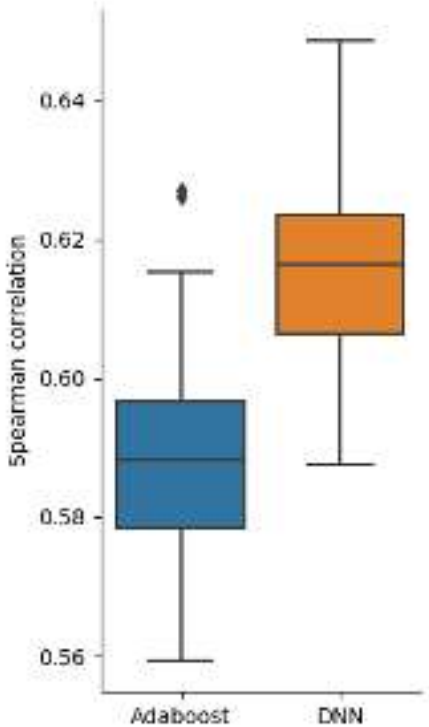

Conclusion: Deep Learning can improve guide efficacy prediction

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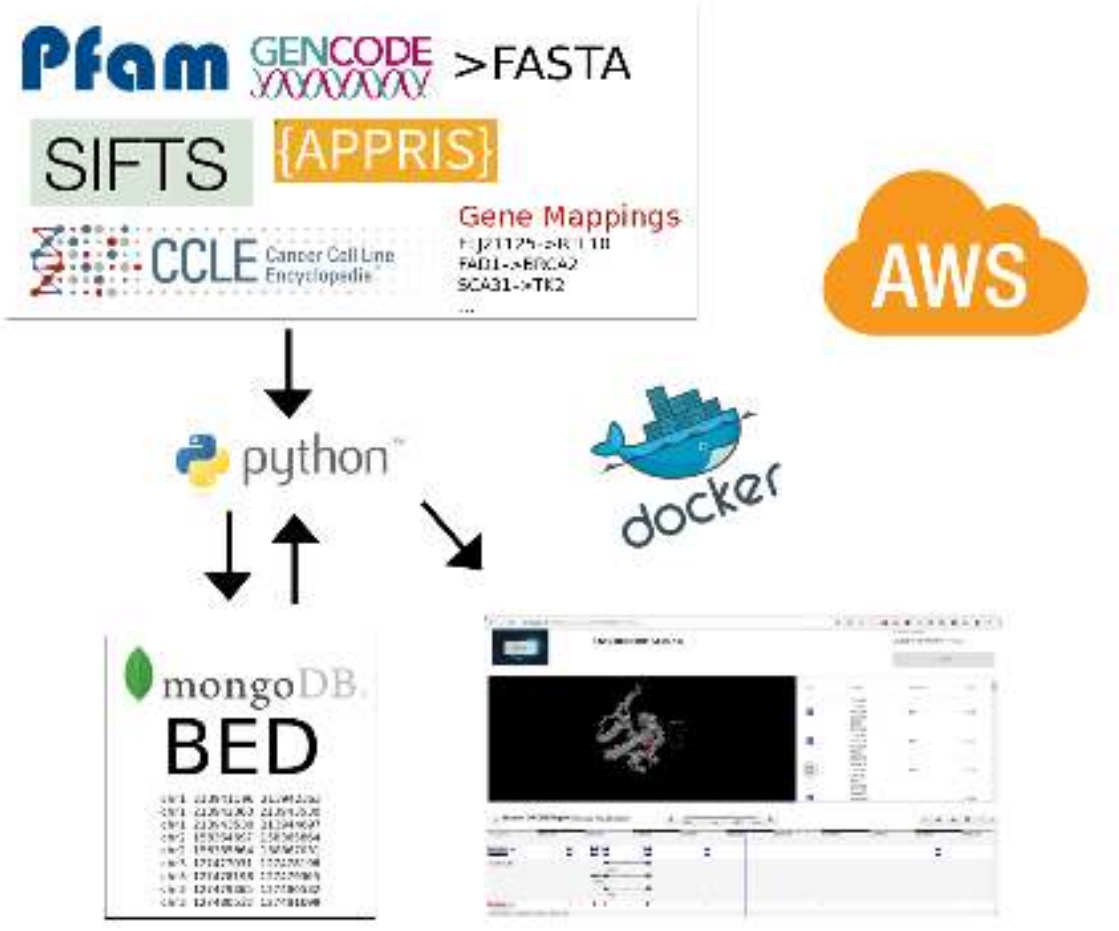
Architecture



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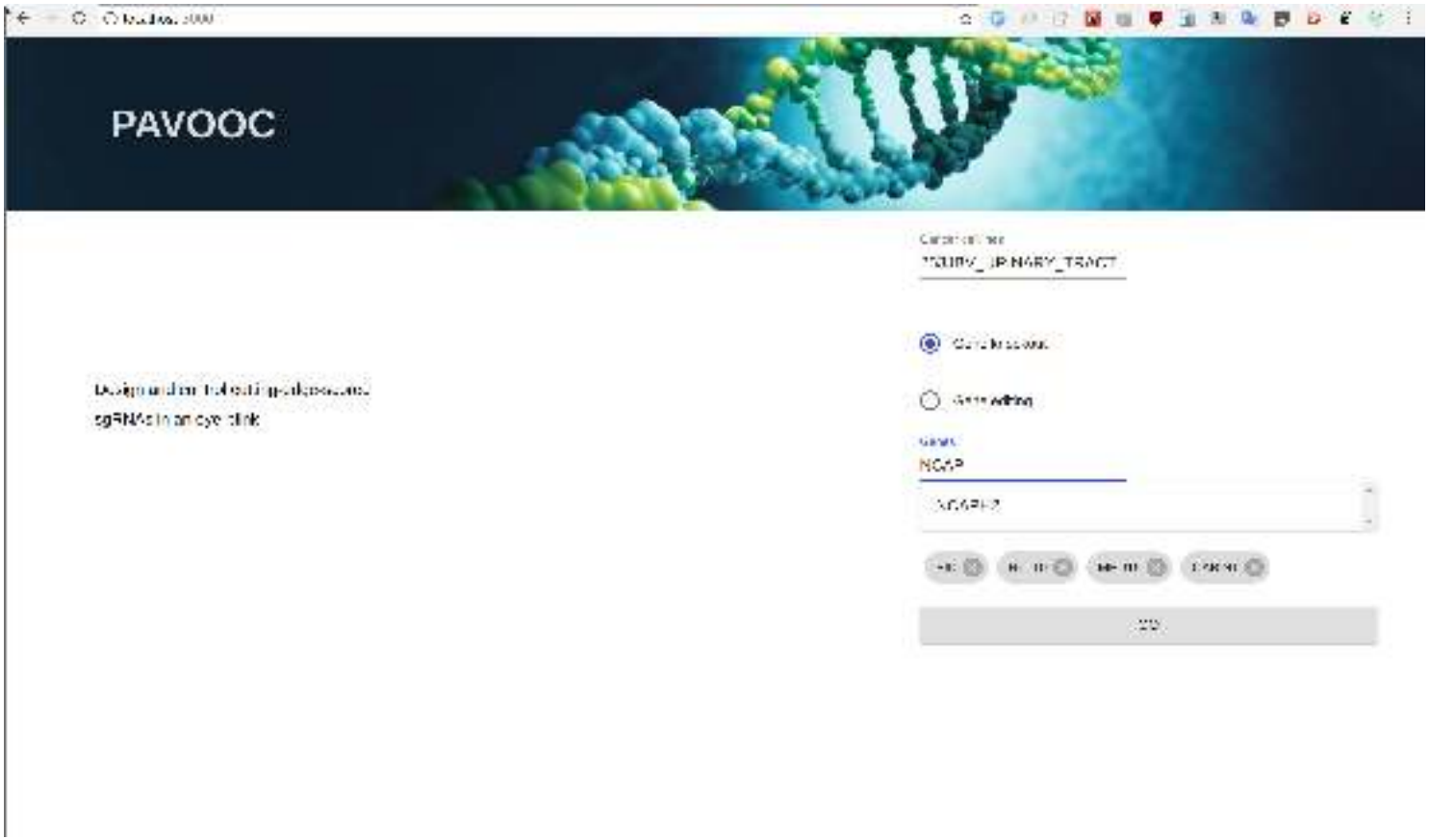
Application overview



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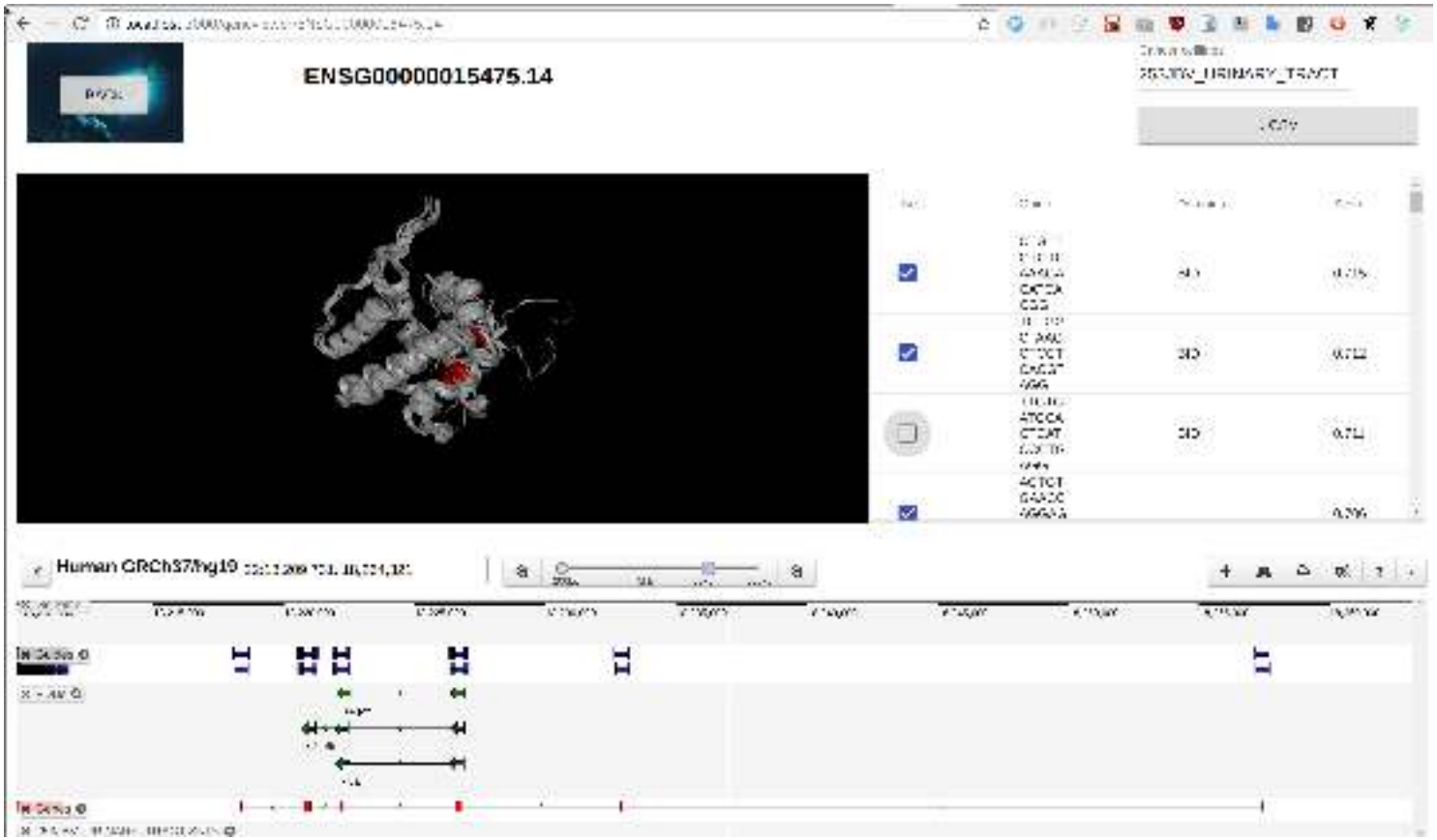

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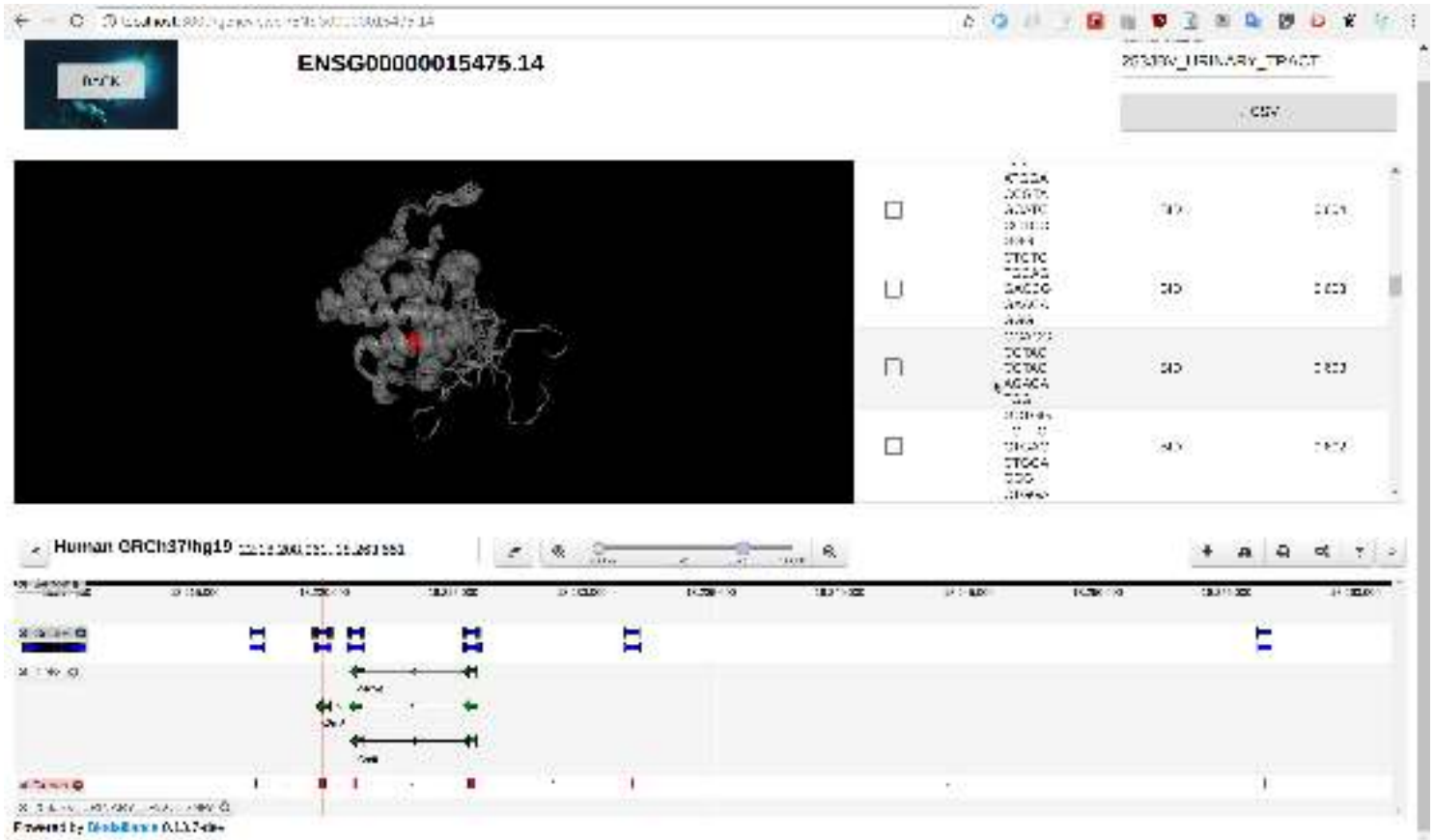
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